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# A Method for the Preparation of Methylmetal Compounds[*]

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*Dedicated to Professor W. Klemm on the occasion of his 70th birthday*

*A new method has been developed for the preparation of methylmetal compounds from methyl chloride and the chlorides of boron, aluminum, silicon, tin, phosphorus, antimony, or mercury. Fused salts are used as solvents, and metals are suspended in these to act as halogen acceptors. The metals are recovered, together with chlorine, by electrolysis. This process, which can be carried out continuously and quantitatively, can be used for the preparation of technically important methylmetal compounds that cannot be obtained directly by the "Mülheim aluminum alkyl method".*

## I. Methylation with Methylmetal Compounds

The discovery of the alkylzinc compounds made possible for the first time the preparation of other organometallic compounds (methylsilicon, alkyltin, and methylboron compounds). However, since dimethylzinc can only be obtained from methyl iodide and zinc, and since it is very volatile and self-inflammable, its use as a methylating agent is confined to special cases.

Dimethylmercury was formerly also obtainable only from methyl iodide, but it has been found that methyl bromide can be used together with sodium amalgam. Despite its toxicity, $Hg(CH_3)_2$ is a very valuable methylating agent, since it is neither self-inflammable nor excessively volatile, and since it is soluble in the common solvents. It has recently become possible to prepare dimethylmercury from methyl chloride, which is both cheap and readily available.

The best-known of the older reactions used for the methylation of metal halides is probably the Grignard synthesis. However, this reaction is difficult to control, proceeds discontinuously, and requires the use of large quantities of ether; moreover, the magnesium chloride formed is usually rejected, in spite of the fact that it contains all the chlorine involved in the reaction, and in spite of the cost of magnesium. It has recently been discovered that the reaction can be controlled if the metal is used in large pieces [2]. The largest Grignard plant, which is used for the large-scale production of organosilicon compounds [3], is in the U.S.A. In spite of its general applicability, the use of the Grignard reaction in industry is restricted to the production of special products, since too many by-products and auxiliary products are involved [4].

An industrial process was developed some years ago for the production of organoaluminum compounds by the reaction of aluminum and hydrogen with olefins [5]; since then, the use of these compounds as alkylating agents has increased [6]. However, it is not possible to make use of all three alkyl groups, except in the alkylation of metal fluorides, or unless alkali metal chlorides are added to bind the aluminum chloride formed [6, 7].

The partially methylated compounds $CH_3AlCl_2$ and $(CH_3)_2AlCl$ [8] can be used as methylating agents, but

[*] 13th Communication on Chemical Reactions in Fused Salts. For a review of earlier communications, see *W. Sundermeyer*, Angew. Chem. *77*, 241 (1965); Angew. Chem. internat. Edit. *4*, 222 (1965).

[1] *W. Verbeek*, Diploma Thesis, Universität Göttingen, 1965.

[2] Belg. Pat. 589471 (April 7th, 1960), F. Hoffmann-La Roche.

[3] *J. F. Hyde*, US.-Pat. 2413049 (Dec. 24th, 1946).

[4] See *W. Noll*: Chemie und Technologie der Silicone. Verlag Chemie, Weinheim 1960, p. 33–37.

[5] *K. Ziegler, H. G. Gellert, H. Lehmkuhl, W. Pohl*, and *K. Zosel*, Liebigs Ann. Chem. *629*, 1 (1960).

[6] *H. Jenkner*, Chemiker-Ztg. *86*, 527, 563 (1962).

[7] *W. P. Neumann*, Angew. Chem. *75*, 225 (1963); Angew. Chem. internat. Edit. *2*, 165 (1963).

[8] US.-Pat. 2848472 (Aug. 12th, 1955), Esso Research and Engeneering Co.

they do not react with some metal halides [6], while in other cases they give very low conversions. The main reason for this is the fact that no reaction medium has yet been found that affords good contact between the reactants at the required temperature and also dissolves the resulting aluminum chloride away from the surface. Furthermore, the alkylaluminum halides are difficult to handle in the free form. Whereas the methylation of trimethylchlorosilane and dimethyldichlorosilane takes place even at low temperatures, the methylation of methyltrichlorosilane and of silicon tetrachloride proceeds only at about 250 °C and about 30 atm. Moreover, the conversion into the technically important dimethyldichlorosilane takes a very long time [9–11], and it is almost impossible to obtain yields greater than 50 %, since the solid methylaluminum chloride does not react completely and appears to be regenerated from aluminum chloride and methylchlorosilanes [12].

Silicates such as bentonite or talc react with methylaluminum chloride to form methylchlorosilanes, but the principal product, with a yield of 74 %, is tetramethylsilane [13]. It is doubtful whether this process, which is carried out discontinuously in the solid phase and in a pressure vessel (300 °C, 250 atm, 6 h), will ever attain industrial importance. However, it shows the extreme conditions required for the preparation of tetramethylsilane, which is essential for the comproportionation reaction. A similar process permits the synthesis of trimethylboron from boron trioxide [14].

## II. Methylation in the Presence of Metals that Bind Halogens

The Wurtz synthesis is particularly useful for the preparation of organometallic compounds from starting materials that are not reduced by the alkali metal before they have entered into the desired combination with the alkyl halide. Thus silicon tetrachloride reacts with methyl chloride in the presence of lithium to form methylchlorosilanes [15], and tin tetrachloride reacts with methyl chloride in the presence of a sodium suspension to form tetramethyltin [16]. However, the use of the Wurtz synthesis is often impossible owing to reduction of the metal halide by the alkali metal, reaction of two alkyl halides with each other, and above all the relatively high cost of the halogen-binding metals (acceptor metals). The reaction of the acceptor metals is generally incomplete, since the halides formed are insoluble in the solvent used, and consequently block the surface of the metal. All the acceptor metal and the halogen with which it has combined are useless at the end of the reaction.

Other acceptor metals have also been used. Thus methyltrichlorosilane has been further methylated to a small extent with methyl chloride at 450 °C in the presence of aluminum or zinc turnings; this reaction was accompanied by thermal decomposition to form more highly methylated chlorosilanes [17] and by dismutation ("automethylation") to form dimethyldichlorosilane and $SiCl_4$. Silicon tetrachloride does not react under these extreme conditions.

Somewhat better results are obtained in reactions in which the metal itself is made to react with methyl chloride in the presence of an acceptor metal. The best-known and economically the most important synthesis of this type is the preparation of tetraalkyl-lead compounds (anti-knock agents) from alkyl chloride and a lead-sodium amalgam [18]. Tin-sodium [19] and tin-magnesium [20] alloys have been converted in a similar manner into tetraalkyltin. The methylated metal can also act as the acceptor metal, and in this case the desired methylmetal halides are obtained directly; unfortunately, however, this possibility is restricted to a few examples [21], the best-known of which is the Rochow synthesis for methylchlorosilanes and phenylchlorosilanes. Even here, however, the dimethylchlorosilane is always accompanied by undesirably large quantities of the other methylchlorosilanes. Methyltrichlorosilane in particular is often a very undesirable by-product. It is difficult to alter the course of the reaction in such a way as to favor the formation of one methylchlorosilane without simultaneously changing the proportions of the other products, particularly the more highly chlorinated $CH_3SiCl_3$ and $SiCl_4$. The commercial grades of silicon react with methyl chloride only at high temperatures, and the reaction proceeds very slowly. Thus, the silicon must have a very high purity, as must the copper or silver catalyst. All these factors [21] combine to make the synthesis expensive and present an obstacle to the wider use of silicones.

The above discussion explains the efforts that have been made to improve the Rochow synthesis, or to find a new route to the methylchlorosilanes [21]. These efforts are being directed particularly towards the preparation of more highly methylated products, since these can be used for the production of dimethyldichlorosilane by reaction with silicon tetrachloride (which can be obtained from inexpensive ferrosilicon or silicon scrap), or for the preparation of organosilicon compounds with organofunctional groups.

## III. Principle of a New Process

The reaction of methyl chloride with halides of boron, aluminum, silicon, tin, phosphorus, antimony, or mercury is particularly satisfactory if the acceptor metal is finely suspended in a melt of a non-oxidizing salt. We shall illustrate this process for the preparation of tetramethylsilane.


[9] *W. Noll* and *H. Jonas*, German Pat. 888852 (June 10th, 1950).

[10] *W. Noll* and *H. Jonas*, German Pat. 908019 (June 10th, 1950).

[11] *B. Lengyel* and *T. Székely*, Z. anorg. allg. Chem. *287*, 273 (1956).

[12] *A. Ya. Yakubovich* and *G. V. Motsarev*, Zh. obshch. Khim. *23*, 771 (1953).

[13] *R. C. Anderson* and *G. J. Sleddon*, Chem. and Ind. *1960*, 1335.

[14] *J. Ioda* and *J. Shiihara*, Bull. chem. Soc. Japan *32*, 304 (1959).

[15] *J. B. Rust* and *C. A. McKenzie*, US.-Pat. 2413582 (Dec. 31st, 1946).

[16] *I. Hechenbleikner* and *K. R. Molt*, Belg. Pat. 600465 (Febr. 22nd, 1961).

[17] *D. T. Hurd*, J. Amer. chem. Soc. *67*, 1545 (1945).

[18] *S. E. Cook* and *T. O. Sistrunk*, US.-Pat. 3049558 (April 29th, 1959).

[19] *S. M. Blitzer* and *J. R. Zietz*, US.-Pat. 2852543 (Sept. 16th, 1956).

[20] *G. J. M. van der Kerk* and *J. G. A. Luijten*, J. appl. Chem. *4*, 301 (1954).

[21] *J. J. Zuckerman*, Adv. inorg. Chem. Radiochem. *6*, 383 (1964).

If silicon tetrachloride and methyl chloride are led into a suspension of aluminum in a sodium chloride/aluminum chloride melt, tetramethylsilane and aluminum chloride are formed in quantitative yield.

$$3\ SiCl_4 + 12\ CH_3Cl + 8\ Al \xrightarrow[180\ °C]{} 3\ (CH_3)_4Si + 8\ AlCl_3 \quad (1)$$

The difference between this reaction and the usual Wurtz synthesis is that the acceptor metal is not an alkali metal, and that the metal halide formed is soluble in the solvent, *i.e.* in the molten salt. Thus a free metal surface is always available until the metal has been completely consumed. Moreover, if the system is chosen correctly, more solvent (in this case $AlCl_3$) is formed in the course of the reaction; ordinary solvents, on the other hand, often become a paste-like mass towards the end of the reaction, owing to the insolubility of the metal halide.

Another important advantage is that the acceptor metal halide can be reconverted into the acceptor metal (Al) and the halogen ($Cl_2$) by electrolysis of the melt.

$$8\ AlCl_3 \rightarrow 8\ Al + 12\ Cl_2 \quad (2)$$

The overall equation is therefore:

$$3\ SiCl_4 + 12\ CH_3Cl \xrightarrow[180-220\ °C]{NaCl/AlCl_3/Al} 3\ (CH_3)_4Si + 12\ Cl_2 \quad (3)$$

The recovered chlorine can be used either for the preparation of fresh silicon tetrachloride or for the oxychlorination of methane.

$$Si + 2\ Cl_2 \rightarrow SiCl_4 \quad (5)$$

$$4\ CH_4 + O_2 + 2\ Cl_2 \rightarrow 4\ CH_3Cl + 2\ H_2O \quad (6)$$

The process is not confined to the preparation of tetramethylsilane but can also be used for the synthesis of other (mostly permethylated) methylmetal compounds. The yields are usually quantitative.

$$CH_3SiCl_3 + 3\ CH_3Cl \rightarrow (CH_3)_4Si + 3\ Cl_2 \quad (7)$$

$$SnCl_4 + 4\ CH_3Cl \rightarrow (CH_3)_4Sn + 4\ Cl_2 \quad (8)$$

$$BCl_3 + 3\ CH_3Cl \rightarrow (CH_3)_3B + 3\ Cl_2 \quad (9)$$

$$SbCl_3 + 3\ CH_3Cl \rightarrow (CH_3)_3Sb + 3\ Cl_2 \quad (10)$$

$$HgCl_2 + 2\ CH_3Cl \rightarrow (CH_3)_2Hg + 2\ Cl_2 \quad (11)$$

$$AlCl_3 + 2\ Al + 3\ CH_3Cl \rightarrow 3\ CH_3AlCl_2 \quad (12)$$

$$3\ PCl_3 + 6\ CH_3Cl + 4\ Al \rightarrow 3\ (CH_3)_2PCl \cdot AlCl_3 + AlCl_3 \quad (13)$$

## IV. Choice of the System Melt/Acceptor Metal

Although there are a large number of possible combinations, most of those given in Table 1 contain salts with low melting points; moreover, the acceptor metal in each case can be recovered from its halide, so that continuous operation is possible.

Melts containing two or three components are used at the eutectic composition, in order that advantage may be taken of the low melting point, since many methylmetal compounds are unstable at high temperatures. The melting points of simple or mixed fluorides are generally too high [22], and for this reason chloride melts are generally used. Since the halogen is completely recovered, it is even feasible in some cases to use the more expensive bromides or iodides. The halogen in the reactants should be the same as that in the melt, and the melt should consist partly of the halide formed from the acceptor metal. Under these conditions, the composition, and hence the melting point, of the melt remains practically constant throughout the reaction.

Table 1. Melt/Acceptor metal systems.

| Melt | Acceptor metal | State of the acceptor metal in the melt | Temp. [°C] |
|---|---|---|---|
| $NaCl/AlCl_3$ (or LiCl) | Al | solid | >90 |
| | Al/Hg | liquid | 120 |
| | Zn | solid | 150 |
| | Mg | solid | 150 |
| | Mg | solid | 150 |
| $NaBr/AlBr_3$ | Al | solid | 200 |
| $HgCl_2/KCl$ | Hg | liquid | 182 |
| $ZnCl_2/KCl$ (or NaCl) | Zn | solid | 230 |
| | Zn/Hg | liquid | 230 |
| | Zn/Mg | solid | 230 |
| $SnCl_2/KCl$ | Sn | liquid | 231 |
| | Sn/Hg | liquid | 231 |
| | Sn/Zn | liquid | 231 |
| LiCl/KCl | Li | liquid | 352 |
| | Li/Sn | liquid | 352 |
| | Li/Pb | liquid | 352 |
| $MgCl_2/KCl/CaCl_2$ | Mg | solid | 425 |
| $CaCl_2/NaCl$ | Na | liquid | 508 |

Alkali metals form true solutions in their molten halides, but only at very high temperatures [23]. This is also true of alkaline earth metals. Most other metals remain suspended in the melt, particularly since the solubility of metals in melts decreases when several salt components are used. The dehalogenation can also be brought about by any "subhalides" that may be formed, but the metals that are most suitable for use as halogen acceptors are capable of forming stable methylmetal halide intermediates, which are soluble in the melt, and which act as transfer agents for the methyl group, *e.g.* aluminum or magnesium.

Even when alkali metal chlorides are added, the reaction cannot be carried out above the melting point of most acceptor metals, owing to the high vapor pressure of the melt, and the instability of the products. The metals, with the exceptions of mercury, tin, lead, bismuth, and certain alloys, can therefore be separated electrolytically only in the form of powders or flakes. Aluminum and zinc separate from the water-clear melts as fine silvery crystals; since these crystals are not covered with an oxide layer, they react with the methyl chloride about three times as rapidly as commercially available aluminum powder. If the aluminum is deposited electrolytically from an equimolar melt of sodium and aluminum chlorides, it contains enough sodium chloride for the complexing of the methylaluminum dichloride during the subsequent reaction with methyl chloride (cf. Section VIII).

[22] *Landolt-Börnstein*: Zahlenwerte und Funktionen aus Physik, Chemie, Astronomie, Geophysik und Technik. Springer, Berlin-Göttingen-Heidelberg 1956, Vol. II/3.

[23] *J. D. Corbett* in *B. R. Sundheim*: Fused Salts. McGraw-Hill, New York 1964, p. 341.

## V. Starting Materials and the Course of the Reaction

Under the conditions used, higher alkyl halides generally form hydrogen halide and olefins. Chlorobenzene and bromobenzene, on the other hand, react to form the phenylmetal compounds [24].

Table 2. Metal halides that can be methylated in salt melts.

| | |
|---|---|
| $BX_3$, $KBF_4$ | (X = F, Cl, Br, I) |
| $AlX_3$ | |
| $SiX_4$, $Na_2SiF_6$ | |
| $SnX_2$, $SnX_4$, $K_2SnX_6$ | |
| $PX_3$, $SbX_3$ | |
| $HgX_2$ | (Y = B, Al) |
| $(R)_nY\,X_{3-n}$ | (Z = Si, Sn) |
| $(R)_nZ\,X_{4-n}$ | (R = Alkyl, Aryl) |

The metal halides used in this reaction are listed in Table 2. It is also possible to use halides of these metals containing organic groups, particularly methyltrichlorosilane, which is obtained by the Rochow synthesis. Owing to the asymmetry of the molecule, this substance is much more easily methylated (95 % conversion, quantitative yield) than silicon tetrachloride (80 % conversion) [11].

Many of the metal halides listed in Table 2, *e.g.* tin tetrachloride and mercury(II) chloride, are directly reduced by the acceptor metal to the metals or to alloys. It is necessary in such cases to use acceptor metals that form a stable methylmetal halide with the methyl chloride introduced initially, *e.g.* aluminum in an $NaCl/AlCl_3$ melt. In the presence of excess sodium chloride, the methylaluminum dichloride formed dissolves as the complex $Na[CH_3AlCl_3]$ and cannot be distilled out of the melt. It is only then that the metal halide is added. This reaction can also be carried out continuously (Section VI). Much higher conversions are obtained with an excess of intermediate in the melt.

Other metal halides (*e.g.* silicon halides) can be introduced together with the methyl chloride into the suspension of the acceptor metal, and electrolysis can be carried out simultaneously with the reaction, so that the reaction proceeds at once in accordance with Equation(3).

Phosphorus trichloride reacts with many metals to form phosphides. In this case, however, even if $Na[CH_3AlCl_3]$ is formed first, the reaction does not yield trimethylphosphine, since the initially formed dimethylchlorophosphine reacts with aluminum chloride to form the complex $(CH_3)_2PCl\cdot AlCl_3$, which is not methylated further. Since this complex is more stable than the $NaAlCl_4$ in the melt, it cannot be destroyed by the addition of sodium chloride. In the system $KCl/AlCl_3$, in fact, it was not possible to isolate even doubly methylated phosphines [25].

## VI. Apparatus

A semicontinuous form of the process (Fig. 1) has been found to be particularly effective on the laboratory scale. The reaction vessel is $^2/_3$ to $^3/_4$ filled with *e.g.* an $NaCl/AlCl_3$ melt. At a potential of about 10 volts (current about 50 amp), aluminum flakes separate out either loosely or in the form of a sponge, while chlorine is liberated. The cathode (a) consists *e.g.* of a disk of sheet steel, and the anode (b) [several rods arranged in a circle, or a cylindrical sheet] is made of tungsten. Since the level of the liquid falls during the electrolysis, the anode must be adjustable in the vertical direction, in order that the current density may be kept constant. The acceptor metal separates out at a current density of more than 3 amp/dm², generally in the form of fine crystals (cf. also [26]). The tendency of the crystallites to grow towards the anode is overcome by slow rotation (about 10 r.p.m.) of the gas-inlet stirrer (c). When enough acceptor metal has been precipitated, the gas volume is flushed with an inert gas to remove the chlorine. Methyl chloride and vaporized metal halide are then introduced, either simultaneously or one after the other, through the tube (d) until all the acceptor metal has been consumed. Before the exhaust gases leave the reaction vessel, they are returned to the melt several times through the gas-inlet stirrer (c), to ensure that conversion is complete. This stirrer sucks in the vapors or gases above the liquid surface through holes in the hollow shaft; the gases are then returned to the melt through the side-arms of the stirrer by centrifugal force (about 2800 r.p.m.). The volume of the melt is the same at the end of the reaction as at the beginning. The electrolysis is then repeated (current yield more than 90 %) in preparation for the next reaction.

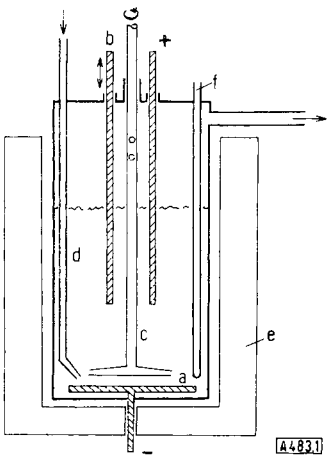


Fig. 1. Semicontinuous process (with formation of an intermediate).
a: Cathode
b: Anode
c: Gas-inlet stirrer
d: Inlet tube
e: Oven
f: Thermocouple

In the continuous process, the electrolysis is carried out during the reaction of the methyl chloride with the metal halide. In this case, the cathode and anode zones, which were arranged one above the other in the semicontinuous method, must be separated to prevent contact of the halogen liberated at the anode with the reactants. If neither the methyl chloride nor the metal halide alone reacts with the acceptor metal, the electrolytic cell may be fitted with a diaphragm, a metal gas-inlet stirrer being used as the cathode.

[24] A report on these experiments, which have not yet been completed, will appear later.

[25] We are grateful to Dr. *R. Schliebs* for providing literature references.

[26] *R. Dötzer*, Chemie-Ing.-Techn. *36*, 616 (1964).

In another form of the continuous (and of the discontinuous) process, the melt in the cathode compartment is layered upon a liquid metal, *e.g.* mercury, tin, or lead; this metal acts as the cathode, and the precipitated acceptor metal dissolves in it to form an alloy. The arms of the gas-inlet stirrer are placed in the liquid metal, and act as an electric lead. It has been found, however, that with liquid metals, most of which are very dense, it is difficult to introduce the gases or to suspend the metal in the melt.

The system $NaCl/AlCl_3/Al$ has been found to be particularly suitable (low reaction temperature, ready reaction of methyl chloride with Al, intermediate formation of $Na[CH_3AlCl_3]$, which can be used in excess). It was therefore desirable to develop a continuous process using this system. Fig. 2. shows a reaction vessel in

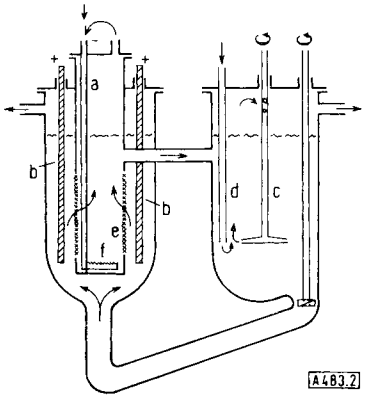


Fig. 2. Continuous process (with formation of an intermediate)

a: Cathode
b: Anode
c: Gas-inlet stirrer
d: Inlet tube
e: Diaphragm
f: Sintered metal

which contact between the $Na[CH_3AlCl_3]$ and the anode is prevented by the use of a diaphragm (e), and in which this intermediate is produced and consumed in two different compartments.

During the electrolysis of the $NaCl/AlCl_3$ melt, methyl chloride is introduced through a sintered metal diaphragm (f), which also acts as the cathode, and which is connected *via* an insulated inlet tube to the source of direct current. The unreacted methyl chloride is recycled, so that the final product no longer contains methyl chloride, and the separation process is therefore eliminated or simplified. The $Na[CH_3AlCl_3]$ formed in the cathode compartment is led into the reaction vessel on the right, where it reacts with the metal halide, which is blown in as a vapor or added as a powder.

The materials balance of the reaction steps is given by the following equations:

$$2\ NaAlCl_4 \rightarrow 2\ NaCl + 2\ Al + 3\ Cl_2$$

$$3\ CH_3Cl + 2\ Al + 2\ NaCl + NaAlCl_4 \rightarrow 3\ Na(CH_3)AlCl_3$$

$$3\ Na(CH_3)AlCl_3 + BCl_3 \rightarrow 3\ NaAlCl_4 + (CH_3)_3B$$

The melt is pumped back into the anode compartment, whence it passes through the diaphragm (e) and back into the cathode compartment. This circulation of the melt ensures that no $Na[CH_3AlCl_3]$ passes through the diaphragm from the cathode to the anode compartment, where it could undergo electrochemical decomposition.

## VII. Results

a) 3000 g of $NaAlCl_4$ electrolysed at 220 °C and 368.2 ampere-hours; 123.5 g of Al and 447 g of chlorine liberated (current yield: 92 %, based on chlorine); 350 g of $CH_3Cl$ introduced over 4 hours.

b) 240 g of $SiCl_4$ introduced over 8 hours, 58 g of $SiCl_4$ recovered (75.6 % conversion); 94.5 g of $(CH_3)_4Si$ obtained (quantitative yield).

c) Preparation as in (a); 170 g of $CH_3SiCl_3$ introduced over 7 hours, 16 g of $CH_3SiCl_3$ recovered (90.5 % conversion); 91 g of $(CH_3)_4Si$ obtained (quantitative yield).

d) Preparation as in (a); 220 g of $SnCl_4$ introduced at 200 °C over 5 hours; complete conversion; 142.6 g of $(CH_3)_4Sn$ obtained (95 % yield).

e) Preparation as in (a); 138 g of $BCl_3$ introduced at 150 °C; quantitative conversion; 65 g of $(CH_3)_3B$ obtained (99 % yield).

f) Preparation as in (a); 210 g of $HgCl_2$ added over 3 hours; 170.5 g of $(CH_3)_2Hg$ obtained (95.5 % yield).

g) Preparation as in (a); 205 g of $SbCl_3$ added over 15 min at 200 °C; 57 g of $(CH_3)_3Sb$ obtained [yield: 48 %, thermal decomposition of the $(CH_3)_3Sb$].

h) Preparation as in (a); $KBF_4$ introduced; immediate reaction to form $BCl_3$, followed by further reaction in accordance with (e); yield: 74.3 %. Some of the $KBF_4$ did not reach the melt (adhesion to the walls) and could not be recovered, hence the poor yield.

i) Preparation as in (a); 130 g of $PCl_3$ introduced over 2 hours at 150 °C; formation of $(CH_3)_2PCl$, which remained in solution as the $AlCl_3$ complex.

k) 300 g of Al electrolytically deposited from 1500 g of $NaAlCl_4$ in 2600 g of mercury; 139 g of $CH_3Cl$ and 137 g of $CH_3SiCl_3$ introduced at 220 °C; conversion: 35 %, yield of $(CH_3)_4Si$: 75 %; formation of ethane.

l) 1500 g of tin under a melt of 924 g of KCl and 4550 g of $SnCl_2$; 210 g of $CH_3Cl$ introduced over 4 hours at 300 °C, 62 g of $CH_3Cl$ unreacted (conversion: 70 %); 106 g of $(CH_3)_3SnCl$ obtained (yield: 54.5 %; the rest remained in solution).

m) 3800 g of tin under 822 g of LiCl and 938 g of KCl; electrolysed at 400 °C until 90 g of lithium were dissolved in the tin (current yield: 91.2 %); 100 g of $CH_3Cl$ and 100 g of $CH_3SiCl_3$ introduced over 5 hours; 18 g of $CH_3Cl$, 6 g of $(CH_3)_4Si$, and 22 g of $(CH_3)_3SiCl$ obtained. Introduction of chlorobenzene and trimethylchlorosilane (1:1) led to a 25 % yield of phenyltrimethylsilane.

n) As in (m), but with a liquid lead cathode; $C_6H_5Cl$ and $(CH_3)_3SiCl$ introduced; yield of $C_6H_5Si(CH_3)_3$: 28 %.

## VIII. Summary

It is possible with the aid of molten salts to prepare methylmetal compounds easily, cheaply, and safely. The need to handle free alkylaluminum and other readily oxidizable organic compounds is eliminated, since these occur (if at all) only in solution. The reactants are generally introduced in the gaseous form, and the products are also removed as gases, so that no changes in the reaction vessel are required during the operation, and the reactions can be carried out continuously. The final products do not contain solvents. The metal halides, which are obtained from crude precursors, are made to react at relatively low temperatures; the use of a salt melt as the solvent permits the quantitative reaction of the acceptor metal and the recovery of all the halogen.

The reaction generally leads to the permethylated metal compound, which can be converted into industrially important methylmetal chlorides. The latter, *e.g.* methyl chlorosilanes, can probably also be obtained directly, if the reaction is allowed to proceed for a long time under pressure and in the presence of an excess of the metal halide, but this process is only semi-continuous [27].

The process is restricted to the preparation of the methyl compounds, since higher alkyl halides are dehalogenated to form olefins, or else react with alkylaluminum dichloride to form higher hydrocarbons [28]. In the reaction of methyl chloride, on the other hand, small quantities of ethane have been found in only a few cases. Another restriction is due to the fact that although metal fluorides are methylated by the $[CH_3AlCl_3]^{\ominus}$ ion, the melt cannot be regenerated by electrolysis in this case.

Many metal chlorides can be methylated with trimethylaluminum, but in many cases only one methyl group of the alkylaluminum is used, owing to the establishment of an equilibrium between the two methyl compounds. Thus zinc and cadmium chlorides react to give the corresponding dimethyl compounds, together with dimethylaluminum chloride [29]. The alkylating power becomes weaker as the number of methyl groups on the aluminum decreases, and none of the Group IIB chlorides can be methylated with methylaluminum dichloride [6]. It is equally surprising to find that while zinc and cadmium chlorides cannot be converted into the methyl compounds by this reagent, mercury(II) chloride reacts with the $[CH_3AlCl_3]^{\ominus}$ ion to form dimethylmercury. This provides a simple method for the preparation of large quantities of this methylating agent. The other permethylated compounds described here have also recently been used for transmethylations. For example, dimethylmercury can be prepared from trimethylboron [30]. Tetramethylsilane can be used for the methylation of gallium chloride [31], and tetramethylstannane is suitable both for the preparation of methylgallium dichloride [31] and for the methylation of germanium halides [32].

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[27] *B. Lengyel, T. Székely, S. Jenei,* and *G. Garzo,* Z. anorg. allg. Chem. *323*, 65 (1963).

[28] *A. G. Pozamantir* and *M. L. Genusov,* Zh. obshch. Khim. *32*, 1175 (1962).

[29] Brit. Pat. 867986 (Jan. 12th, 1960), Continental Oil Comp.

[30] *J. B. Honneycutt* and *J. M. Riddle,* J. Amer. chem. Soc. *82*, 3051 (1960).

[31] *H. Schmidbaur* and *W. Findeiss,* Angew. Chem. *76*, 752 (1964); Angew. Chem. internat. Edit. *3*, 696 (1964).

[32] *V. F. Mironov* and *A. L. Kravchenko,* Izv. Akad. Nauk S.S.S.R. *158*, 656 (1964).

# Applications and Limitations of Magnetic Methods in Free-Radical Chemistry

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*Dedicated to Wilhelm Klemm in memory of the work done together*

*The paper describes the application and limitations of magnetic methods to the problems of free-radical chemistry (detection and quantitative investigation of the free-radical state, relationships between structure and free-radical formation, "distribution" of the unpaired electron, detection of mesomeric C, O, N, P, As, and Sn radicals, g-factors, triplet states, and hyperfine structure). The problem of the diradical is described, and the paper closes with a discussion of the "Selwood effect".*

## A. Introduction

In 1934, *E. Müller, W. Klemm,* and *W. Schüth* [2] published the first paper describing attempts to settle the long disputed problem of the existence of diradicals on the basis of an investigation into the magnetic properties of diphenyldiazomethane. The negative result was contrary to the opinion prevalent at that time, and further studies were therefore necessary.

Since only one attempt [3] to determine the paramagnetism of a free radical had been published prior to this paper, it was necessary first to lay the foundations of the magnetochemistry of free radicals. This work was carried out between 1933 and 1936 in Danzig in collaboration with *I. Müller-Rodloff, W. Bunge, W. Wiesemann,* and *F. Teschner.* The Gouy balance was used for the determination of the paramagnetism.

[1] With the co-operation of Dr. *M. Bauer* and Dr. *B. Zeeh.*

[2] *Eu. Müller, W. Klemm,* and *W. Schüth,* Naturwissenschaften *22*, 335 (1934).

[3] *N. W. Taylor* and *G. N. Lewis,* Proc. nat. Acad. Sci. USA *11*, 456 (1925); further references: *Eu. Müller,* Naturwissenschaften *25*, 545 (1937).

## B. Applications and Limitations of the Gouy Method

### 1. Principles

The Gouy method [4] is based on the fact that a paramagnetic substance is drawn into a non-homogeneous magnetic field, whereas a diamagnetic substance is repelled. Thus if the samples in question are suspended from a sensitive balance in a non-homogeneous magnetic field, this effect produces an apparent increase in the weight of a paramagnetic substance or an apparent decrease in the weight of a diamagnetic substance. The molar susceptibility found from the apparent change in weight consists of three components: the diamagnetic susceptibility $\chi_{dia}$, which is independent of temperature, the paramagnetic susceptibility $\chi_{para}$, which is temperature-dependent, and an additional term $\chi_\rho$, which is usually small, and which is independent of temperature:

$$\chi_{mol} = \chi_{dia} + \chi_{para} + \chi_\rho.$$

For the determination of small paramagnetic susceptibilities, the diamagnetic susceptibility, which is then appreciably greater, must be known very accurately if the error of the method is to remain small. For this reason, measurements on free radicals are always accompanied by the determination of the diamagnetic susceptibility of the non-radical containing one hydrogen atom more; the diamagnetic susceptibility of the free radical is then found by subtraction of the Pascal increment for one H atom. We shall return to this during the discussion of the "Selwood effect".

The term $\chi_\rho$, which is usually small, is generally neglected. It has been attributed to internal magnetic polarization. *H. J. Dauben, Jr.* [5] recently expressed the view that $\chi_\rho$ is due to the magnetic anisotropy of the compound, and could be used for the determination of the aromaticity of aromatic and quasi-aromatic compounds. Future work must show whether this view is correct and can be applied reliably.

A self-recording version of the Gouy balance has been developed by *W. Rüdorff* and *D. Greifeneder* [6].

[4] For a more detailed description see: *Eu. Müller* in *Houben-Weyl*: Methoden der organischen Chemie. 4th. ed., Thieme, Stuttgart 1955, Vol. III/2.

[5] *H. J. Dauben, Jr.*, Science (Washington) *150*, 370 (1965).

### 2. Detection of Free Radicals with the Gouy Balance

#### a) Monoradicals

The first step in our magnetochemical studies was to decide whether the paramagnetism of free radicals is due to spin and orbital moments or simply to the spin moment of the unpaired electron. The latter is the case if the Curie law or the Curie-Weiss law

$$\chi_P\,(T-\Theta) = C$$

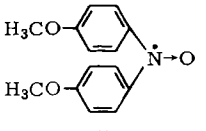
is valid for $\Theta \ll T$ and a monomeric free radical gives $\mu_{eff} = \sqrt{3} = 1.73$ Bohr magnetons. Radicals of this type are in the $^2\Sigma_{1/2}$ state.

It is important that the substance under examination be very pure. For this reason we first studied the nitrogen radicals *(1)–(3)* (Table 1) which can be relatively easily obtained in the pure form [7]. The $\mu_{eff}$ values obtained agree with those expected from theory. Difficulties were encountered in the preparation of Goldschmidt's hydrazyl *(3)*; similar difficulties have been reported by other workers [8].

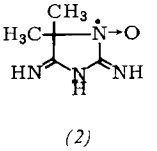
The carbon radicals studied were Ziegler's pentaphenylcyclopentadienyl *(4)* and Schlenk's tribiphenylmethyl

Table 1. Magnetic behavior of some nitrogen, carbon, and oxygen radicals.

| Radical | Θ | $\mu_{eff}$ | Temp. [°K] |
|---|---|---|---|
| *(1)* | − 3° | 1.71 | 291 |
| *(2)* | − 6° | 1.76 | 293 |
| *(3)* | −10° | 1.74 | 293 |
| *(4)* | −12° | 1.7 | 293 |
| *(5)* | −18° | 1.7 | 293 |
| + 1 $C_6H_6$ (solid) | −18° | 1.6 | 90 |
| in 2.82 % benzene soln. | −18° | 1.78 | 294 |
| in 2.82 % benzene soln. | −18° | 1.84 | 348 |
| *(6)* | + 8° | 1.61 | 200 |



*(1)*



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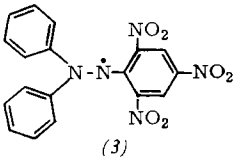
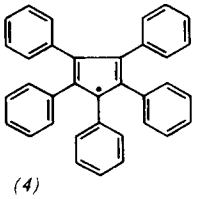
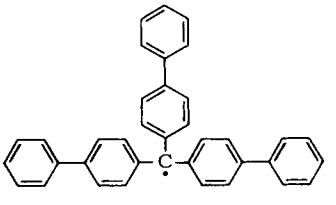
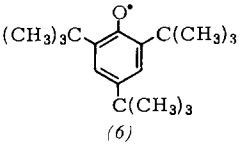


*(3)*


*(4)*


*(5)*



*(6)*

[6] *D. Greifeneder*, Diploma Thesis, Universität Tübingen, 1965. Cf. also *W. Duffy, Jr.*, J. chem. Physics *36*, 490 (1962); *T. R. McGuire* and *C. T. Lane*, Rev. Sci. *20*, 489 (1949).

[7] *Eu. Müller, I. Müller-Rodloff*, and *W. Bunge*, Liebigs Ann. Chem. *520*, 235 (1935); cf. *Eu. Müller* and *I. Müller-Rodloff*, *ibid. 521*, 81 (1935).

[8] a) *H. J. Friedrich*, Z. Naturforsch. *19b*, 663 (1964); b) *J. J. Lothe* and *G. Eia*, Acta chem. scand. *12*, 1535 (1958); c) *T. Laederich* and *P. Traynard*, C. R. hebd. Séances Acad. Sci. *254*, 1826 (1962).

*(5)* [9]. On theoretical grounds [10], *(4)* is expected to possess both spin and orbital moments. The measurements showed, however, that even in this case there is no appreciable orbital moment, but only a spin moment ($^2\Sigma_{1/2}$ state) (Table 1).

It is particularly difficult to obtain tribiphenylmethyl *(5)* in the pure state [11]. It is generally prepared as the benzene adduct, a value for which is given in Table 1. According to this value, *(5)* must be almost completely monomeric in the solid state and, according to other values, in dilute solution. Slight association appears to take place only at low temperatures.

The Gouy method has also proved suitable for the study of the aroxyls. Thus at the time of the discovery of the first stable aroxyl, 2,4,6-tri-t-butylphenoxyl *(6)*, this was the only method by which it could be identified as a completely monomeric free radical [12].

The existence of a $^2\Sigma_{1/2}$ state in organic free radicals gives rise to further applications of the Gouy method. Thus it has been found from magnetic measurements that the heat of dissociation of hexaphenylethane in benzene is $-11.6 \pm 1.7$ kcal/mole [13]. This is in excellent agreement with the value of $-11.3$ kcal/mole found by *K. Ziegler* [14] by another method. *W. Theilacker* and his co-workers used the Gouy method to study the steric effect of *ortho*-groups in triarylmethyls, and showed that hexa-(*o*-methylphenyl)ethane in a 0.1 M solution in benzene at 19 °C is 87 % free radical, while *o*-t-butylphenyldiphenylmethyl is practically 100 % free radical [15].

Dimethylpyronepotassium, 2-methylchromonepotassium, and 2,3:6,7-dibenzoxanthonepotassium, which are regarded as metal ketyls because of their bright, intense colors in the solid state, are diamagnetic in the solid state, *i.e.* they are not free radicals. In xanthonepotassium, there is one free spin for every four xanthone molecules. The structures of these and similar compounds (*e.g.* benzilpotassium) are not yet known. Other metal ketyls, particularly those that are soluble, such as benzophenonepotassium or tetraphenylcyclopentadienonepotassium, exist more or less as free radicals in a pinacol anion/ketyl equilibrium. The potassium derivative of Michler's ketone is the first known compound that exists completely in the form of the ketyl radical [16, 17].

[9] Cf. [7] and *Eu. Müller* and *I. Müller-Rodloff*, Ber. dtsch. chem. Ges. *69*, 665 (1936).

[10] *E. Hückel*, Trans. Faraday Soc. *30*, 16 (1934).

[11] *W. Theilacker et al.*, Angew. Chem. *69*, 322 (1957).

[12] *Eu. Müller* and *K. Ley*, Chem. Ber. *87*, 922 (1954).

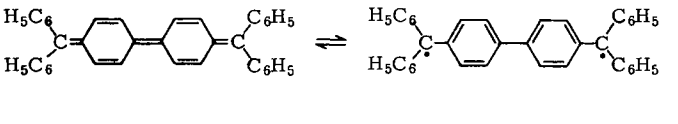
[13] *Eu. Müller* and *I. Müller-Rodloff*, Liebigs Ann. Chem. *521*, 89 (1935).

[14] Review: *K. Ziegler*, Angew. Chem. *61*, 168 (1949).

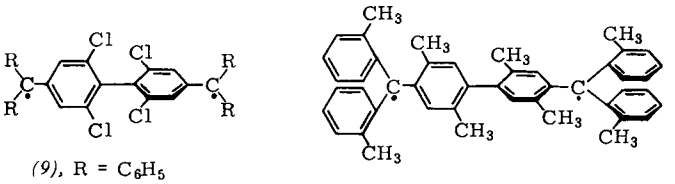
[15] *W. Theilacker* and *M.-L. Wessel-Ewald*, Liebigs Ann. Chem. *594*, 214 (1955).

### b) Detection of Diradicals by the Gouy Method

Measurements carried out with the Gouy balance have shown that the Chichibabin hydrocarbon *(7)* (which was formerly regarded as a typical carbon diradical) and many similar compounds are diamagnetic and should therefore be formulated as quinonoid structures (limits of error: 1–3 % of diradical, cf. also [11]).



*(7)* *(8)*



*(9)*, R = $C_6H_5$

*(10)*, R = $C_6H_4$-$C_6H_5$ *(11)*

In order to obtain carbon diradicals, it is necessary to prevent the formation of a quinonoid arrangement. Thus, since *meta*-quinones cannot exist, the Schlenk hydrocarbon *(8)* should behave as a "double" triphenylmethyl [18]. This substance is in fact paramagnetic [19]. Unfortunately, however, its association behavior has not yet been elucidated.

Formation of a quinonoid form is also impossible in the case of biphenyls of the type *(9)* and *(10)* [20, 21]. The free radical *(11)* is also unable to undergo association [22]; in accordance with the theory, therefore, $\mu_{eff} = 2.43\ \mu_B$ (theoretical value: $\sqrt{6} = 2.45\ \mu_B$) [11].

Finally, diradicals can also be obtained if the free-radical centers are separated by saturated and suitably substituted carbon atoms [23]. Even triradicals and tetraradicals with structures of this type are known [24], and it is quite conceivable that polyradicals exist in polymeric compounds.

[16] *Eu. Müller* and *W. Janke*, Z. Elektrochem. angew. physik. Chem. *45*, 380 (1939) and earlier publications.

[17] Recent ESR studies on ketyls: *N. Hirota* and *S. I. Weissman*, J. Amer. chem. Soc. *82*, 4424 (1960); *83*, 3533 (1961); *N. Hirota*, J. chem. Physics *37*, 1884 (1962); *V. M. Kasakova* and *Ya. K. Ssyrkin*, Dokl. Akad. Nauk S.S.S.R. *133*, 112 (1960); Chem. Zbl. *1964*, 34–0715; *P. H. Rieger* and *G. K. Fraenkel*, J. chem. Physics *37*, 2811 (1962); *R. Dehl* and *G. K. Fraenkel*, *ibid. 39*, 1793 (1963); *R. L. Ward*, *ibid. 36*, 2230 (1962); *G. R. Luckhurst* and *L. E. Orgel*, Mol. Phys. *7*, 297 (1964); *P. B. Ayscough* and *R. Wilson*, Proc. chem. Soc. (London) *1962*, 229.

[18] *E. Hückel*, Z. Physik. Chem. (B) *34*, 339 (1936).

[19] *Eu. Müller* and *I. Müller-Rodloff*, Liebigs Ann. Chem. *517*, 134 (1935).

[20] *Eu. Müller* and *H. Neuhoff*. Chem, Ber. *72*, 2063 (1939); together with *E. Tietz*, *ibid. 74*, 807 (1941).

[21] *W. Theilacker* and *W. Ozegowski*, Chem. Ber. *73*, 33 (1940).

[22] Regarding the theory of diradical polymerization, cf. *Eu. Müller*, Z. Elektrochem. angew. physik. Chem. *51*, 23 (1945).

[23] *Eu. Müller* and *H. Pfanz*, Chem. Ber. *74*, 1051, 1075 (1941).

[24] *G. Schmauß*, *H. Baumgärtel*, and *H. Zimmermann*, Angew. Chem. *77*, 619 (1965); Angew. Chem. internat. Edit. *4*, 596 (1965); *R. Kuhn*, *F. A. Neugebauer*, and *H. Trischmann*, Angew. Chem. *77*, 43 (1965); Angew. Chem. internat. Edit. *4*, 72 (1965); *M. B. Neiman*, *E. G. Rozantsev*, and *V. A. Golubev*, Izv. Akad. Nauk S.S.S.R., Otdel. khim. Nauk *1965*, 548; *E. G. Rozantsev et al.*, *ibid. 1965*, 718; *J. Heidberg* and *J. A. Weil*, J. Amer. chem. Soc. *86*, 5173 (1964).

### 3. Limitations of the Gouy Method

The disadvantages of the Gouy method are as follows:

1. The diamagnetic "ballast" is always included in the measurements.
2. Relatively large quantities of the substance are required (0.1–1 g).
3. The measurements generally take several hours.
4. Because of 3, only long-lived radicals (half-lives $\gg$ 1 h) can be studied.

One distinct advantage of the Gouy method, however, is that it can be used for the quantitative determination of the free radical content of a sample.

## C. Applications and Limitations of the ESR Method

### 1. Principles

Paramagnetic substances can now be studied in much greater detail by electron spin resonance (ESR) [25] than by means of the Gouy balance.

#### a) Electron Spin Resonance

The electron spin of a free radical may align either parallel to or anti-parallel to an external magnetic field. These two states differ in their energies, the difference being proportional to the field strength $H_o$:

$$\Delta E = g \cdot \mu_B \cdot H_o$$

($\mu_B$ = Bohr magneton; g = a constant, which is specific for the free radical in question, and which is approximately 2 for $^2\Sigma_{1/2}$ states, see below). Exposure of the free-radical sample to electromagnetic waves of the frequency $\nu$ for which the resonance condition

$$h\nu = g \cdot \mu_B \cdot H_o$$

is satisfied leads to transitions between the two energy levels, resulting in measurable absorptions of the radiation energy [26]. Nearly all ESR studies are carried out with 3 cm waves, which correspond to a field strength of $H_o \approx 3300$ gauss.

The relaxation times ($10^{-5}$ to $10^{-6}$ sec) typical of organic free radicals in solution are such that it is possible, in routine work, to detect a free-radical concentration of $10^{-6}$ mole/l in a volume of about 0.5 ml.

#### b) The g-Factor

The position of the spectrum in the magnetic field is determined by the magnitude of the factor g. Deviations of this factor for organic radicals from the value for a completely free electron (2.0023) are due to spin-orbital coupling of the unpaired electron. This coupling is so slight in the case of the light elements that the g-factors of the common organic radicals are within 0.2% of that of the free electron. Larger deviations indicate some localization of the unpaired electron on a heavy atom. Thus an accurate knowledge of the spin-orbital coupling would enable us to draw conclusions regarding the spin-density distribution.

In triplet ground states (two unpaired electron spins $\uparrow\uparrow$), transitions between the terms with $m_s = +1$ and $m_s = -1$ are no longer forbidden, owing to the interaction of the two unpaired electrons. Since the difference in the energies of these terms is given, to a first approximation, by

$$\Delta E = 2 \cdot g \cdot \mu_B \cdot H_o$$

this transition gives rise to an ESR signal at the field strength 0.5 $H_o$, with a formal g-factor of

$$g' = 2\,g \approx 4.$$

The intensities of these half-field transitions are closely related to the difference between the energies of the triplet and singlet states. Where there is complete degeneracy of the two states, these transitions are strictly forbidden. This provides a method of differentiating between the triplet state of a radical (with a higher singlet state) and a diradical (triplet-singlet degeneracy, cf. p. 14).

#### c) Hyperfine Structure

By far the most important phenomenon of an electron-resonance signal is its splitting into several components, *i.e.* the hyperfine structure (HFS) [26]. This is due to the magnetic interaction of the free electron with atomic nuclei ($^1H$, $^{14}N$, $^{13}C$, $^{17}O$, *etc.*) in the molecule. The magnitude of this interaction is proportional to the probability that the unpaired electron will be found on the nucleus in question, and is reflected in the distances between the components of the signal, *i.e.* in the coupling parameters a of the various nuclei. Thus, in many cases measurement of the coupling parameters can provide information about the probability that the unpaired electron will be found on the various nuclei and their neighbors (or more precisely, about the spin density of the unpaired electron on the nuclei). For example, in a free radical of the type $\dot{>}C-H$, the spin density $\rho_C$ of the p-electron on the carbon satisfies the equation

$$a_H = Q\rho_C$$

($a_H$ = coupling parameter of the proton; $Q \approx -23$ gauss). Spin densities on other nuclei can be calculated from the HFS with the aid of fundamentally similar equations.

### 2. Applications of the ESR Method

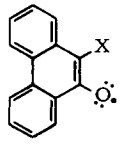
#### a) Detection of Free Radicals

ESR measurements have shown that several compounds, which had previously been regarded as free radicals, exhibit little or no paramagnetism. Thus the "stable

[25] *E. Zavoiskii*, J. Physics (Moscow) *9*, 245 (1945); Chem. Zbl. *40*, 1073 (1946).

[26] Detailed descriptions of the ESR method: a) *K. Scheffler*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 439 (1961); b) *A. Horsfield*, Chimia *17*, 42 (1963); c) *K. H. Hausser*, Chimia *14*, 153 (1960); d) *J. R. Morton*, Chem. Reviews *64*, 453 (1964); e) *M. C. R. Symons*, Adv. phys. org. Chemistry *1*, 284 (1963); f) *D. J. E. Ingram*: Free Radicals as Studied by Electron Spin Resonance, Butterworths, London 1958.

oxygen radicals" *(12)–(16)* [27] have been found by ESR measurements to be diamagnetic [the free-radical content of *(16)* is approximately 0.1% [28]; no paramagnetism in *(15)*]. When solutions of the dimer of *(16)*



*(12)*, X = $OCH_3$
*(13)*, X = $OC_6H_5$
*(14)*, X = Br
*(15)*, X = Cl
*(16)*, X = $OC_2H_5$

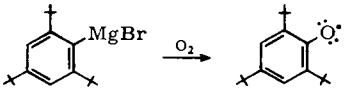
in benzene or toluene were kept in the dark, no dissociation could be detected with the magnetic balance at temperatures of up to 50 °C [29].

On the other hand, the free-radical nature of other compounds was first demonstrated by the ESR method. In addition to the sulfur radicals (which will be discussed later), these substances include the unstable carbon radicals such as methyl [30], 2-cyano-2-propyl [31], and other alkyl radicals [30], as well as cyclopentyl [30], cyclopentadienyl [32], cyclohexyl [30], cyclohexenyl [32], cyclohexadienyl [30], cycloheptyl [30], and tropyl [33].

A useful method for the ESR investigation of less stable radicals is the irradiation of suitable compounds in solution, in the solid state, at low temperatures, or in an olefin or alcohol matrix [30,32,34]. For ESR studies on free radicals in biological systems, the reader is referred to the literature [35].

The ESR method has recently been used for the detection of free-radical intermediates in chemical reactions. Thus studies have been carried out on the decomposition of aliphatic peroxides to form peroxy radicals [36] and the formation of aroxyls from quinonoid peroxides [37]. 4-Dimethylaminophenoxyl [38] was shown to occur during the photolysis of aryldiazonium salts, and free radicals have even been detected in Friedel-Crafts reactions [39] and in the addition of HBr to olefins catalysed by ultraviolet light [40].

Finally, ESR signals of free radicals have been observed when Grignard compounds were treated with oxygen or quinones [41]; for example, in the presence of air, 2,4,6-tri-t-butylphenylmagnesium bromide forms the aroxyl *(6)*.

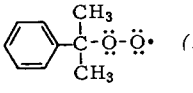


*(6)*

### b) Investigations Based on the g-Factor

#### α) *Monoradicals (g ≈ 2)*

Apart from the detection of free radicals by the observation of an ESR signal, the accurate determination of the g-factor is also important, particularly for solid samples, which do not exhibit hyperfine structure.



*(17)*

Thus the g-factor of *(17)* is 2.0187 [36,42]. The unpaired electron in *(17)* must therefore be largely localized on a heavier element (participation of orbital magnetism), *i.e.* on oxygen.

A similar situation is found in free radicals containing sulfur, selenium, or phosphorus [43,44]. Thus when diphenyl disulfide vapor or tetraphenyldiphosphine vapor is exposed to light, a paramagnetic solid is deposited on a cold finger cooled with liquid air; the only method by which these solids could be shown to exhibit the character of sulfur radicals or phosphorus radicals was by determination of their g-factors [44].

#### β) *Triplet States (g ≈ 4)*

Triplet states occur in bisaroxyls, such as bisgalvinoxyl *(18)* [45] and fluorenylidenebisphenoxyl *(19)* [46].

In the case of the radical *(20)*, on the other hand, the halffield resonance could not be observed [47]. The

[27] *St. Goldschmidt* and *W. Schmidt*, Ber. dtsch. chem. Ges. *55*, 3197 (1922); *St. Goldschmidt*, *A. Vogt*, and *M. A. Bredig*, Liebigs Ann. Chem. *445*, 123 (1925).

[28] *Eu. Müller*, *K. Schurr*, and *K. Scheffler*, Liebigs Ann. Chem. *627*, 132 (1959).

[29] *H. G. Cutforth* and *P. W. Selwood*, J. Amer. chem. Soc. *70*, 278 (1948). When these solutions were exposed to light, a paramagnetism corresponding to a free-radical content of 6% was found. Our own ESR measurements [28] failed to confirm this result.

[30] *R. W. Fessenden* and *R. H. Schuler*, J. chem. Physics *39*, 2147 (1963).

[31] *J. T. Pearson*, *P. Smith*, and *T. C. Smith*, Canad. J. Chem. *42*, 2022 (1964).

[32] *S. Ohnishi* and *I. Nitta*, J. chem. Physics *39*, 2848 (1963).

[33] *J. dos Santos-Veiga*, Mol. Phys. *5*, 639 (1962).

[34] Examples are given by *K. Maruyama*, *R. Tanikaga*, and *R. Goto*, Bull. chem. Soc. Japan *37*, 1893 (1964); *Yu. D. Tsretkov*, *J. R. Rowlands*, and *D. H. Whiffen*, J. chem. Soc. (London) *1964*, 810; *R. B. Ingalls* and *D. Kivelson*, J. chem. Physics *38*, 1907 (1963); *K. A. Maas* and *D. H. State*, Trans. Faraday Soc. *60*, 1202 (1964); *P. B. Ayscough* and *H. E. Evans*, *ibid. 60*, 801 (1964); *S. Ohnishi*, *T. Tanei*, and *I. Nitta*, J. chem. Physics *37*, 2402 (1962); *I. Miyagava* and *W. Gordy*, J. Amer. chem. Soc. *83*, 1036 (1961).

[35] *M. S. Blois, Jr.*, *H. W. Brown*, *R. M. Lemmon*, *R. O. Lindblom*, and *M. Weissbluth*: Free Radicals in Biological Systems. Academic Press, New York and London 1961; *G. Schoffa*: Elektronenspinresonanz in der Biologie. G. Braun, Karlsruhe 1964.

[36] *M. Bersohn* and *J. R. Thomas*, J. Amer. chem. Soc. *86*, 959 (1964).

[37] *C. D. Cook* and *M. Fraser*, J. org. Chemistry *29*, 3716 (1964).

[38] *P. J. Zandstra* and *E. M. Evleth*, J. Amer. chem. Soc. *86*, 2664 (1964).

[39] *R. E. Banks*, *L. F. Farnell*, *R. N. Haszeldine*, *P. N. Preston*, and *L. H. Sutcliffe*, Proc. chem. Soc. (London) *1964*, 396.

[40] *P. I. Abell* and *L. H. Piette*, J. Amer. chem. Soc. *84*, 916 (1962).

[41] *A. Rieker*, Lecture at the NMR and ESR Conference, Freiburg (Germany), on October 22nd, 1964; cf. Angew. Chem. *76*, 601 (1964); Angew. Chem. internat. Edit. *3*, 654 (1964).

[42] Cf. *K. U. Ingold* and *J. R. Morton*, J. Amer. chem. Soc. *86*, 3400 (1964).

[43] *K. Scheffler* and *H. B. Stegmann*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *67*, 864 (1963).

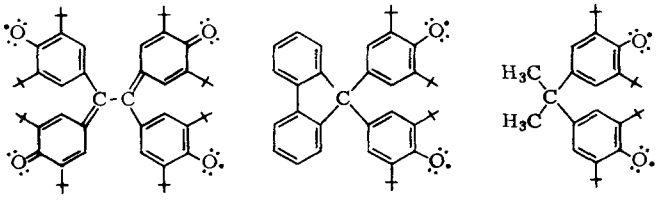
[44] *U. Schmidt*, Angew. Chem. *76*, 629 (1964); Angew. Chem. internat. Edit. *3*, 602 (1964); *U. Schmidt*, *F. Geiger*, *A. Müller*, and *K. Markau*, Angew. Chem. *75*, 640 (1963); Angew. Chem. internat. Edit. *2*, 400 (1963).

[45] *E. A. Chandross*, J. Amer. chem. Soc. *86*, 1263 (1964).

[46] *E. A. Chandross* and *R. Kreilick*, J. Amer. chem. Soc. *86*, 117 (1964).

[47] *E. A. Chandross* and *R. Kreilick*, J. Amer. chem. Soc. *85*, 2530 (1963); *A. Rieker*, *H. Kaufmann*, *R. Mayer*, and *Eu. Müller*, Z. Naturforsch. *19b*, 558 (1964).

(g = 4)-resonance has not so far been found even for carbon diradicals [48].

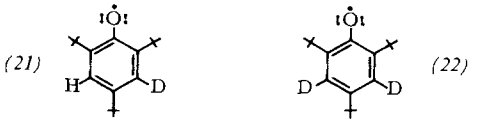


(18) (19) (20)

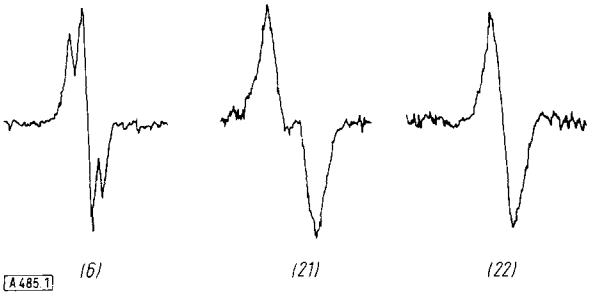
## c) Examples of Hyperfine Structure Studies

The following shows a number of applications of HFS studies for the case of the aroxyls [54].

The ESR spectrum of 2,4,6-tri-t-butylphenoxyl *(6)* and the spectra of radicals with similar structures consist of three lines having the relative intensities 1:2:1 (Fig. 1). Thus the unpaired electron is not localized on the oxygen atom; instead, the spectrum shows the existence of an interaction between the odd electron and the nuclear spin of the equivalent *meta*-protons of the aromatic ring.



(21) (22)



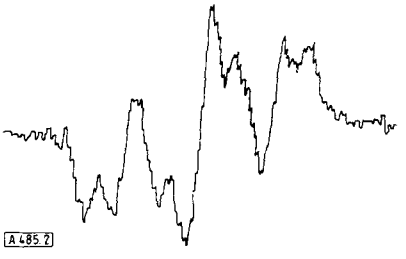
A 485.1 (6) (21) (22)

Fig. 1. ESR spectra of the free radicals *(6)*, *(21)*, and *(22)*.

In order to check this conclusion, the *meta*-protons were successively replaced by deuterium [*(21)*, *(22)*]. As expected [55], the triplet becomes a doublet (1:1) when the first proton is replaced, and a singlet when both protons are replaced (Fig. 1) [56,57]. To check for a free electron density on C-1 of the ring, [1-$^{13}$C]-2,4,6-tri-t-butylphenoxyl *(23)* [58] was synthesized with a $^{13}$C content of 53.1 %. The ESR spectrum of this aroxyl (Fig. 2) contains seven components. These are to be

(23) (24)

expected from the superposition of the triplet due to the unlabelled aroxyl (46.9 %) on the doublet of triplets due to the [1-$^{13}$C]-aroxyl (53.1 %) if there is any coupling of the unpaired electron with C-1 ($^{13}$C: I = $^1/_2$, $\mu_I$ = 0.70216 $\mu_K$).



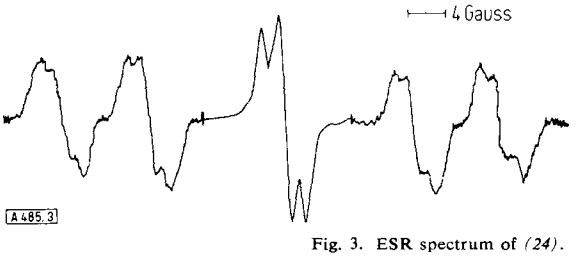
A 485.2

Fig. 2. ESR spectrum of *(23)*.

The coupling parameter $a_{^{13}C}$ = 9.6 gauss gives approximately 1.75 % for the 2s component of the unpaired electron on C-1 of the ring.

The ESR spectrum of [$^{17}$O]-2,4,6-tri-t-butylphenoxyl *(24)* containing 6 % of $^{17}$O (Fig. 3) [superposition of the triplet due to the unlabelled *(6)* on the sextet of triplets due to *(24)*] shows that the spin density for the oxygen atom in *(6)* and *(24)* is also finite ($a_{^{17}O}$ = 10.23 gauss, corresponding to a 2s component of 1.25 %) [59].

With better resolution, *(6)* exhibits an additional HFS due to the t-butyl groups (Fig. 4) [26a,60]. It is found that




A 485.3

Fig. 3. ESR spectrum of *(24)*.

[48] Carbenes [49], nitrenes [50], hydrocarbon ions carrying two negative charges [51], hydrocarbon cations [52], or excited triplet states [53], all of which are extreme cases, are not taken into account.

[49] *E. Wasserman* and *R. W. Murray*, J. Amer. chem. Soc. *86*, 4203 (1964) and earlier publications.

[50] *E. Wasserman, L. Barash*, and *W. A. Yager*, J. Amer. chem. Soc. *87*, 2075 (1965); *E. Wasserman, G. Smolinsky*, and *W. A. Yager, ibid. 86*, 3166 (1964).

[51] *R. E. Jesse, P. Biloen, R. Prins, J. D. W. van Voorst*, and *G. J. Hoijtink*, Mol. Phys. *6*, 633 (1963).

[52] *R. Breslow, R. Hill*, and *E. Wasserman*, J. Amer. chem. Soc. *86*, 5349 (1964).

[53] *C. A. Hutchison* and *B. W. Mangum*, J. chem. Physics *29*, 952 (1958); *34*, 908 (1961); *J. H. van der Waals* and *M. S. deGroot*, Mol. Phys. *2*, 333 (1959); *J. B. Farmer, C. L. Gardner*, and *C. A. McDowell*, J. chem. Physics *34*, 1058 (1961).

[54] Reviews: [26].

[55] Deuterium: I = 1, $\mu_I$ = 0.857 $\mu_K$. The deuterium splitting of about 0.28 gauss is no longer observed at the resolution achieved.

[56] *Eu. Müller, A. Rieker*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 92 (1961).

[57] *Eu. Müller, H. Eggensperger, A. Rieker, K. Scheffler, H.-D. Spanagel, H. B. Stegmann*, and *B. Teissier*, Tetrahedron *21*, 227 (1965).

[58] *A. Rieker, K. Scheffler*, and *Eu. Müller*, Liebigs Ann. Chem. *670*, 23 (1963).

[59] *A. Rieker* and *K. Scheffler*, Tetrahedron Letters *1965*, 1337; cf. *K. Dimroth, F. Bär*, and *A. Berndt*, Angew. Chem. *77*, 217 (1965); Angew. Chem. internat. Edit. *4*, 240 (1965).

[60] Cf. *N. M. Atherton, E. J. Land*, and *G. Porter*, Trans. Faraday Soc. *59*, 818 (1963); *K. H. Hausser, H. Brunner*, and *J. C. Jochims*, Mol. Physics, in the press. We are grateful to Prof. *Hausser* for permission to publish the spectrum shown in Fig. 4.

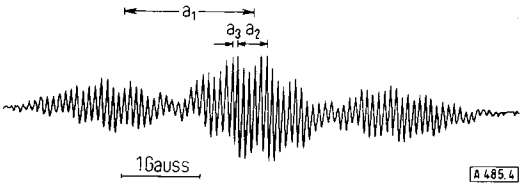



Fig. 4. ESR spectrum of *(6)* at higher resolution than in Fig. 1.

$a_2$ = 0.37 gauss for the *para*-t-butyl group, and $a_3$ = 0.074 for the *ortho*-t-butyl groups ($a_1 = a_{Hmeta}$). The unpaired electron must therefore have a finite spin density on all the ring carbon atoms and on the oxygen atom of *(6)* ("shared" electron) [61].

Similar observations have been made for many other aroxyls [57,62] (including the unsubstituted phenoxyl [63]) and for semiquinones [64].

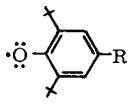
Studies by *G. A. Russel et al.* [65] on alicyclic semiquinones have shown that conclusions regarding the conformations of these compounds can be drawn from the ESR hyperfine structure. This method should be useful im the study of steroid ketones.

The interactions between the substituents and the aromatic ring in the aroxyls were studied in detail. Substituents modify the spin density distribution in the ring, and the unpaired electron can have a finite spin density on certain atoms of a substituent, characterized by the coupling parameters a of the HFS splitting. A few examples are given in Table 2.

$a_{Hmeta}$ increases by a factor of from 3 to 5 as we pass from substituents with a (+E) effect to electron-attracting substituents; however, there is no linear relationship with Hammett's σ-values. It can also be seen from Table 2 that there is a finite spin density even on atoms situated some distance away from the aroxyl ring and linked to the ring by multiple bonds, hetero-atoms, or even single bonds. Owing to the resulting HFS splitting, the ESR method provided the first means of detecting mesomeric selenium, phosphorus, arsenic, and tin radicals.

The spin density distribution can be determined in a similar manner for other radicals, such as nitrogen radicals [56] or hydrocarbon anion-radicals [73].

Table 2. Coupling parameters in aroxyls

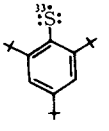


(in benzene at 20 °C).

| R | Coupling parameters [gauss] $a_{Hmeta}$ | Coupling parameters [gauss] Other a-values | Lit. |
|---|---|---|---|
| $N(CH_3)_2$ | <0.15 | $a_N$ = 5.04; $a_{CH_3}$ = 4.54 | [66] |
| NC | 0.88 | $a_N$ = 5.06 | [66] |
| $OPO(C_6H_5)_2$ | 1.55 | $a_P$ = 6.66 | [67] |
| $SeC(CH_3)_3$ | 1.57 | $a_{77Se}$ = 11.1 | [68] |
| $P(C_6H_5)_2$ | 1.60 | $a_P$ = 6.8 | [57] |
| $C_6H_5$ | 1.68 | $a_{o'}$ = 1.68; $a_{p'}$ = 1.68; $a_{m'}$ = 0.68 | [69] |
| $CH{=}N{-}OCH_3$ | 1.7 | $a_{H\alpha}$ = 2.55 [a]; $a_N$ = 4.25; $a_{CH_3}$ = 0.85 | [70] |
| $Sn(C_6H_5)_3$ | 1.82 | $a_{117Sn}$ = 58.13; $a_{119Sn}$ = 61.00 | [71] |
| $AsS(C_6H_5)_2$ | 2.0 | $a_{As}$ = 14.4 | [57] |
| $NO_2$ | 2.14 | $a_N$ = 2.14 | [66] |
| $CO_2CH_3$ | 2.15 | $a_{CH_3}$ = 0.65 | [26a] |
| C≡N | 2.2 | $a_N$ = 1.3 | [72] |
| $P^{\oplus}(C_6H_5)_2C_2H_5\ BF_4^{\ominus}$ | 2.35 | $a_P$ = 16.8 | [57] |

[a] The hydrogen of the methine group is taken as Hα.

The first evidence for the existence of sulfur radicals in solution was recently provided by the observation of a $^{33}S$-hyperfine structure in the ESR spectrum of the radical *(25)* in solution [74].



*(25)*

The hyperfine structure can also be used for the study of solvent effects on free radicals [75]. Owing to complexing of the free radical with the solvent, the overall electron distribution, and hence also the spin density distribution (the a values) will depend on the solvent.

The electron distribution, and hence the hyperfine structure of the ESR spectrum, can also vary with temperature, possibly as a result of a change in the ease of rotation of certain substituents (*e.g.* the $NH_2$ group [76] or the O=CH group [77].

[61] For quantitative data on spin density distribution in aroxyls, cf. [56].

[62] Reviews [26,57]; cf. also *P. L. Kolker* and *W. A. Waters*, Chem. and Ind. *1963*, 1205; *T. J. Stone* and *W. A. Waters*, J. chem. Soc. (London) *1964*, 213; *W. D. Pokhodenko, L. N. Ganyuk, Ye. A. Yakovleva, A. I. Shatenshtein*, and *A. I. Brodski*, Dokl. Akad. Nauk S.S.S.R. *148*, 1314 (1963); Chem. Zbl. *1965*, 9–0784; *M. B. Neiman* and *A. L. Buchachenko*, Izv. Akad. Nauk S.S.S.R., Otdel. khim. Nauk *1961*, 1742; *C. Steelink*, J. Amer. chem. Soc. *87*, 2056 (1965).

[63] *T. J. Stone* and *W. A. Waters*, Proc. chem. Soc. (London) *1962*, 253.

[64] *Eu. Müller, F. Günter, K. Scheffler, P. Ziemek*, and *A. Rieker*, Liebigs Ann. Chem. *688*, 134 (1965); *E. A. C. Lucken*, J. chem. Soc. (London) *1964*, 4234, 4240; *E. W. Stone* and *A. H. Maki*, J. chem. Physics *36*, 1944 (1962); *H. L. Strauss* and *G. K. Fraenkel, ibid. 35*, 1738 (1961); *T. J. Stone* and *W. A. Waters*, J. chem. Soc. (London) *1965*, 1488; *R. W. Brandon* and *E. A. C. Lucken, ibid. 1961*, 4273; *Y. Matsunaga*, Canad. J. Chem. *38*, 1172 (1960) and earlier publications; *A. Fairbourn* and *E. A. C. Lucken*, J. chem. Soc. (London) *1963*, 258; cf. [17].

[65] *G. A. Russel, R. D. Stephens*, and *E. R. Talaty*, Tetrahedron Letters *1965*, 1139 and earlier publications.

[66] *A. Rieker, K. Scheffler, R. Mayer, B. Narr*, and *Eu. Müller*, unpublished work.

[67] *A. Rieker*, unpublished work.

[68] *Eu. Müller, H. B. Stegmann*, and *K. Scheffler*, Liebigs Ann. Chem. *657*, 5 (1962).

[69] *A. Rieker* and *K. Scheffler*, Liebigs Ann. Chem. *689*, 78 (1965).

[70] *Eu. Müller, R. Mayer, B. Narr, A. Rieker*, and *K. Scheffler*, Liebigs Ann. Chem. *645*, 19 (1961).

[71] *H. B. Stegmann* and *K. Scheffler*, Tetrahedron Letters *1964*, 3387.

[72] *Eu. Müller, A. Rieker, K. Ley, R. Mayer*, and *K. Scheffler*, Chem. Ber. *92*, 2278 (1959).

[73] *F. Gerson*, Helv. chim. Acta *47*, 1941 (1964); *F. Gerson, B. Weidmann*, and *E. Heilbronner, ibid. 47*, 1951 (1964).

[74] *W. Rundel* and *K. Scheffler*, Angew. Chem. *77*, 220 (1965); Angew. Chem. internat. Edit. *4*, 243 (1965).

[75] *K. Scheffler* and *H. B. Stegmann*, Z. physik. Chem. *44*, 353 (1965); *P. Ludwig, T. Layloff*, and *R. N. Adams*, J. Amer. chem. Soc. *86*, 4568 (1964); *E. W. Stone* and *A. H. Maki, ibid. 86*, 454 (1964); *J. Gendell, J. H. Freed*, and *G. K. Fraenkel*, J. chem. Phyics *37*, 2832 (1952).

[76] *K. Scheffler* and *H. B. Stegmann*, Tetrahedron Letters *1964*, 3035.

[77] *E. W. Stone* and *A. H. Maki*, J. chem. Physics *38*, 1999 (1963).

### 3. Advantages and Disadvantages of the ESR Method

Since the ESR method can be used for low free-radical concentrations and small measuring volumes, the sensitivity of detection is very much greater than with static methods.

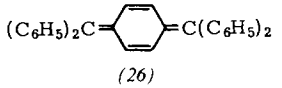
Another advantage of ESR spectroscopy as compared with the Gouy method is the fact that the former is not affected by the diamagnetism of the sample.

In the quantitative evaluation of the ESR signals by comparison with the spectra of standard substances, interference may arise as a result of differences in the relaxation time. Furthermore, the accuracy of such an evaluation depends on the state of the standard. This can be an important disadvantage in the determination of free-radical contents.

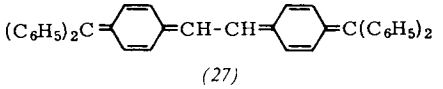
### D. The Ortho-Para Hydrogen Conversion

When high-temperature equilibrium hydrogen is adsorbed on charcoal at the temperature of liquid air, it is converted into a mixture containing from 40 to 50 % of para-hydrogen (nuclear spins: ortho ↑↑, para ↑↓). The o:p ratio is displaced back towards the equilibrium value (3 o-$H_2$: 1 p-$H_2$ at room temperature) by collision of the ortho/para $H_2$ molecules with free radicals. The content of para-hydrogen is determined by measurement of the thermal conductivity between 100 and 200 °K, since the specific heats of ortho- and para-hydrogens differ most at 170 °K. *G.-M. Schwab* [78] has shown that this method can be used for the determination of carbon monoradicals and diradicals.

However, the free radical contents found by this method for the Thiele hydrocarbon *(26)*, the Chichibabin hydrocarbon *(7)*, and the compound *(27)* (which was synthesized by *Wittig*) are higher than those found by the Gouy [79] or ESR methods (cf. p. 14).



*(26)*



*(27)*

Recent calculations by *H. Hartmann* [80] have shown that even in the singlet ground state, the compounds *(26)*, *(7)*, and *(27)* bring about a para-ortho hydrogen conversion. The calculated rates of the conversion agree in their sequence and in their order of magnitude with the values found experimentally by *Schwab*. Thus the ortho-para hydrogen conversion is not a suitable method for the study of substances of this type (diradicaloids [79]).

The method has the advantage, however, that it depends only on the presence of the nuclear spin moments (of $H_2$) and the electron spin in the free radical, and is therefore unaffected by the diamagnetic ballast. Moreover, it is not a difference method, and it is as sensitive as the Gouy method.

### E. Susceptibility Determinations by Measurement of the Nuclear Magnetic Resonance

The position of a nuclear resonance signal depends on the strength H of the magnetic field that acts on the nucleus. H is made up of the external magnetic field $H_o$, the magnetic field $H_{dia}$ induced by the external field, and the field $H_{para}$ of the paramagnetic particles present in the sample. Thus under the influence of $H_{dia}$ and $H_{para}$, the $H_o$ signal undergoes a characteristic shift

$$\Delta H/H = (2\pi/3)\cdot\Delta\chi_V$$

provided that cylindrical cells are used [81,82]. ($\Delta\chi_V$ is the change in the volume susceptibility of the sample; the total susceptibility $\chi = \chi_{dia} + \chi_{para}$).

Thus the shift $\Delta H/H$ can be used to find the magnetic susceptibility of a free radical by examination of the solution of a standard substance alone in one part of a (cylindrical) concentric double tube, and with the addition of the free radical in the other part. If the observed shift is $\Delta f$ [c/s], the gram susceptibility $\chi$ of the solution can be calculated [83] from:

$$\chi = 3\,\Delta f/2\pi f m + \chi_s + \chi_s\,(d_s - d_l)/m$$

(f = measuring frequency in c/s, m = quantity of substance in 1 ml of solution, $\chi_s$ = gram susceptibility of the solvent, $d^s$ = density of the solvent, $d_l$ = density of the solution). It is assumed that there is no interaction between the standard and the paramagnetic sample.

*H. J. Friedrich* [8a,83] confirmed the above two equations by careful measurements. For very pure [7,81] α,α-diphenyl-β-picrylhydrazyl *(3)* in nitromethane with 10 % by volume of acetonitrile, he found $\chi_{para} = +1273 \times 10^{-6}$ (20 °C), and hence $\mu_{eff} = 1.73\ \mu_B$; this is in excellent agreement with the values found earlier [7] by the Gouy method (cf. Table 1).

*Friedrich* showed [84] that a number of free-radical ammonium salts of the type $(R \cdots X \cdots X \cdots R)^{\oplus}\ Y^{\ominus}$ [85], in which *e.g.* R=*N*-ethylquinol-2-yl, X=N, and $Y=ClO_4$ [85], exist as monomers.

According to *K. H. Hausser* [60], the NMR method can also be used to investigate the structures of free radicals [as, for

[78] *G.-M. Schwab* and *E. Agallidis*, Z. physik. Chem. Abt. B *41*, 59 (1938); *G.-M. Schwab* and *N. Agliardi*, Ber. dtsch. chem. Ges. *73*, 95 (1940); *G.-M. Schwab* and *E. Schwab-Agallidis*, Naturwissenschaften *28*, 412 (1940); *G.-M. Schwab* and *J. Voitländer*, *ibid. 40*, 439 (1953).

[79] Cf. *Eu. Müller*, Fortschr. chem. Forsch. *1*, 325 (1949).

[80] *H. Hartmann*, *G. Gliemann*, and *H. Gebler*, Theoret. chim. Acta *1*, 144 (1963).

[81] *W. C. Dickinson*, Physic. Rev. *81*, 717 (1951).

[82] Cf. *D. F. Evans*, J. chem. Soc. (London) *1959*, 2003.

[83] *H. J. Friedrich*, Z. Naturforsch. *19b*, 280 (1964).

[84] *H. J. Friedrich*, Angew. Chem. *76*, 496 (1964); Angew. Chem. internat. Edit. *3*, 440 (1964).

[85] *S. Hünig et al.*, Liebigs Ann. Chem. *676*, 32, 36, 52 (1964).

example, *(6)*], as long as the ESR coupling parameters a and the viscosity of the solvent are small, whereas the radical concentration and the temperature must be high. From such NMR spectra coupling parameters a can be found which are below the limits of detectability of the ESR method.

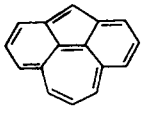
## F. Unsolved Problems

### 1. The Diradical Problem

In an atropic diradical such as *(7)*, the spins of the two unpaired electrons are practically independent of each other. The singlet ($^1\Sigma$) and triplet ($^3\Sigma$) states are degenerate, and the spin moments are present in the ratio of their statistical weights ($\uparrow\downarrow : \uparrow\uparrow = 1:3$). This gives a magnetic moment of $\sqrt{6}\ \mu_B$, which agrees with the value found by the Gouy method (see p. 8). According to p. 9, there should be no (g = 4)-resonance in the ESR spectra of these compounds. Carbon radicals of this type are known as diradicals [79].

These diradicals should be distinguished from compounds with a true triplet state ($\uparrow\uparrow$, $\mu_{eff} = \sqrt{8}\ \mu_B$ [79]) which is at a lower energy level than the singlet state. The latter can, in principle, be detected by susceptibility measurements and by the presence of the half-field resonance ($g \approx 4$). This situation is found in the oxygen molecule ($O_2$), as well as in *e.g.* the oxygen diradicals *(18)* and *(19)*.

An example of a hydrocarbon that should have a triplet ground state [86], or at least a triplet state that can be easily excited by heat, is cyclohepta[*def*]fluorene *(28)*; however, this compound has not yet been prepared [87].



*(28)*

Singlet-triplet transitions in nitrogen radicals have already been described [88]. (For nitrogen triradicals, see [24].)

Let us now consider the Chichibabin hydrocarbon *(7)* and its analogs. According to the Gouy method these substances are diamagnetic, and should be assigned quinonoid structures. However, the much more sensitive ESR method indicates the presence of free radicals in concentrations of up to 4% [90]. The triplet state ($g' \approx 4$) cannot be detected. The $^{13}C$ hyperfine structure indicates the presence of two independent half-molecules (radicals) [91]. Thus the paramagnetic components of these substances, which can be assigned a quinonoid structure, appear to be present as diradicals [92], and are therefore similar to *e.g.* the Schlenk hydrocarbon *(8)* [93].

Former differences between theoretical calculations and experimental results (which were referred to as paradoxes in the physical sense [94]) appear to have been eliminated by recent calculations [95].

However, compounds of the type *(7)* differ from atropic diradicals in their high reactivities, their intense colors, and the fact that (where the biphenyl system is planar) they can be formulated as quinones. If there were no physical difference between these substances and the atropic diradicals, how would we explain the difference in their chemical properties? Is this, therefore, another paradox?

### 2. The "Selwood Effect"

In the course of attempts to measure the heats of dissociation of hexa-*p*-biphenylethane and hexa-*p*-t-butylphenylethane, *Selwood* and *Dobres* [96] found only 70% dissociation into monoradicals, instead of the expected 100%. Moreover, the apparent degree of dissociation was independent of the temperature. Since the Gouy method and the hydrogen ortho-para conversion led to different conclusions for compounds like the Chichibabin hydrocarbon *(7)* (cf. however [80]), the authors tried to find an explanation for this difference. They assumed that it was due to a fundamental error in the determination of the diamagnetic correction. As has already been mentioned, this correction can be found, for example, by measurement of the diamagnetic susceptibility of the non-radical compound with one hydrogen atom more, and subtraction of the Pascal increment for the hydrogen atom from the result. If this correction where found to be wrong for one radical, doubt would be cast on the Gouy method as a whole. *Selwood* proposed the following explanation for this effect. According to quantum theory, the additional resonance that is possible in free radicals such as the triarylmethyls (distribution of the unpaired electron over all the carbon atoms of all the aromatic nuclei)

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[86] *P. Baumgartner, E. Weltin, G. Wagnière,* and *E. Heilbronner,* Helv. chim. Acta *48*, 751 (1965).

[87] For the excitation of the triplet state in rubrene, cf. *M. Wilk,* Z. Elektrochem. *64*, 936 (1960). This author gives the dark value $\chi_{mol} = -620$ ($\times 10^{-6}$) for rubrene. The correct value, however, is −340. Thus the difference from the value on irradiation (−280) is only +60, *i.e.* equivalent to a diradical content of 1 to 2%; this value is within the limits of error, cf. [19].

[88] *R. Kuhn, H. Katz,* and *W. Francke,* Naturwissenschaften *22*, 808 (1934), were the first to report the temperature-dependence of the magnetism of porphyrindin. Our measurements [89] showed the presence of a diamagnetic low-temperature form ($\uparrow\downarrow$) and a paramagnetic high-temperature form ($\uparrow\uparrow$) ($\Delta W \approx 0.5$ kcal/mole).

[89] *Eu. Müller* and *I. Müller-Rodloff,* Liebigs Ann. Chem. *521*, 81 (1935).

[90] *C. A. Hutchison, A. Kowalsky, R. C. Pastor,* and *G. W. Wheland,* J. chem. Physics *20*, 1485 (1952).

[91] *D. C. Reitz* and *S. I. Weissman,* J. chem. Physics *33*, 700 (1960).

[92] Singlet-triplet degeneracy as in the atropic diradicals.

[93] The dependence of the ESR intensity on the temperature could be explained by an energy difference of 2 to 3 kcal/mole between the singlet and triplet states, but it could also be due to dimerization or polymerization; cf. *R. K. Waring, Jr.,* and *G. J. Sloan,* J. chem. Physics *40*, 772 (1964).

[94] *H. M. McConnell,* J. chem. Physics *33*, 1868 (1960).

[95] *A. I. Burshtein* and *Yu. I. Naberukhin,* Proc. Acad. Sci. USSR Chem. Sect. (English translation) *140*, 754 (1961).

[96] *P. W. Selwood* and *R. M. Dobres,* J. Amer. chem. Soc. *72*, 3860 (1950); *P. W. Selwood*: Magnetochemistry. 2nd ed., Interscience, New York and London 1956, p. 262.

contributes to the stability of the radical. Owing to the increase in the ring current, this additional resonance gives rise to an additional diamagnetism perpendicular to the plane of the aromatic ring. In other words, the additional resonance stabilization of free triarylmethyl radicals is accompanied by a marked increase in the molecular anisotropy. The susceptibility values obtained by *Selwood* lead to reasonable results (100 % dissociation) if the diamagnetic correction is increased by 80 %. This means an increase of 240 % in the total molecular susceptibility perpendicular to the plane of the ring. No theoretical explanation has yet been found for this anisotropy effect. Attempts to prove the "Selwood effect" have so far shown the opposite [97].

We have already referred [79] to the experimental difficulties encountered in the preparation of radicals such as those studied by *Selwood* (cf. [111]). Moreover, the usual diamagnetic corrections were found to give radical contents of 100 % for other radicals (cf. p. 7/8). We are therefore of the opinion that, in spite of *Selwood*'s objections, the magnetochemical method as described by Gouy is still suitable for use in susceptibility measurements on free radicals [98].

*The Gouy method may be regarded as the precursor of many physical methods (such as infrared, ESR, and NMR spectroscopy) that have now become indispensable aids to the organic chemist. Eugen Müller is very grateful to Wilhelm Klemm for the opportunity to take part in the early development of this method.*

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German version: Angew. Chem. *78*, 98 (1966)
Translated by Express Translation Service, London

[97] *M. Meyot, G. Berthier,* and *B. Pullman,* J. Chim. phys. *50,* 176 (1953).

[98] We are presently checking *Selwood*'s views. With very pure *(1)* and *(3)* as the ESR standards, *(4)* is being studied both in the solid form and in solution at various concentrations and temperatures, both by the Gouy method and by the ESR method.

# The Separation of Zirconium and Hafnium by Liquid-Liquid Partition of their Thiocyanates [1]

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INSTITUT FÜR ANORGANISCHE CHEMIE DER TECHNISCHEN HOCHSCHULE HANNOVER (GERMANY)

*Dedicated to Professor W. Klemm on the occasion of his 70th birthday*

*The partition equilibria of zirconium and hafnium thiocyanates between water and methyl isobutyl ketone have been studied under various conditions. Since the system shows extremely marked deviations from Nernst's distribution law, the two elements cannot be prepared in a very pure state by a simple multi-stage partition. By the use of suitable additives and a new scheme of material flow, however, a continuous process using 23 mixer settlers has been developed, by means of which $ZrO_2$ containing less than 10 p.p.m. of $HfO_2$ and $HfO_2$ containing only 0.3 % of $ZrO_2$ can be obtained from a zirconium-hafnium mixture (hafnium content: 1 to 2 %).*

Methods based on distribution between two liquid phases are particularly valuable for the separation of substances with very similar properties. The advantages of these methods are the ease of multi-stage repetition of the individual steps, the possibility of continuous and automatic operation, the fact that the process can be carried out at room temperature, and the consequent savings in time and power. Since there is no interference due to adsorption, formation of mixed crystals, *etc.*, the efficiency of separation remains essentially constant up to very high purities. The separation of zirconium and hafnium by distribution of their thiocyanates between two solvents has the additional advantages that the separation factors are relatively high, and that high concentrations can be used in both phases, so that the volumes of liquid required and the dimensions of the equipment need not be large.

Nevertheless, there are also a number of difficulties. The problems of the ease of oxidation of thiocyanic acid and the susceptibility of zirconium and hafnium salts to hydrolysis can be overcome by careful operation. However, fundamental problems arise as a result of the marked variation of the distribution coefficient with experimental conditions (temperature, concentrations of the necessary five or six reactants). Because of this variation, it is almost impossible to obtain a complete picture of the position of all the equilibria, and the extremely wide variations of the partition coefficients lead to special difficulties in the multi-stage solvent extraction.

[1] 16th Communication on the separation of inorganic substances by partition between two liquid phases. 15th Communicaton: *W. Fischer, K.-J. Bramekamp, M. Klinge,* and *H.-P. Pohlmann,* Z. anorg. Chem. *329,* 44 (1964).

Some 15 years ago the separation of zirconium and hafnium became important in nuclear technology, owing to the large difference between the neutron capture cross sections of the two elements and because of the desirable properties of metallic zirconium. Since the purity requirements were high (*e.g.* $<100$ p.p.m. of Hf in Zr), liquid-liquid extraction seemed to offer a particularly suitable method of separation. For this reason, American workers (1949) and the present authors (1950) tried to make use of an earlier observation [2] that high separation efficiencies could be achieved by the distribution of the thiocyanates of the two elements between water and diethyl ether. However, in view of the volatility of ether and the associated fire hazard, as well as its tendency to promote the oxidation of thiocyanic acid, it was desirable to use some other solvent. When the results of the American workers (which had originally been kept secret) [3] became available, it was found that they, like we ourselves [4], had also found aliphatic ketones to be suitable. The most readily available of these ketones is methyl isobutyl ketone [5], which will be referred to as hexanone in the remainder of this paper. Industrial processes have been developed [6] both in the U.S.A. and in Germany on the above basis.

The present paper, which is confined to partition between water and hexanone, will deal with the rather complex chemistry of the process, insofar as it has been elucidated; we shall also describe a plant for separation on the kilogram scale [7], which differs in a number of important points from previous designs.

## I. Chemical Principles

The partition coefficient K is defined as the ratio of the total concentrations of all the species of an element or substance in the two phases existing in equilibrium, *i.e.*, $K = c_H/c_W$ (H = hexanone, W = water). The separation factor $\beta$ is the ratio of the partition coefficients, *i.e.* $\beta = K_{Hf}/K_{Zr}$. For other definitions, see [8]. The zirconium and hafnium contents of a sample are always expressed as the percentages by weight of $ZrO_2$ and $HfO_2$ in the oxide prepared from the sample.

The partition coefficient of thiocyanic acid between water and hexanone at 20 °C and at concentrations of 1–2.3 M in the aqueous solution is about 1.8 [9,11]. It is 3 % smaller at 35 °C than at 15 °C. It is slightly depressed by the addition of $(NH_4)_2SO_4$, and considerably increased by $NH_4SCN$ or $H_2SO_4$. This common ion effect indicates that thiocyanic acid is not completely dissociated [9]. Hexanone extracts only 5 % of the ammonium thiocyanate from an equal volume of an almost saturated aqueous solution of this salt. No sulfate can be detected in hexanone that has been equilibrated with 2 M aqueous sulfuric acid, and chloride enters the hexanone phase only to a very small extent [9].

The procedure used in the work described in this section was very similar to that reported earlier [9]. The two phases were always used in equal volumes. The Zr and Hf contents were determined either by X-ray analysis (for apparatus see [10]) or by neutron activation analysis [12].

The partition of Zr and Hf thiocyanates exhibits considerable temperature-dependence. In the extraction of zirconium from a 1.3 M aqueous solution of HSCN containing from 1.5 to 22 g/l of $ZrO_2$, the partition coefficient of zirconium decreases by about 2 % per degree as the temperature is raised from 15 to 35 °C. The experiments described below were carried out at 20 ± 0.5 °C. When the desired temperature was reached, the distribution equilibria were already established.

### a) Effect of Concentration

The partition of zirconium and of hafnium between solutions of thiocyanic acid in water and in hexanone was first studied in the absence of other substances. The two elements were added to the solutions as the solid oxide chlorides. Figs. 1 and 2 show how the partition coefficient of zirconium is affected by its concentration in the aqueous phase at various constant thiocyanic acid concentrations in the hexanone phase, and *vice versa*. The curves for hafnium follow a similar trend, but the values of K are always higher (*i.e.*, hafnium has a greater tendency to enter the organic phase), generally by a factor of about 5 [9,11].

The thiocyanic acid concentrations were always measured before the zirconium or hafnium salts were added because small quantities of added salts have practically no effect on the distribution of the acid, while large quantities interfere with its determination.

The partition coefficients vary by two powers of ten in the concentration range studied. If these values were also valid for mixtures of the two elements, separation factors, $\beta$, of higher than 50 should be obtained at high zirconium concentrations and low hafnium concentrations, while when the relative concentrations are reversed, $\beta$ should be less than 1, *i.e.*, the zirconium should pass preferentially into the hexanone. In practice, however, the partition of each element is influenced by the addition of the other in the same manner as by an increase in its own concentration. For this reason, all separation factors obtained in the partition of mixtures ($ZrO_2$:$HfO_2$ = 99:1 to 5:95) are between 3 and 6 [9,11].

[2] *W. Chalybaeus*, Dissertation, Universität Freiburg 1942; *W. Fischer* and *W. Chalybaeus*, Z. anorg. allg. Chem. *255*, 79 (1947); *W. Fischer*, *W. Chalybaeus*, and *M. Zumbusch*, *ibid. 255*, 277 (1948).

[3] a) *L. G. Overholser*, *C. J. Barton*, and *W. R. Grimes*, USAEC-Reports Y 431 and Y 477 (1949), declassified Nov. 17th, 1955; b) *J. W. Ramsey* and *W. K. Whitson, Jr.*, USAEC-Report Y 817 (1951), declassified Nov. 17th, 1955.

[4] German Patent 1010061 (Oct. 18th, 1955), inventors: *W. Fischer*, *H. Heitsch*, and *G. Otto*.

[5] We used a product supplied by Shell, Hamburg.

[6] *S. M. Shelton*, *E. D. Dilling*, and *J. H. McClain*: Proc. Internat. Conf. Peaceful Uses of Atomic Energy. New York 1956, Vol. 8, p. 520ff. Includes references to other American reports. *M. Becker*, *F. Endter*, *W. Neugebauer*, and *H. Renner*, Proc. II. Internat. Conf. Peaceful Uses of Atomic Energy, Geneva 1958, Vol. 4, p. 276.

[7] *B. Deierling*, Diploma Thesis 1960, Dissertation 1963, Technische Hochschule, Hannover.

[8] *W. Fischer et al.*, Chemie-Ing.-Techn. *36*, 85 (1964); Angew. Chem. internat. Edit. *3*, 791 (1964).

[9] a) *K. Adam*, Diploma Thesis, Technische Hochschule, Hannover, 1958; b) *H.-P. Pohlmann*, Dissertation, Technische Hochschule, Hannover 1961; c) *W. Fischer*, *H.-P. Pohlmann*, and *K. Adam*, Z. anorg. allg. Chem. *328*, 252 (1964).

[10] *K. H. Grothe* and *W. Fischer*, Z. analyt. Chem. *204*, 161 (1964); *K. H. Grothe*, *ibid. 211*, 401 (1965).

[11] *K. Reinhardt*, Diploma Thesis, 1962, and Dissertation, 1964, Technische Hochschule Hannover, and unpublished results.

[12] *K. H. Grothe* and *K. Reinhardt*, Z. analyt. Chem. *204*, 176 (1964).

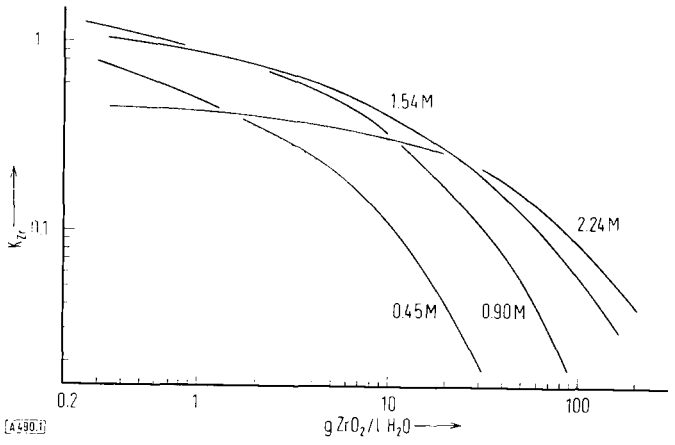


Fig. 1. Partition coefficient of zirconium, $K_{Zr}$, as a function of the equilibrium concentration of zirconium in the aqueous phase, for various concentrations of HSCN in hexanone (in equilibrium with the aqueous phase before the zirconium salt is added).

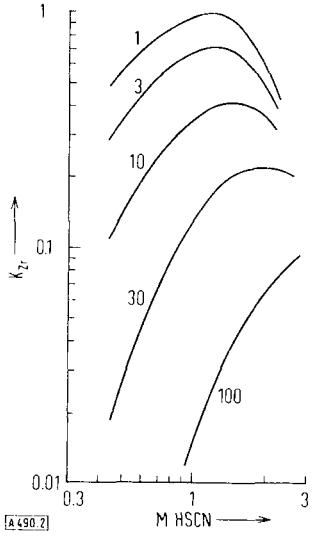


Fig. 2. Partition coefficients of zirconium, $K_{Zr}$, as a function of the concentrations of HSCN in hexanone (in equilibrium with the aqueous phase before the Zr salt is added). The numbers beside the curves denote the concentrations (in g/l) of $ZrO_2$ in the aqueous phase (after partition).

They increase with increasing HSCN concentrations, and high metal concentrations [100 to 150 g/l of (Zr, Hf)$O_2$ in the aqueous phase] also seem to favor β values near the upper limit. Experiments with radioactive tracers or using neutron activation analysis [12] showed [11] that the separation factors are also of this order in the range of $ZrO_2$:$HfO_2$ ratios from $10^2$ to $10^5$ that are of interest for the preparation of zirconium compounds with very low hafnium contents. No confirmation was found for an earlier observation [9] that β increases with decreasing hafnium content.

A quantitative treatment of the experimental results with a view to finding what chemical species are involved is impossible at the high concentrations used, since the activities of the species are unknown. The results reported here, as well as those of unpublished work [13], indicate the following two points to be important for a qualitative interpretation:

1. The aqueous phase must be assumed to contain numerous complexes of zirconium with $SCN^-$, $OH^-$, and $H_2O$, of which only non-electrolytes with a high SCN content, such as $Zr(SCN)_4$, can be extracted. For a given quantity of thiocyanic acid, an increase in the zirconium content will lead to an increase in the proportion of non-extractable complexes with low SCN contents, and hence to a decrease in the partition coefficient (see Fig. 1). This explains the unusual observation that as the concentration of zirconium in the aqueous phase *increases*, the concentration in the organic phase passes through a maximum and then *decreases* (see Fig. 3). The zirconium concentration at which the maximum occurs increases with the quantity of thiocyanic acid available. The slopes of the curves in Fig. 1 become smaller at lower zirconium concentrations, *i.e.* the partition coefficient tends towards a constant value. This probably means that the zirconium in each phase is largely present as a single species; the number of Zr atoms per complex molecule must be the same in each phase, and the species themselves may even be identical. In agreement with this, the zirconium contents at which the curves in Fig. 1 approach the horizontal increase with the concentration of thiocyanic acid. – Similar relationships are found in the case of hafnium. Thus the effects of zirconium and hafnium on each other are due to competition for thiocyanate ions. The reason for the preferential extraction of hafnium, therefore, is either that the extractable species of this metal are more stable than those of zirconium or that they have higher (individual) partition constants.

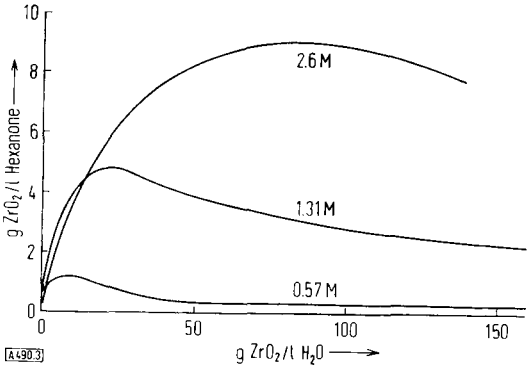


Fig. 3. Concentration of zirconium in the hexanone phase as a function of its concentration in the aqueous phase. The concentration of HSCN in hexanone (in equilibrium with the aqueous phase before the Zr salt is added) is shown on the curves.

2. The relationships described would require a monotonic increase in the partition coefficient with HSCN concentration at a given Zr concentration. The observed maximum (Fig. 2) is probably due to the facts that one liter of pure hexanone corresponds to only 8 moles, and that solvation of the thiocyanic acid at higher concentrations leads to a considerable decrease in the quantity of "free" hexanone available for the extraction of the zirconium thiocyanate. At high Zr concentrations (Fig. 2), a large proportion of thiocyanate is bound by the zirconium, so that both phases contain less free thiocyanic acid; consequently, the maximum then occurs at higher concentrations. The increase in $K_{Zr}$ with increasing HSCN concentration before the maximum is reached is not due to the suppression of hydro-

[13] *G. Dittrich*, Diploma Thesis, Technische Hochschule, Hannover 1964, and unpublished results.

lysis by the increasing $H^+$ concentration. In fact, the effect of the hydrogen ions acts in the opposite direction; thus the partition coefficients are unchanged by addition of $NH_4Cl$, whereas they are reduced by addition of hydrochlorid acid [9]. This hydrogen-ion effect is probably due to suppression of the dissociation of thiocyanic acid, resulting in the displacement of the distribution in favor of hexanone (see above). The consequent decrease in the thiocyanate content of the aqueous phase must have a depressing effect on the extraction of the zirconium, and this effect is aggravated, in our view, by the accompanying decrease in the quantity of "free" hexanone present.

b) Addition of Sulfates

Already in our first experiments with ether [2], we found that sulfate ions have a favorable effect on the separation efficiency. It was assumed that while the more stable of the (non-extractable) sulfate complexes is that of zirconium, the more stable (extractable) thiocyanate complex is that of hafnium.

Fundamentally similar results were obtained in systematic experiments [7] in which hexanone was used instead of ether. Figs. 4 and 5, in which (in contrast to Figs. 1 and 2, where a logarithmic presentation is used) the values are plotted on linear scales, show the effect of added ammonium sulfate on the partition of zirconium and of hafnium (separately) between aqueous and ketonic solutions of HSCN.

The equilibrium concentrations of thiocyanic acid are changed slightly by the addition of ammonium sulfate; thus $c_{Hexanone}$ is decreased from 2.2 to 2.0 and $c_{water}$ increased from 1.2 to 1.4 M HSCN by an $(NH_4)_2SO_4$ concentration of 1.11 M. The uppermost curve in Fig. 4 [no $(NH_4)_2SO_4$] corresponds to the curve for 2.24 M HSCN in hexanone in Fig. 1.

The addition of ammonium sulfate leads to a decrease in the partition coefficient, this decrease being greater for zirconium than for hafnium. In comparing Figs. 4 and

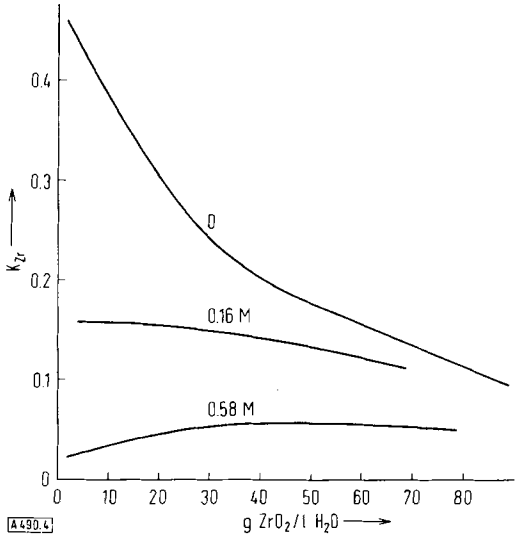


Fig. 4. Influence of ammonium sulfate on the partition coefficient $K_{Zr}$ of zirconium. HSCN concentration before the addition of the other substances 1.2 M in water and 2.2 M in hexanone. The values beside the curves denote the molarity of $(NH_4)_2SO_4$/l in water.

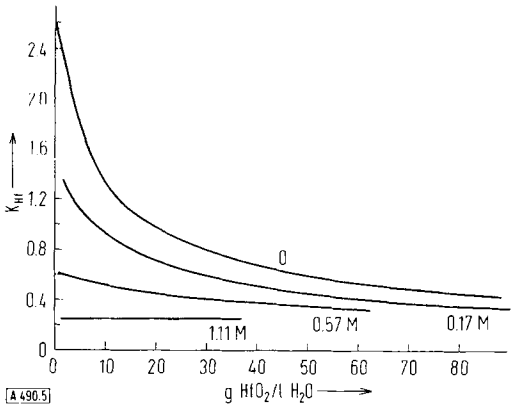


Fig. 5. Influence of ammonium sulfate on the partition coefficient of hafnium, $K_{Hf}$. See legend to Fig. 4.

5, it should be noted that the results shown for hafnium extend to higher sulfate concentrations. The sulfate effect is relatively stronger at low metal concentrations than at high concentrations, and in the case of zirconium this leads to the appearance of a maximum at higher sulfate concentrations. At low Zr concentrations, *i.e.* when there is a large excess of sulfate and thiocyanate, the non-extractable sulfate complex is evidently formed in preference to the thiocyanate complex. At intermediate Zr concentrations, the sulfate is no longer present in sufficient excess to bind such a large proportion of the zirconium, so that more of the latter is available for the formation of thiocyanate complexes. When the Zr concentration is further increased, the proportion of extractable zirconium is again decreased as a result of the effect demonstrated in Fig. 1 and described in Section I a.

If the ammonium sulfate is replaced by sulfuric acid, the partition coefficient of hafnium is further reduced by the hydrogen-ion effect described above. This effect has little influence on zirconium.

The addition of sulfate favors the separation of Zr and Hf by intensifying the differences in the behavior of the two metals; at the same time, however, the partition of both elements is considerably displaced in favor of the aqueous phase, with the result that separations on the preparative scale require large volumes of hexanone. It is known [2,4] that the addition of ammonium thiocyanate leads to a displacement in favor of the organic solvent, and that this effect is stronger for hafnium, so that the separation is further improved. Fig. 6 shows this effect for zirconium; for further data, see [7]. The maximum produced by the addition of sulfate is accentuated when ammonium thiocyanate is also present.

The addition of thiocyanate has a very different effect on the partition of hafnium in the presence of sulfate. The effect is strong even at low Hf concentrations, so that the difference between the behavior of Hf and Zr is very pronounced in this concentration range (see Fig. 7). Moreover, the dependence of the effect on the metal concentration is not the same for the two elements. The situation is further complicated by the fact that a change in the initial concentration of thiocyanic acid (which was kept constant in the experiments to which Figs. 6 and 7 refer) has a very marked effect on the partition coefficient [7].

Similar experiments on Zr-Hf mixtures gave even better results than were expected from Fig. 7. Fourteen experiments were carried out with from 2 to 23 g of metal oxide per liter of aqueous phase and from 30 to 95 % of $HfO_2$ in the (Zr-Hf) starting material, and with HSCN

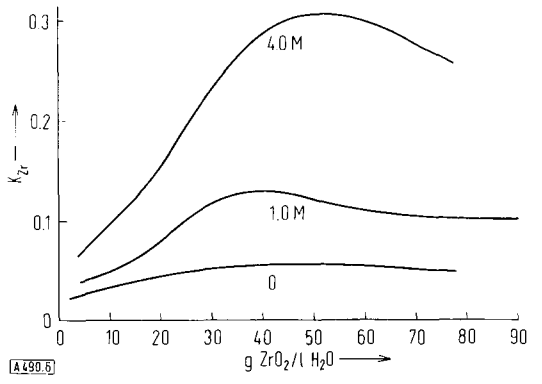


Fig. 6. Influence of $NH_4SCN$ (concentrations in water noted on the curves) on the partition coefficient of zirconium, $K_{Zr}$. The aqueous phase is also 0.57 to 0.58 M in ammonium sulfate. HSCN concentration before the addition of any other substances: 1.2 M in water and 2.2 M in hexanone.

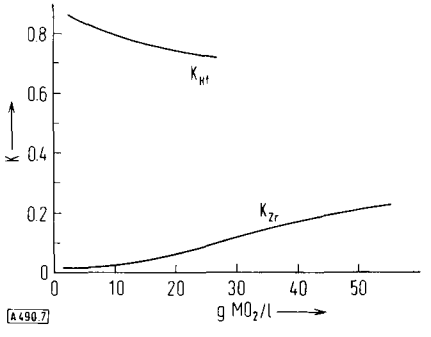


Fig. 7. Partition coefficients $K_{Hf}$ and $K_{Zr}$ as functions of the metal concentration, g $MO_2$/l, in the aqueous phase after the addition of 1.1 mole of $(NH_4)_2SO_4$ and 4.0 moles of $NH_4SCN$ per liter of aqueous phase. HSCN concentration before the addition of other substances: 1.2 M in water and 2.2 M in hexanone.

concentrations ranging from 0.4 to 2.6 M in hexanone; 1.1 mole of $(HN_4)_2SO_4$ and 4 moles of $NH_4SCN$ were added per liter of aqueous phase. With one exception, these experiments gave separation factors $\beta$ from 40 to 110. This method can be used with success for the separation of smaller quantities of material, and particularly for the preparation of very pure samples.

These conditions are less suitable for the processing of large quantities of material by multi-stage distribution, since it then becomes desirable to recover the large quantities of thiocyanate that must be used, and since the separation factors are probably lower at higher metal concentrations.

In the presence of 0.57 to 1.1 M $(NH_4)_2SO_4$, addition of 4 moles of $NH_4SCN$ per liter of aqueous phase causes the concentration of HSCN in the hexanone to increase from 2.2 to 2.6 or 2.7, while the concentration in the aqueous phase decreases from 1.2 to 0.7 or 0.8.

Frequent checks on (Zr, Hf) solutions with and without sulfate, and containing at least 1 M HSCN, revealed no changes in the partition coefficients when the solutions were stored for 24 hours at 20 °C, although such changes (probably due to slow hydrolysis) had been troublesome in earlier work with a different procedure [2].

### c) Oxidation of Thiocyanic Acid

In the course of several weeks' operation of the mixer settlers described below, air oxidation of the thiocyanic acid (which can be recognized by the precipitation of yellow products with very low solubilities in water and in hexanone) led to only a light deposit on the walls of the vessels, and did not cause any troublesome decrease in the HSCN concentration, provided that this was not appreciably greater than 2.6 M in the hexanone or than 1.4 M in the aqueous phase, and provided that the (Zr, Hf) sample to be processed had been largely freed from iron (*e.g.* by recrystallization as the oxide chloride from concentrated hydrochloric acid), since iron catalyses the oxidation of thiocyanic acid.

## II. Technical Principles

The multiplicative separation experiments were carried out in a multi-stage plant, which was capable of operating up to 36 of the previously developed [14] mixer settlers. The material flow scheme, with periodic addition of the mixture to be separated, differed from conventional practice in that the aqueous phase was introduced and discharged in batches, while the hexanone moved continuously in counter-current to the aqueous phase in such a way that at any moment, each mixer settler contained a finite volume of aqueous solution, together with only a minimum of the ketonic solution. The process was described in detail in an earlier publication [8] and its operation has been studied mathematically by *Horn* [15]. It differs from the usual processes (*e.g.* with two continuously moved solvent streams) in that only half as many mixer settlers are required in order to obtain a given separation efficiency, and the quantity of solvent required is also somewhat smaller.

The process is periodic in operation. Under quasi-stationary conditions, each successive period or cycle is identical with every other. For example, one cycle of an 11-stage partition (the results of which will be discussed below) is as follows (see Fig. 8): The plant comprises 14 mixer settlers (also referred to below as partition units or simply units) arranged in two lines or in a circle. Three of these (light circles in Fig. 8) are held in reserve. Numbers 1 to 10 are taken over, with their contents, from the previous cycle. A volume of the heavier solvent (water) is introduced into no. 11, where it remains as long as this mixer settler is in use. At the beginning of the cycle, no. 6 is supplied with a quantity of the mixture to be separated. Light solvent is then fed at a constant rate into no. 1. As the lighter solvent is introduced, brought into contact with the heavier phase, and then separated from the latter again, it is passed directly into no. 2 (so that no. 1 always contains the absolute minimum working volume of the light phase). In no. 2 it is treated in exactly the same manner, and so on. When a certain volume of the

[14] *W. Fischer et al.*, Angew. Chem. *66*, 317 (1954).
[15] *F. Horn*, Chemie-Ing.-Techn. *36*. 99 (1964).

light phase has passed in this way through stages 1 to 11 and has left no. 11 as the head fraction, the heavy phase from no. 1 is taken off as the tail fraction. This mixer settler is then taken into reserve, and the reserve unit next to no. 11 is charged with aqueous solution. Thus there are still 11 units in operation, but these are displaced by one unit in a clockwise direction from those used in the previous cycle. The new set of operating units are then re-numbered from 1 to 11 [8]. This completes one cycle.

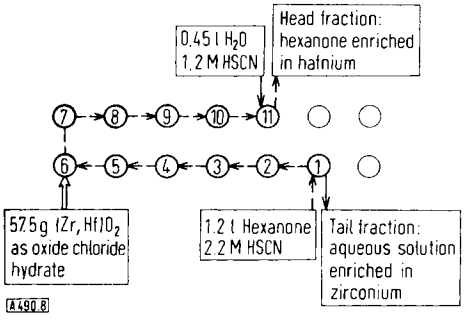


Fig. 8. Scheme of a partition cycle.
→ aqueous phase; — — → hexanone phase.

In conventional processes in which two solutes are to be separated by means of two liquid phases flowing in opposite directions, $v_l/v_h$ must be such that the extraction factor of one of the substances $G_1 = K_1 v_l/v_h > 1$, while that of the other $G_2 = K_2 v_l/v_h < 1$ ($v_l$ and $v_h$ are the volumes of the light and heavy phases, respectively, passing through the system per unit time or per cycle). Owing to the unsymmetrical flow of the two phases in our process, the reference value 1 is replaced by a somewhat different value [8]; however, we can disregard this in the following discussion.

If the partition factors in a plant fluctuate, the separation efficiency must suffer. If both G values in some part of the plant are greater than 1, for instance, both substances will move with the light phase, while in other parts they are moving in opposite directions.

Often the mixture to be separated is introduced as a solution in one of the solvents. If the mixture is dissolved in the heavy solvent, the ratio $v_l/v_h$ is lowered between the feed stage and heavy-phase discharge, so that the G values of all the species present will also be lower in this part of the plant. If, on the other hand, the mixture is dissolved in the light solvent, $v_l/v_h$ is increased in the other part of the plant. Both effects lower the overall separating effect of the plant. For this reason it is generally preferable to introduce the mixture in the solid form, particularly if the partition coefficients, K, of the components of the mixture are not very different [16].

In our case the G values are very inconstant, owing to the large variation of the partition coefficients. The concentration of the mixture to be separated is necessarily greatest in the feed stage. In the case of a mixture with an initial $HfO_2$ content of 1 to 2 %, there is only a slight decrease in concentration on the zirconium side of the plant, whereas the decrease on the hafnium side is very rapid. This leads to a wide variation of the partition coefficients. For large-scale separations it is desirable that the volumes of liquids used be as small as possible, *i.e.* that the concentrations be as high as possible. Under these conditions, however, the partition coefficient is most strongly affected by changes in concentration (see Fig. 1). Furthermore, the influence of the thiocyanic acid concentration and of any added sulfate or thiocyanate must also be taken into account. Even in the absence of the latter effects the K values, and hence the G values, of zirconium and hafnium can be expected to vary at least by a factor of ten in a multi-stage distribution plant, whereas the two values normally differ by a factor of only 5. It is therefore doubtful whether any extensive separation of Zr and Hf could be achieved in a single operation by multiplicative distribution; in any case, the difficulties would probably be very considerable. Owing to the complexity of the chemistry involved, the most favorable operating conditions could not be calculated in advance. The only profitable approach was that of systematic experiments, the results of which are discussed below.

## III. Development of a Multi-Stage Liquid-Liquid Extraction Process

Since the partition equilibria are strongly dependent on the temperature, the experiments were carried out in a room maintained at 20 ± 1 °C. The materials used were samples of zirconium oxide chloride hydrate containing 1.4 or 2 % of $HfO_2$ (based on the oxide). It is extremely important to ensure that the samples are free from products of further hydrolysis and from powdered zirconium ore. Since these substances are insoluble in water, they do not take part in the partition equilibria; when they are peptized or suspended and are not retained by the filters, they remain in the aqueous phase with the zirconium, with the result that the hafnium content of the latter cannot be reduced beyond a certain limit. As a precaution, we used oxide chloride samples prepared below 70 °C by the introduction of zirconium tetrachloride into hydrochloric acid and recrystallization from 6 M hydrochloric acid.

In choosing the conditions for the technical separation of large quantities by continuous multi-stage liquid-liquid extraction, it is not essential that the separation factor should be as high as possible. A lower separation efficiency of one partition operation can generally be compensated by the use of a larger number of stages; while this raises the initial cost of the plant, it does not complicate the operation appreciably. It is more important that other conditions, including economic restrictions, should be satisfied, *e.g.* insensitivity to small variations in procedure, easy processability of the final fractions, good phase separation, avoidance of corrosion, recovery of additives, low solvent consumption, *etc.* On the basis of these considerations, the Zr-Hf starting material was introduced as the solid oxide chloride hydrate and distributed between hexanone and water containing HSCN at concentrations of 2.2 M and 1.2 M respectively (for the preparation of the solutions see [9]), although the separation factors obtained by this method were only 4 to 5.

[16] German Patent 1134662 (Sept. 16th, 1960), Degussa; inventors: *W. Fischer* and *H. Renner*.

A point that has no bearing on the separation, but which is advantageous in practice, is that the hexanone solution leaving the plant as the head fraction should be passed through 2 or 3 other mixer settlers, each of which contains 500 ml of 3 M $H_2SO_4$; this set of units is changed after each cycle in the same way as the set used for the separation. The "washing stage" taken out of the process at each cycle then contains the Hf(+Zr) of the head fraction; the "washed" hexanone, on the other hand, contains only HSCN, and is re-used after correction of the HSCN concentration.

The procedure described below was used to determine the operating data for the plant described in Section II and to improve on the results obtained. The following factors were initially kept constant (cf. Fig. 8):

1. number of stages,
2. composition of starting mixture,
3. stage into which the mixture is fed,
4. quantity of mixture added per cycle,
5. HSCN contents of the solvents introduced at the ends of the plant,
6. volume of aqueous HSCN solution added per cycle.

Thus the only variable is the volume of hexanone introduced per cycle. If this is too large, the quantity of hafnium removed in the head fraction is larger, and the quantity of zirconium in the tail fraction smaller, than the quantities of the two elements added per cycle with the starting mixture. Consequently, the Hf/Zr ratio gradually decreases in all the stages, including that into which fresh mixture is fed at the beginning of each cycle. If the volume of hexanone used per cycle is too low, the situation is reversed. With the optimum hexanone feed, the Hf/Zr ratio in this stage is roughly equal to that in the starting mixture, and the quantities of the two metals removed are equal to the quantities added.

The Hf and Zr contents of the head and tail fractions, respectively, and the Hf/Zr ratio in the feed stage were systematically determined, and the quantity of hexanone introduced per cycle was varied until the above requirements were satisfied for at least some 10 cycles. The above "fixed" factors were then altered with the object of improving the purity of the fractions. The results are shown in Table 1.

Table 1. Operating data for the distribution plant under various operating conditions. Solvent added per cycle: 450 ml of 1.2 M aqueous HSCN ($v_h$) and various volumes (column 3, $v_l$) of 2.2 M HSCN in hexanone.

| Up to cycle no. | Number of stages | $v_l$ (ml) | Mixture [b] added in stage no. | Tail fraction, % of $HfO_2$ in the oxide | Head fraction, % of $ZrO_2$ in the oxide |
|---|---|---|---|---|---|
| 20 | 11 | 1200 | 6 [c] | 0.14 | 46 |
| 36 | 11 | 1100 | 6 [d] | 0.05 | 42 |
| 53 | 11 | 750 | 6 [e] | 0.04 | 25 |
| 70 | 13 | 780 | 6 [e] | — | 13 |
| 108 | 17 | 780 | 8 [e] | 0.04 | 12 |
| 131 | 17 | 880 [a] | 7 [e] | 0.02 | 0.3 |
| 168 | 23 | 900 [a] | 13 [e] | $<$0.001 | $0.2_5$ |

[a] Plus 0.05 M $H_2SO_4$ in the aqueous phase.

[b] 57.5 g of (Zr, Hf)$O_2$ containing 1.4 or 2 wt-% of $HfO_2$ were added per cycle, in the form of the oxide chloride hydrate.

[c] No addition of ammonium thiocyanate.

[d] Plus 20 g of ammonium thiocyanate.

[e] Plus 40 g of ammonium thiocyanate.

The result of the first 20 cycles corroborated the result of a 33-cycle fractionation carried out under similar conditions[9b, 17]; in this case a total of 5 kg of (Zr, Hf)$O_2$ was processeed in an apparatus with a larger capacity, and the products obtained were a $ZrO_2$ sample containing 0.13 % of $HfO_2$ and an $HfO_2$ sample containing 50 % of $ZrO_2$.

After the twentieth cycle, the state of the plant was checked by analysis (see Table 2 a). The concentration of metal in the aqueous phase showed a very large change, amounting to roughly a factor of 40 between the middle and the hafnium side. Consequently, the partition coefficients K changed by a factor of 6 between stage 1 and stage 11. The partition factors $G = Kv_l/v_h$ should always be $> 1$ for hafnium and $< 1$ for zirconium. Since $v_l/v_h$, according to Table 1, is equal to $1.2/0.45 = 2.7$, $G_{Hf}$ in stage 1 is only 1.1, while $G_{Zr}$ in stages 9 and 11 is greater than 1. The separation must therefore be poor. This is clear from the separating effect S, which is equal to the Hf/Zr ratios in the aqueous phases of two adjacent stages:

$$S = (Hf/Zr)_n/(Hf/Zr)_{n-1}$$

For the flow scheme used, the average separating effect S should be roughly equal to the separation factor $\beta$ [8, 15]. However, a comparison of the last two columns in Table 2 shows that while the $\beta$ values for the multistage plant (as in the individual experiments) are between 4 and 5, the separating effects S are much smaller, and (as expected) their values between stages 9 and 11 are close to 1 (S = 1 means that there is no separation).

The $HfO_2$ content of the oxide removed from stage 11 in the hexanone phase after cycle 20 (Table 2: 39.7 %) is not the same as the $HfO_2$ content of the oxide in the head fraction of cycle 20 (Table 1: 54 %). This is because the head fraction is the total hexanone removed during the cycle, whereas the instantaneous concentrations vary with the periodicity of the cycle[8, 15].

To obtain a better separation, it is necessary to reduce the variation of the partition coefficients. Since these vary with the concentration of the metal, we could introduce a partial phase reversal (reflux) at the hafnium end of the plant, where the resulting hold-up would lead to the desired increase in the concentration of the metal. However, this would be very laborious in the present case. We therefore chose a chemical method. If ammonium thiocyanate is introduced into stage 6 with the (Zr, Hf) mixture, most of the thiocyanate remains in the aqueous phase. In the course of the successive cycles, therefore, this substance moves with the zirconium, and so increases the partition coefficients in stages 1 to 6, *i.e.* just where an increase is required. Part of the ammonium thiocyanate could also form thiocyanic acid with any $H^+$ ions that might result from further hydrolysis of the (Zr, Hf) oxide chloride. The distribution of this thiocyanic acid would favor the hexanone phase, *i.e.* the acid would migrate with the hafnium through stages 7 to 11, where it would lower the partition coefficients in accordance with Fig. 2. However, SCN determinations in the various stages of the plant showed that this effect is of practically no importance in comparison with the increase in the partition coefficients in stages 1 to 6[7].

Table 2. The state of the partition plant
(a) after cycle 20 (11 stages, mixture added in stage 6, no $NH_4SCN$ added),
(b) after cycle 53 (11 stages, mixture added in stage 6, 40 g of $NH_4SCN$ added per cycle)

| Stage no. | Aqueous phase | | Hexanone phase | | $K_{Hf}$ | $K_{Zr}$ | Separation factor $\beta = K_{Hf}/K_{Zr}$ | Average separating effect, S |
|---|---|---|---|---|---|---|---|---|
| | g of $(Zr,Hf)O_2$/l | % of $HfO_2$ in oxide | g of $(Zr,Hf)O_2$/l | % of $HfO_2$ in oxide | | | | |
| | | | | a) after cycle 20 | | | | |
| 1 | 109.4 | 0.14 | 9.8 | 0.66 | 0.42 | 0.089 | 4.7 | 1.8 |
| 3 | 139.5 | 0.48 | 15.0 | 2.5 | 0.56 | 0.106 | 5.3 | 1.7 |
| 5 | 142.2 | 1.3 | 15.3 | 6.0 | 0.49 | 0.102 | 4.8 | 1.55 |
| 7 | 34.6 | 3.1 | 9.75 | 13.1 | 1.18 | 0.25 | 4.7 | 1.55 |
| 9 | 8.6 | 7.2 | 4.6 | 24.3 | 1.80 | 0.44 | 4.1 | 1.27 |
| 11 | 3.5 | 11.0 | 2.6 | 39.7 | 2.66 | 0.50 | 5.3 | |
| | | | | b) after cycle 53 | | | | |
| 1 | 105.7 | 0.04 | 21.4 | 0.26 | 1.0 | 0.202 | 5 | 2.7 |
| 3 | 144.8 | 0.3 | 37.3 | 1.2 | 1.0 | 0.255 | 3.9 | 2.2 |
| 5 | 152.2 | 1.4 | 43.4 | 2.6 | 0.53 | 0.281 | 1.9 | 1.3 |
| 7 | 84.3 | 2.5 | 30.7 | 7.2 | 1.05 | 0.35 | 3.0 | 1.8 |
| 9 | 11.2 | 7.8 | 6.0 | 31.5 | 2.16 | 0.40 | 5.4 | 2.1 |
| 11 | 2.3 | 26.5 | 2.8 | 69.3 | 3.16 | 0.51 | 6.2 | |

It can be seen from Table 1 that the purity of the final fractions is appreciably increased by the addition of 20 or 40 g of ammonium thiocyanate (corresponding to concentrations of 0.6 and 1.2 moles/liter of aqueous phase, respectively). The larger concentration leads to a change by a factor of 3 in the $HfO_2/ZrO_2$ ratios of the two fractions. This is due to the increase in the partition coefficients on the zirconium side of the plant (Table 2), which leads to a considerable improvement in the separating effect S (last column in Table 2). Owing to the higher partition coefficients, moreover, the volume of hexanone used per cycle can be reduced from 1200 to 750 ml. Further, the values of $K_{Hf}$ and $K_{Zr}$ have been smoothed out in spite of the fact that the variation of the metal concentrations is even greater than after cycle 20.

After cycle 53, the number of stages was increased in an attempt to obtain a further increase in the purity of the final fractions. As can be seen from Table 1, two extra stages give a slight improvement in the purity of the hafnium fraction, but no further improvement is obtained by the use of four more stages. All the S values (Table 3a) are, accordingly, very low after cycle 108. Experience with other systems shows that this result is generally valid: where there is a wide variation of the partition coefficients, an increase in the number of stages brings little or no improvement. In the present case this is because $K_{Zr}$ again varies widely (by a factor of 4), and because in spite of the low volume ratio $v_l/v_h = 0.78:0.45 = 1.7$ (see Table 1), the calculated values of $G_{Zr}$ for stages 13 to 17 are greater than 1. Table 3a also shows that the separation factors $\beta$ in stages 3 to 9, *i.e.* in the zirconium part of the plant (with the exception of stage 1) are relatively low (close to 3). This phenomenon had already become noticeable after cycle 53, and is in agreement with Fig. 7 for the high metal concentrations present on the Zr side of the plant. It is probably also a result of the addition of $NH_4SCN$, and for this reason the quantity of the latter added should not be further increased.

An improvement can be expected only if the variation in the partition coefficients can again be reduced, and particularly if that of Zr in stages 13 to 17 can be lowered sufficiently to give an extraction factor G of less than 1.

Table 3. The state of the partition plant
(a) after cycle 108 (17 stages, mixture added in stage 8, 40 g of $NH_4CNS$ added per cycle),
(b) after cycle 131 (17 stages, mixture added in stage 7, 40 g of $NH_4SCN$ added per cycle, aqueous phase also contains $H_2SO_4$ at a concentration of 0.05 M).

| Stage number | % of $HfO_2$ in the oxide | | $K_{Hf}$ | $K_{Zr}$ | $\beta$ | S |
|---|---|---|---|---|---|---|
| | Aqueous phase | Hexanone phase | | | | |
| | | a) after cycle 108 | | | | |
| 1 | 0.04 | 0.17 | 0.8 | 0.20 | 4 | 2.1 |
| 3 | 0.18 | 0.60 | 0.77 | 0.23 | 3.3 | 1.5 |
| 5 | 0.42 | 1.40 | 0.87 | 0.26 | 3.4 | 1.4 |
| 7 | 0.80 | 2.9 | 1.05 | 0.28 | 3.7 | 1.7 |
| 9 | 2.3 | 6.1 | 0.95 | 0.35 | 2.8 | 1.7 |
| 11 | 6.1 | 25.4 | 2.12 | 0.41 | 5.2 | 1.6 |
| 13 | 14.5 | 43.5 | 2.67 | 0.59 | 4.5 | 1.3 |
| 15 | 22.0 | 60.6 | 3.53 | 0.65 | 5.5 | 2.0 |
| 17 | 54.1 | 80.6 | 2.83 | 0.80 | 3.5 | |
| | | b) after cycle 131 | | | | |
| 1 | 0.02 | 0.13 | 1 | 0.18 | 6 | 2.7 |
| 3 | 0.15 | 0.55 | 0.8 | 0.22 | 3.7 | 1.6 |
| 6 | 0.6 | 2.3 | 1.0 | 0.25 | 3.9 | 1.9 |
| 8 | 2.2 | 8.9 | 0.93 | 0.21 | 4.4 | 2.4 |
| 10 | 11.9 | 46.0 | 2.01 | 0.32 | 6.3 | 2.4 |
| 12 | 44.5 | 87.3 | 2.26 | 0.26 | 8.6 | 2.6 |
| 14 | 84.0 | 97.6 | 2.23 | 0.29 | 7.7 | 2.7 |
| 16 | 97.4 | 99.5 | 2.16 | 0.4 | 5 | |

This can be achieved by the addition of a small quantity of sulfate to the aqueous phase, as was shown in Section I. The concentrations of Hf and Zr in the hafnium side of the plant are low. According to Figs. 4 and 5, therefore, even a small quantity of sulfate should lead to a marked decrease in $K_{Zr}$ and to a smaller decrease in $K_{Hf}$, with the additional result that the separation factor should be increased. On the zirconium side of the plant, on the other hand, the metal concentrations are very high, so that a small quantity of added sulfate should have very little effect. This is confirmed by the results of cycle 131 (Tables 1 and 3) for 0.05 mole of $H_2SO_4$ per liter of water, where the same number of stages is used as before. The hafnium content of the zirconium fraction is reduced by half, while the zirconium content of the hafnium fraction is reduced to $^1/_{40}$th of its original value. The partition coefficients of the two elements differ by a factor of only 2. Owing to the reduction of the partition coefficients on the hafnium side, the quantity of hexanone introduced per cycle

must be increased slightly, *i.e.* from 780 to 880 ml. However, the improvement in the separation, which is also reflected in the S values, is not due entirely to the decrease in the variation of the partition coefficients; the sulfate has also increased the separation factors $\beta$, even on the Zr side of the plant. When this procedure was used, the metal concentration in stage 7 after the addition of the mixture increased to 235 g of (Zr, Hf)$O_2$ per liter of water.

Under these circumstances, an increase in the number of stages could now be expected to have a favorable effect. The addition of six stages to the Zr side, so that the mixture was introduced in stage 13 instead of stage 7, produced no appreciable change in the Hf fraction (Table 1), but reduced the $HfO_2$ content of the zirconium fraction to less than $^1/_{20}$th of its original value. This was confirmed by neutron activation analysis [12] on most of the tail fractions between cycle 144 and cycle 168. Even in stage 5, the $HfO_2$ content is less than 60 ppm. Thus the overall separating effect [8], *i.e.* the change in the $HfO_2/ZrO_2$ ratio between the head fraction and the tail fraction, is $4 \times 10^7$.

The American process mentioned in the introduction gives a zirconium product containing less than 100 ppm of hafnium and a hafnium product containing about 2 % of Zr from a starting material comparable to that used in the present work, *i.e.* the overall separating effect is $5 \times 10^5$ [3b]. This process is also based on partition between water and hexanone in the presence of HSCN and $NH_4SCN$. The essential differences between this and the process described in the present paper are: (a) the mixture is introduced in the form of an aqueous solution; (b) 3.5 M hydrochloric acid is used as the aqueous phase, probably to achieve a partial reflux; (c) the apparatus consists of spray columns. In order to achieve the purities mentioned above, it is necessary to use many columns in series to give a total length of 305 ft (93 m) (excluding washing and recovery plant).

The fact that the overall separating effect obtained by us with only 23 mixer settlers was almost two powers of ten higher is probably mainly due to the following factors:

1. Better attainment of equilibrium in mixer settlers than in columns.
2. Special mode of operation of the new materials flow scheme.
3. Constant attempts to restrict the variation of the partition coefficients within the plant.
4. The effect of added sulfate, which has a favorable effect on both the partition coefficients and the separation factors, the partition coefficients being affected only in the part of the plant in which this is desirable.

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Translated by Express Translation Service, London

[17] *W. Böhmer*, Dissertation, Technische Hochschule Hannover 1961.

# The Chemistry of Protactinium

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*Dedicated to Professor W. Klemm in honor of his 70th birthday*

*Protactinium exhibits an ambivalent chemical behavior. In non-aqueous solutions and in the solid state, both quadrivalent and quinquevalent protactinium has properties which characterize it as a typical actinide element. On the other hand, investigations in aqueous solution show quinquevalent protactinium to be a homologue of niobium and tantalum. It exhibits – except in hydrofluoric acid solutions – a marked tendency to undergo irreversible hydrolysis and condensation reactions, which leads to the situation that tracer amounts (ca. $10^{-12}$ mole/l) and macroscopic amounts ($10^{-3}$–$10^{-6}$ mole/l) of protactinium often behave differently. Reduction with strong reducing agents gives aqueous solutions of Pa(IV), the properties of which again correspond in general to those of Th(IV) and show no relation to Nb(IV). Our knowledge of the chemical behavior of this rare radioelement has been advanced, in particular, by the production in 1958–1960 of 100 g of pure protactinium – the largest amount so far – from residues of the British production of uranium.*

## 1. Introduction

Element 91, protactinium, comes between thorium and uranium in the periodic table. On the basis of the radioactive displacement laws, *Fajans*, *Russell*, and *Soddy* predicted in 1913 that the decay of UI ($^{238}U$) to UII ($^{234}U$) must take place through an isotope of thorium and the then unknown element 91. *Fajans* and *Göhring* [1] later found this intermediate ($UX_2$ = $^{234m}Pa$)

[1] *K. Fajans* and *O. Göhring*, Naturwissenschaften *1*, 339 (1913).

and, because of its short half-life of 1.2 min, gave it the name "Brevium". In 1918, *Hahn* and *Meitner*[2] isolated a long-lived isotope of $UX_2$ from pitchblende residues and, because it is the parent of actinium, called it "protoactinium". This name was later changed to protactinium, and has been accepted internationally. With the discovery of UZ, the ground state of $^{234}Pa$, *Hahn* discovered the first example of nuclear isomerism[3].

The first chemical investigations with macroscopic amounts of protactinium were carried out by *von Grosse* at the end of the 'twenties in *Hahn*'s Institute. A more detailed study was begun only during the second world war within the framework of the Manhattan Project. Numerous papers on protactinium also appeared from the 'thirties onwards from the Curie Laboratory of the Institut du Radium in Paris; thus, for example, *Haissinsky* and *Bouissières* demonstrated a lower valence state of protactinium, Pa(IV)[4]. However, it was only the isolation of 100 g of $^{231}Pa$ at Springfield and Harwell (England) in about 1960 that permitted the chemistry of this rare radioelement to be investigated on a broader basis. The growing interest devoted to this element both scientifically and technically is demonstrated by two symposia (Gatlinburg, 1963, and Orsay, 1965) dealing solely with its chemistry.

## 2. Isotopes and the Nuclear Chemistry of Protactinium

Fourteen isotopes of protactinium, with mass numbers ranging from 224 to 237, are known (Table 1). Only three are relatively important:

Table 1. Isotopes of protactinium [5].

| Mass number | Formation reactions | Formation cross-section $\sigma_{max}$ [mb] (at E [MeV]) | Half-life | Mode of decay [a] | Decay energy [MeV] | Capture ($\sigma_c$) and fission ($\sigma_f$) cross-section for thermal neutrons [b] |
|---|---|---|---|---|---|---|
| 224 | $^{232}Th(d,10n)$ | | 0.6 sec | α | $E_\alpha$ = 7.75 | |
| 225 | $^{232}Th(d,9n)$ | | 2.0 sec | α | $E_\alpha$ = 7.3 | |
| | $^{232}Th(p,8n)$ | | | | | |
| 226 | $^{232}Th(\alpha,p9n)$ | | 1.8 min | α | $E_\alpha$ = 6.81 | |
| 227 | $^{232}Th(d,7n)$ | 18 (47—54) | 38.3 min | α: 15 % | $E_\alpha$ = 6.294—6.526; 11 lines | |
| | $^{232}Th(p,6n)$ | 48 (72—85) | | E.C.: 85 % | strongest line (49.5 %) = 6.46 | |
| 228 | $^{232}Th(d,6n)$ | | 22 h | α: 2 % | $E_\alpha$ = 5.707—5.138; 27 lines | |
| | $^{232}Th(p,5n)$ | | | E.C.: 98 % | $E_\gamma$ = 0.06—1.89 | |
| 229 | $^{232}Th(d,5n)$ | | 1.4 d | α: 0.25 % | $E_\alpha$ = 5.315—5.665; 13 lines | |
| | $^{230}Th(d,3n)$ | | | E.C.: 99 % | | |
| 230 | $^{232}Th(p,3n)$ | 500 (22—29) | 17d | $\beta^-$ (10 %) | $E_{\beta(max)}$ = 0.410 | $\sigma_c$ = 21.4 |
| | $^{232}Th(d,4n)$ | 90 (< 40) | | E.C.: 90 % | $E_\gamma$ = 0.053—1.010 | $\sigma_f$ = 1500 ± 250 |
| | $^{232}Th(\alpha,p5n)$ | | | α: 0.003 % | | |
| | $^{230}Th(p,n)$ | | | $\beta^+$ (0.03 %) | | |
| | $^{230}Th(d,2n)$ | | | | | |
| | $^{231}Pa(n,2n)$ | | | | | |
| | $^{231}Pa(p,pn)$ | | | | | |
| | $^{231}Pa(d,p2n)$ | | | | | |
| | $^{233}U(d,\alpha n)$ | | | | | |
| | $^{233}U(d,\alpha n)$ | | | | | |
| 231 | U-235-family | | 32480a ± 260a | α | $E_\alpha$ = 4.660—5.042; 10 lines | |
| | $^{230}Th(n,\gamma)^{231}Th \xrightarrow{\beta^-}$ | | 32800a | | 26 % with 5.006 | $\sigma_f$: 200 ± 15 |
| | $^{232}Th(n,2n)$ | | | | $E_\gamma$ = 0.019—0.356 | $\sigma_f$: 0.01 ± 0.005 |
| 232 | $^{232}Th(d,2n)$ | | 1.31 d | $\beta^-$ | $E_{\beta(max)}$ = 0.320 (98 %) | $\sigma_c$: 760 ± 100 |
| | $^{232}Th(p,n)$ | 28.6 (> 26) [b] | | | $E_\gamma$ = 0.04—1.153 | $\sigma_f$: 700 ± 100 |
| | $^{232}Th(\alpha,p3n)$ | | | | | |
| | $^{232}Th + {}^6Li$ | 170 (37 and 46) | | | | |
| | $^{232}Th + {}^7Li$ | 100 (50) | | | | |
| | $^{231}Pa(d,p)$ | | | | | |
| | $^{231}Pa(n,\gamma)$ | | | | | |
| 233 | $^{232}Th(n,\gamma)^{233}Th \xrightarrow{\beta^-}$ | | 27.4 d | $\beta^-$ | $E_{\beta(max)}$: 0.568 (5 %) | $\sigma_c$: 59 ± 4 |
| | $^{232}Th(d,n)$ | 40 (10—16) | | | 0.256 (57 %) | $\sigma_c$: 29 to Pa-234m |
| | $^{232}Th(\alpha,p2n)$ | 22 (> 46) [b] | | | 0.140 (38 %) | 20 to Pa-234 |
| | | | | | $E_\gamma$ = 0.016—0.416 | $\sigma_f$: < 0.1 |
| $234^m(UX_2)$ | U-238-family | | 1.18 min | $\beta^-$ (99.82 %) | $E_{\beta(max)}$: 2.290 (98 %) | $\sigma_f$ < 500 |
| | | | | IT (0.18 %) | $E_\gamma$ = 0.043—1.83 | |
| 234 (UZ) | U-238-family | | 6.7 h | $\beta^-$ | $E_\beta$ = 0.16—1.2 | $\sigma_f$ < 5000 |
| | $^{232}Th(\alpha,pn)$ | 22 (37—46) | | | $E_\gamma$ = 0.043—1.68 | |
| 235 | $^{232}Th(\alpha,p)$ | | | | | |
| | $^{234}Th(n,\gamma)^{235}Th \xrightarrow{\beta^-}$ | | 23.7 min | $\beta^-$ | $E_{max}$: 1.4 | |
| | $^{238}U(d,\alpha n)$ | 2 (19) | | no γ | | |
| | $^{238}U(p,\alpha)$ | 0.03 (9.5) | | | | |
| | | 21 (340) [b] | | | | |
| 236 | $^{238}U(d,\alpha)$ | | 12.5 min | $\beta^-$ | $E_{\beta(max)}$ = 3.35 | |
| 237 | $^{238}U(d,2pn)$ | | 10.5 min (?) | $\beta^-$ | | |
| | $^{238}U(\gamma,p)$ | | 39 min | | | |

[a] IT = Isomeric transition; E.C. = electron capture. [b] Not $\sigma_{max}$.

[2] *O. Hahn* and *L. Meitner*, Physik. Z. *19*, 208 (1918).

[3] *O. Hahn*, Naturwissenschaften *9*, 84 (1921).

[4] *M. Haissinsky* and *G. Bouissières*, C. R. hebd. Séances Acad. Sci. *226*, 573 (1948).

[5] A review of protactinium isotopes is given by *E. K. Hyde*, *I. Perlman*, and *G. T. Seaborg*: The Nuclear Properties of the Heavy Elements. Prentice Hall, Englewood Cliffs 1964, Vol. II, p. 693.

$^{231}$Pa is the only isotope of Pa having a sufficiently long half-life to allow work with weighable amounts. To obtain this isotope, we must still, in essence, resort to the working up of residues from the production of uranium. Later, it may also be profitable to isolate the $^{231}$Pa formed by the reaction

$$^{232}\text{Th(n,2n)}^{231}\text{Th} \xrightarrow{\beta^-} {}^{231}\text{Pa}$$

from the residues of the reprocessing of $^{232}$Th-$^{233}$U (Table 2).

Table 2. Calculated composition of a sample of Th (100 g) after irradiation in $\Phi$ (thermal) = 5 $10^{14}$ n/cm$^2$sec, $\Phi$ (epithermal) = $^1/_{12}$ $\Phi$ (thermal) for 28 days (total flux = 1.2 $10^{21}$ n/cm$^2$) [10, 11].

| | |
|---|---|
| $^{232}$Th: | 98.6 g |
| $^{231}$Pa: | 1 mg |
| $^{233}$Pa: | 950 mg |
| $^{233}$U: | 320 mg |
| $^{234}$U: | 65 mg |
| $^{235}$U: | 5 mg |
| fission products: | 60 mg |

The threshold energy of the $^{232}$Th(n,2n) reaction is 6.35 MeV [6], and the effective $^{232}$Th(n,2n)$^{231}$Th cross-section for neutrons with the energy distribution of the fission spectrum is 12.4 ± 0.6 mbarn [7]. The fission threshold for $^{231}$Pa is 0.4 MeV. The effective fission

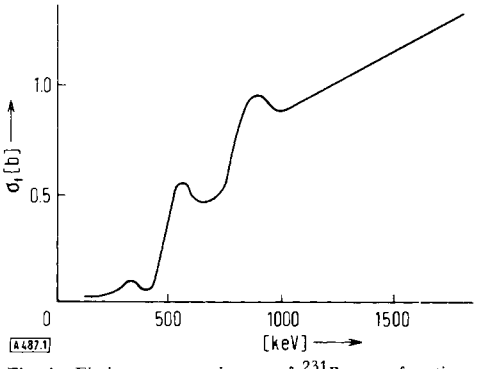


Fig. 1. Fission cross-section $\sigma_f$ of $^{231}_{91}$Pa as a function of the neutron energy.

cross-section increases markedly with increasing neutron energy (Fig. 1) [8]. The half-life of spontaneous fission of $^{231}$Pa is $1.1\times10^{16}$ years [9], which corresponds to 0.3 disintegrations by spontaneous fission per gram per minute.

$^{233}$Pa is an intermediate in the breeding of $^{233}$U from $^{232}$Th according to

$$^{232}\text{Th(n,}\gamma)^{233}\text{Th} \xrightarrow[22.4\ \text{min}]{\beta^-} {}^{233}\text{Pa} \xrightarrow[27.0\ \text{d}]{\beta^-} {}^{233}\text{U}.$$

It is frequently used as a tracer nuclide in chemical investigations.

Because of its short half-life, $^{234m}$Pa is used for demonstrating rapid radiochemical separations [12].

## 3. X-Ray Spectrum and Electronic Configuration of Protactinium

In the X-ray spectrum of $^{231}$Pa, *von Grosse et al.* found 21 lines of the L-series ($\lambda = 586.6\times10^{-11}$ to $1088.5\times10^{-11}$ cm) and 14 lines of the M-series ($\lambda = 252.2\times10^{-11}$ to $518.2\times10^{-11}$ cm) [13–15]. The emission lines at 3957.8 and 4090.1 Å are the most suitable for the spectrographic determination of $^{231}$Pa [14].

According to the "actinide hypothesis", protactinium should possess two 5f electrons. However, the change in atomic radii with atomic number [16] and the Pa–O distance in PaO [17] suggest indirectly a filling of the 6d shell. This finding agrees with calculations of *Cap* [18] on the energies of the 5f and 6d configurations. *Roof* [19] also found no indications of 5f electrons from an analysis of the X-ray absorption coefficients, whereas *Couchois* [20] concluded from irregularities in the X-ray absorption coefficients – in agreement with theoretical considerations due to *Friedel* [21] – that both 5f and 6d electrons are present in Th, Pa, and U. On the other hand, *Jørgensen* [22] showed that the absorption spectrum of Pa(IV) indicates the presence of one 5f electron. A 5f arrangement can also be deduced from the energy of the electron level in a $^{233}$Pa beam [23] and from optical and magnetic investigations on Pa(IV)-doped $Cs_2ZrCl_6$ [24, 25]. The occupancy of the 5f and 6d orbitals of Pa is thus still uncertain. Because of the small differences in energy of the two electron configurations, an easy 5f–6d-transition seems possible.

## 4. Preparation of Pure $^{231}$Pa and $^{233}$Pa

### 4.1. Enrichment and Purification of $^{231}$Pa from Waste Products of the Production of Uranium

As a secondary decay product of $^{235}$U, $^{231}$Pa occurs in uranium minerals in about the same amount as radium (equilibrium concentration 0.3 ppm). The first pure


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specimen of Pa was prepared by *von Grosse* in 1927 [26]. From a Pa concentrate (6 mg of $^{231}Pa$ in 525 g) prepared by *Hahn* and *Meitner* [27], *von Grosse* isolated 2 mg of $^{231}Pa_2O_5$. Using a process based only on precipitation methods, in the following years *von Grosse* and *Agruss* [28] obtained 100 mg of pure $^{231}Pa_2O_5$ from 1000 kg of residues (60 % $SiO_2$) of the processing of Joachimsthal uranium ore. The main step in the separation process was the elimination of the $SiO_2$ by an alkali hydroxide fusion and leaching out of the resulting silicate with water. The $^{231}Pa$ was enriched by several $ZrP_2O_7$ precipitations; Zr and Pa were separated by repeated fractional crystallization of $ZrOCl_2$ from 25 % hydrochloric acid.

After 1945, several processes were developed for obtaining weighable amounts of $^{231}Pa$ [29–35]. Coprecipitation processes were always used for the initial enrichment of Pa present in the ppm range, while preliminary and final purifications were carried out mainly with extraction or ion-exchange processes. According to a Russian process [29], more than 95 % of the Pa is coprecipitated with $MnO_2$ from > 1 M $HNO_3$. In a French process [30], Pa(V) is reduced to Pa(IV) with Zn amalgam and is then precipitated as $PaF_4$. In a process of the Mound Laboratories [31], the enrichment of Pa is carried out *via* the precipitation of titanium phosphate.

Between 1950 and 1960, more than 100 g of $^{231}Pa$ was obtained from wastes of the production of uranium at Springfield in England [32–33]. The starting material was about 40 tons of residues from the isolation of uranium (ethereal sludge) containing about 3 ppm of Pa. The residues were leached with cold 4 N nitric acid (2 liters/kg). The uranium was extracted from the resulting solution with tributyl phosphate, and the addition of ammonia then gave a hydroxide precipitate which was dissolved to give a solution 1 N in hydrochloric acid. On addition of aluminum chloride a precipitate was formed containing 75 % of the original Pa. The precipitated product was digested with warm 30 % sodium hydroxide (removal of Al, Si, P) and was then dissolved in concentrated hydrochloric acid. Extraction with diisobutyl ketone separated 95 % of the Pa from the solution, and back-extraction of the organic phase with 8 N HCl + 0.5 N HF led to 52.4 liters of solution with a total of 108.2 g of $^{231}Pa$. Final purification was carried out by anion-exchange.

### 4.2. Separation of $^{233}Pa$ from Irradiated Thorium

Neutron-irradiated metallic thorium is dissolved in a mixture of concentrated HCl + 0.2 N HF. After the addition of borax or $AlCl_3$ (to mask the fluoride ions) the solution is transferred to a small column (height 55 mm, diameter 3 mm) containing an anion-exchange resin (Dowex-1) [36]. Pa, Zr, and Nb remain on the column; Th is not adsorbed. Zr is eluted with 6 N HCl and then Pa with 9 N HCl + 0.1 N HF. The Pa eluate is shaken with an equal volume of diisopropyl ketone, which extracts traces of Fe(III), Sn(IV), and Nb(V). After the addition of borax to the aqueous solution, Pa(V) is extracted with fresh diisopropyl ketone and is thus separated from U, Th, Ti, Zr, *etc.* After back-extraction into 2 N HCl, the Pa(V) is again adsorbed from 10 N HCl on a 3 mm×12 mm column of anion-exchange resin and is eluted with 2.7 N HCl. The first 3–6 drops contain more than 90 % of the original $^{233}Pa$.

Other methods for the purification of $^{233}Pa$ use either a coprecipitation of $^{233}Pa$ with $MnO_2$ [37, 38], $PbO_2$ or $SnO_2$ [39], $Nb_2O_5$ [40], $BaZrF_6$ [41], zirconium phosphate [42], zirconium mandelate [43], or zirconium iodate [42,44], or extraction methods – *e.g.*, extraction with tertiary amines [45], with thionyltrifluoroacetone (TTA) [46,47], with tributyl phosphate (TBP) [48] or tributylphosphine oxide [49], or with branched ketones and alcohols [50].

The separation of Pa from Th by coprecipitation with $MnO_2$ has been used by *Codding et al.* [10,11] to obtain 1 g of $^{233}Pa$ (*ca.* $2\times10^4$ curie) from 200 g of irradiated metallic Th. Here the last purification step was the precipitation of Pa periodate. The heat developed by the pure preparation was sufficient to dry it and to partially decompose the periodate.

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## 5. Chemistry of Protactinium in Aqueous Solutions

### 5.1. Ionic Species in Aqueous Solution

Similarly to the chemistry of niobium and tantalum, that of aqueous quinquevalent protactinium is very complicated, apart from solutions in hydrofluoric and sulfuric acids. It is impossible in practice to obtain solutions of Pa(V) which remain stable for a long period and do not gradually undergo unpredictable changes, even in concentrated hydrochloric, nitric, or perchloric acid. This instability can be observed both in solutions of tracer amounts of $^{233}Pa$ and in solutions containing millimole amounts of $^{231}Pa$. In general, the instability increases with increasing concentration of Pa. Consequently, it is now believed that the irreversible changes are due not to hydrolysis, but to condensation reactions [51]:

$$\gtrless Pa\text{-}OH + X^- \underset{\text{reversible}}{\rightleftharpoons} \gtrless Pa\text{-}X + OH^-$$

$$\downarrow\uparrow$$

$$\left[\gtrless Pa\text{-}O\text{-}Pa\lesssim\right]_n : \text{reversible for } n < 4$$

$$\downarrow$$

$$\left[\gtrless Pa\text{-}O\text{-}Pa\lesssim\right]_n : \text{irreversible for } n > 4$$

The re-conversion of the condensed species into the hydroxyl-containing species, which alone are capable of forming complexes by exchange reactions, takes place only slowly, and this explains, for example, why the partition equilibrium in the extraction of Pa(V) with 0.03 M trilaurylamine in diethylbenzene [52] or with 0.1 M 8-hydroxyquinoline in chloroform [53] is still far from being established after several days.

From extraction investigations in the two-phase system Pa(V), $(Li,H)ClO_4/TTA,C_6H_6$, *Guillaumont* [54–57] concluded that in the case of tracer concentrations of $^{233}Pa$ in 1–3 N $H^+$ solutions of Pa(V), the ion $Pa(OH)_3^{2+}$ or $PaO(OH)^{2+}$ is present, and this is hydrolysed to $Pa(OH)_4^+$ or $PaO(OH)_2^+$ at higher pH. From the extraction data, the hydrolysis constant $K_1$ of $Pa(OH)_3^{2+}$ (Fig. 2) was found to be:

$$K_1 = [Pa(OH)_4^+]\,[H^+]\,[Pa(OH_3)_3^{2+}]^{-1} = 9\times10^{-2} \text{ mole/l (at 25 °C).}$$

In contrast, the situation in hydrofluoric acid solutions of Pa(V) is very simple. Raman spectra show that the complex ions $PaF_6^-$ and $PaF_7^{2-}$ present in crystalline double fluorides are also present in hydrofluoric acid solutions [58]. The conductometric titration of $Pa_2O_5 \cdot aq$ with hydrofluoric acid demonstrates the presence of all the intermediate members of the series $PaF^{4+}$ to $PaF_8^{3-}$.

[51] *A. P. Maddock*, see [10].

[52] *D. O. Campbell*, see [10].

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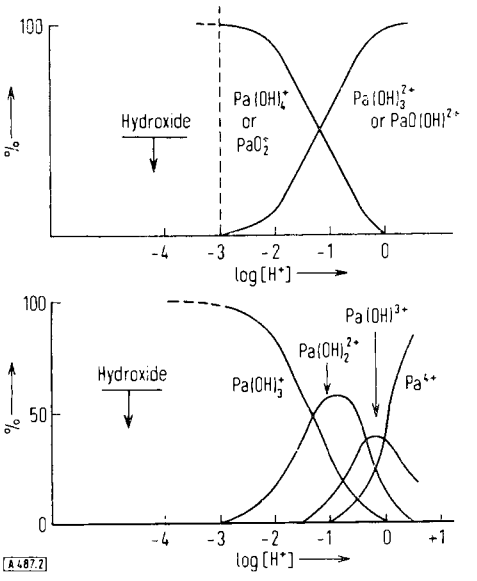


Fig. 2. Hydrolysis of $Pa(OH)_3^{2+}$ (top) and $Pa^{4+}$ (bottom) as a function of the acid concentration at 3 M $(Li,H)ClO_4$.

On the other hand, in mineral acid solutions Pa(IV) behaves as a true actinide(IV) ion. The hydrolysis of $Pa^{4+}$ takes place stepwise (Fig. 2) through $Pa(OH)^{3+}$ (hydrolysis constant $K_{1,1} = 0.725$) and $Pa(OH)_2^{2+}$ ($K_{1,2} = 0.302$) to $Pa(OH)_3^+$ ($K_{1,3} = 0.017$), before $Pa(OH)_4$ precipitates.

Stability constants for $Pa(OH)_3^{2+}$ and $Pa^{4+}$ can be determined from the change in the partition coefficients on the addition of complexing agents (Table 3).

Table 3. Stability constants K of Pa(V) and Pa(IV), determined from the change in the partition coefficients in the extraction of Pa with thionyltrifluoroacetone (TTA) in the presence of complexing agents [55]. Ionic strength 3 M.

| Pa(V) | | Pa(IV) | |
|---|---|---|---|
| Complex [a] | K | Complex | K [b] |
| $Pa(OH)_3Cl^+$ | 1.2 | $PaCl^{3+}$ | 1 |
| $Pa(OH)_2SO_4^+$ [c] | 20 | $PaCl_2^{2+}$ | 1 |
| $Pa(OH)_2(SO_4)_2^-$ | 320 | $PaSO_4^{2+}$ | 42 |
| $Pa(OH)_2(C_2O_4)^+$ | 150 | $Pa(SO_4)_2$ | $1.53\times10^2$ |
| $Pa(OH)_2(C_2O_4)_2^-$ | $5\times10^4$ | $PaF^{3+}$ | $5.35\times10^4$ |
| $Pa(OH)_2F^{2+}$ | $3.6\times10^3$ | $PaF_2^{2+}$ | $1.8\times10^8$ |
| $Pa(OH)_2F_2^+$ | $4.5\times10^7$ | | |
| $Pa(OH)_2F_3$ | $8\times10^{10}$ | | |

[a] Formulation as an oxygen complex, *e.g.* $PaOSO_4^+$, cannot be excluded.

[b] For the reaction $Pa^{4+} + nXm^- \rightleftharpoons PaXn^{(4-nm)+}$.

[c] For the reaction $Pa(OH)_3^+ + HSO_4^- \rightleftharpoons Pa(OH)_2SO_4^+ + H_2O$.

In this way it has been shown that the tendency of $Pa^{4+}$ towards complex formation is greater than that of $Pa(OH)_3^{2+}$ but smaller than that of $Zr^{4+}$. The values for $Pa^{4+}$ fit well into the sequence for the corresponding actinide(IV) complexes.

### 5.2. The Extraction Behavior of Protactinium

Numerous papers have been published on the extraction of quinquevalent protactinium, but little information is available on Pa(IV). From the available investigations on the chemistry of Pa(IV) in solution, it must be

concluded that there are at most only minor differences between Pa(IV) and Th(IV) or U(IV).

In addition to phosphoric acid esters and to amines, which are universal extractants, long-chain branched ketones and alcohols are the best and most specific extracting agents for Pa(V). On the other hand, ethers and carboxylic esters extract Pa(V) extremely poorly. The highest partition coefficients and the best reproducibilities are obtained in extraction from hydrochloric acid solutions. Small amounts of sulfuric acid markedly depress the partition coefficients, except in the case of amines. In nitric or perchloric acid solutions, Pa(V) is hydrolysed readily to polymeric species, which explains the discordant results of different authors. The presence of complexing agents and of $H_2O_2$ substantially prevents the extraction of Pa(V), and extraction is not possible in the presence of fluoride ions.

### 5.2.1. Extraction with Esters of Phosphoric Acid

When undiluted tri-n-butyl phosphate (TBP) is used, the partition coefficient $K_D$ increases with increasing concentration of hydrochloric acid in the aqueous phase [48,59]; in 5 N HCl $K_D \approx 40$, in 8 N HCl $K_D \approx 4.5\times10^3$, and in 12 N HCl $K_D \approx 10^5$. The partition coefficients decrease with increasing dilution of the TBP (*e.g.* with benzene) [60,61]. They are constant over a wide range of Pa(V) concentrations. From the constancy of $K_D$ with time, it must be concluded that $10^{-4}$–$10^{-6}$ M solutions of Pa(V) in *ca.* 3 N $HNO_3$ are stable at 21 °C for at least 100 hours. In 1 N $HNO_3$, on the other hand, $K_D$ decreases rapidly with time, and about 95 % of the Pa(V) is hydrolysed after 3 days [62]. In the extraction of various metal ions with 20 % TBP/kerosine from 2 N $HNO_3$, the partition coefficients decrease in the sequence U(VI) > Np(VI) > Pu(IV) > Pu(VI) > Th(IV) > Np(IV) > Pa(V) > Zr(IV) > Md(III).

Contamination of the TBP with dibutyl phosphate – formed, for example, by hydrolysis or radiolysis of the P–O–C bond – raises $K_D$ markedly; thus, for purified TBP (30 % in kerosine) from 6 N $HNO_3$ $K_D \approx 2.6$, while for TBP containing $10^{-2}$ M of dibutyl phosphate, $K_D \approx 50$ [60].

High partition coefficients for Pa(V) are also exhibited by the mono- and, in particular, the dialkyl esters of phosphoric acid (frequently called liquid cation-exchangers) and by phosphonic esters [60,63–66]. In the extraction of Pa(V) with di-n-octyl phosphate (HX) [*] from hydrochloric acid solution, extraction of $ClO(HX_2)PaX_2Pa(HX_2)OCl$ has been inferred from the distribution curve [67].

### 5.2.2. Extraction with Amines

Amines, frequently called liquid anion exchangers, possess the advantage that extraction is possible even from sulfuric acid solution. With approximately equal numbers of carbon atoms in the amine, $K_D$ decreases in the sequence primary amine > secondary amine > tertiary amine. The partition coefficients depend markedly on the structure of the amine. For example, aromatic groups or double bonds in the carbon chain considerably increase $K_D$ [68]. The type of organic diluent for the amines is not without influence in this connection, *e.g.* $K_D$ for 5 % tributylamine increases with the logarithm of the dielectric constant of the diluent [69]. No radiation effects on the extraction of Pa(V) have been observed for a secondary amine up to a dose of $5\times10^7$ r of $^{60}Co$ γ-radiation [70].

The partition coefficients decrease with increasing concentration of sulfuric acid in the aqueous phase [68,69,71]. Two different slopes of the extraction curves with a break at 7–9 M $H_2SO_4$ have been obtained. In extraction with tribenzylamine in the range 0.4–0.9 M $H_2SO_4$, the extracted Pa(V) sulfato complex contains 2 molecules of amine per Pa atom [72].

Nitrobenzene and benzonitrile have no advantages over ketones as extractants; more than 95 % extraction of Pa(V) takes place only from 7.5 or 8.5 N HCl [69].

While Pa(V) is quantitatively extracted with 5 % tri-n-octylamine from about 6 N HCl, Pa(IV) passes into the organic phase to the extent of more than 95 % only from 10 N HCl [73].

### 5.2.3. Extraction with Alcohols and Ketones

The partition coefficient of Pa(V) increases with increasing acid concentration of the aqueous phase, and, at constant concentration of the acid, they are larger from hydrochloric acid than from nitric acid. At a constant HCl concentration, $K_D$ increases with the concentration of chloride ions. Extraction from HBr solution takes place only at higher acid concentrations than from HCl solution. The extracted Pa(V) species has a solvation number of three in diisobutyl ketone and diisopropyl ketone [74], and only two in amyl acetate and TBP [60]. Under otherwise identical conditions, $K_D$

[59] *H. L. Scherff* and *G. Hermann*, Z. Elektrochem. *64*, 1022 (1960).

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[61] *S. Shankar*, *K. S. Venkateswarlu*, and *C. Copinathan*, J. inorg. nuclear Chem. *25*, 57 (1963).

[62] *C. J. Hardy* and *D. Scargill*, Proceedings of the Protactinium Chemistry Symposium Gatlinburg/Tenn. (U.S.A.), Report TID-7675 (1963), p. 1.

[63] *V. B. Sherchenko*, *V. A. Mikhailov*, and *Y. P. Zavalskii*, Zh. neorg. Khim. *3*, 1955 (1958).

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[65] *J. M. Chilton*, see [62], p. 15.

[66] *F. E. Butler*, Analytic. Chem. *37*, 340 (1965).

[*] Present in benzene solution as the dimer ($H_2X_2$).

[67] *G. W. Mason*, *C. Andrejasich*, *S. Lewey*, and *D. F. Peppard*, see [10].

[68] *D. O. Campbell*, see [62], p. 87.

[69] *A. G. Gobble* and *A. G. Maddock*, J. inorg. nuclear Chem. *7*, 94 (1958).

[70] *F. Ichikawa* and *S. Uruno*, Bull. chem. Soc. Japan *33*, 569 (1960).

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[72] *R. Muxart*, *R. Guillaumont*, and *H. Arapaki-Stapelias*, see [10].

[73] *G. Bouissières*, *C. Ferradini*, *M. Garçon*, *R. Guillaumont*, *M. Hussonois*, *R. Muxart*, *H. Pezerat*, *D. Robertson*, and *T. Stchouzkoy*, see [62], p. 160.

[74] *A. G. Goble*, *J. Golden*, and *A. G. Maddock*, Canad. J. Chem. *34*, 284 (1956).

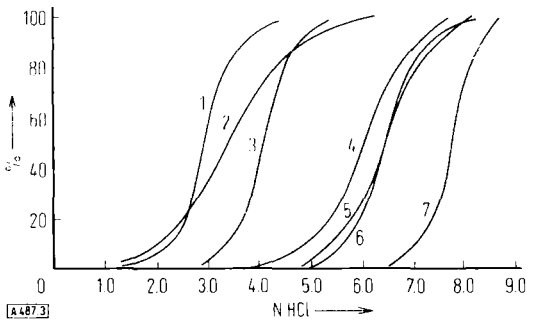


Fig. 3. Percent extraction of tracer amounts of protactinium from hydrochloric acid solution with various solvents as a function of HCl concentration.

1. Diisopropylmethanol
2. Tributyl phosphate
3. Acetophenone
4. 5 % trilaurylamine in benzene
5. Di-(β-chloroethyl) ether
6. Benzonitrile
7. Nitrobenzene

decreases in the sequence mesityl oxide > diethyl ketone > acetophenone > methyl n-hexyl ketone > diisobutyl ketone > diisopropyl ketone (Fig. 3)[69,74]. From the change in $K_D$ on the addition of fluoride or oxalate, the following sequence of complex-forming tendencies has been established[69,75]:

with respect to fluoride: Pa, Zr > Nb > Ta

with respect to oxalate: Nb > Ta > Pa, Zr

Long-chain alcohols such as diisopropylmethanol[76,77] and diisobutylmethanol[59,76] also have good extraction properties for Pa(V). For the latter, no dependence of partition coefficient on the concentration of Pa(V) was found in the range $10^{-4}$–$10^{-14}$ M of Pa(V)[78].

### 5.2.4. Extraction as a Chelate

The chelate of Pa(V) with hydroxylamine derivatives [such as cupferron (ammonium salt of *N*-nitrosophenylhydroxylamine) and *N*-benzoyl-*N*-phenylhydroxylamine] can be extracted with various organic solvents over a wide range of experimental conditions[38,79–82]. Tartrate and citrate do not interfere with the extraction, and oxalate does so only slightly, while fluoride ions prevent extraction. Extraction with high yield also takes place with salicylic acid at pH 4 from a solution saturated with $CaCl_2$, or with phenylarsonic acid from 0.1–9 M $H^+$ solution[83,84]. In the presence of 8-hydroxyquinoline, Pa(V) can be extracted at pH 3–9 by chloroform to the extent of more than 99.9 % (Fig.4)[53].

The rate of decrease in $K_D$ at pH > 9 shows that the extracted chelate is a dibasic acid.

The extraction of Pa(V) with thionyltrifluoroacetone (TTA or HX) has been investigated thoroughly. A 0.5 M solution of TTA in benzene extracts 80–90 % of Pa(V) from 1–10 N HCl [85]. From the decrease in $K_D$ in the sequence $ClO_4^- > NO_3^- > Cl^- > SO_4^{2-} > F^-$ it may be concluded that the complex-forming tendency

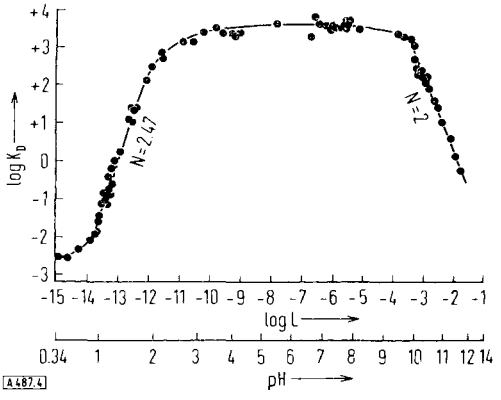


Fig. 4. Extraction of trace amounts of Pa(V) with 0.1 M 8-hydroxyquinoline in chloroform. (Ionic strength 0.1 M (Na,H) $ClO_4$; the partition coefficients were determined by back-extraction). L = concentration of the ionic form of the ligand. The N values on the curves denote the number of 8-hydroxyquinoline ligands per Pa atom.

of Pa(V) increases in this order. Four molecules of TTA are bound per Pa(V) atom in the range 0.5–3 N HCl, and three molecules in the range 0.5–0.015 N HCl. It is therefore concluded that the species $Pa(OH)_3X_2 \cdot 2\,HX$ and $Pa(OH)_4X \cdot 2\,HX$, respectively, are extracted[55,86,87]. In the extraction of Pa(V) from 3 N $HClO_4$ by a 1:1 solution of TBP and TTA in benzene, a synergistic effect has been observed. In this case the extracted species is $Pa(OH)_3X_2 \cdot 2$ TBP[103]. At TTA:TBP ≈ 10:1, however, $Pa(OH)_3X_2 \cdot HX \cdot$TBP is extracted. With > 0.3 M TTA/benzene, about 90 % of the Pa(IV) is extracted as $PaX_4$[88].

## 5.3. The Ion-Exchange Behavior of Protactinium

### 5.3.1. Anion Exchange

Above 3 M $H^+$, the extent of adsorption of Pa(V) from nitric acid and hydrochloric acid solutions on anion exchange resins increases with increasing concentration of the acid[89–93]. In the range 1–4 N $HNO_3$, *Nowikow*

[75] *R. A. Dyachkova* and *V. I. Spitsyn*, Ukr. fiz. Zh. *31*, 158 (1965).

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[82] *S. Y. Lyle* and *A. D. Shendrikav*, Talanta *12*, 573 (1965).

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[85] *M. Myassoedov* and *R. Muxart*, Bull. Soc. chim. France *1962*, 237.

[86] *F. Boulanger* and *R. Guillaumont*, Bull. Soc. chim. France *1964*, 3032.

[87] *R. Guillaumont*, Bull. Soc. chim. France *1965*, 132.

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[92] *C. Keller*, Radiochim. Acta *1*, 147 (1963).

[93] *J. Nowikow* and *G. Pfrepper*, Z. Naturforsch. *18b*, 993 (1963).

and *Pfrepper*[93] found Pa(V)–$NO_3^-$ complexes of composition 1:1 (formulated as $[PaO_x(OH)_yNO_3]$), 1:2($[PaO_x(OH)_y(NO_3)_2]$), and 1:4($[PaO_x(OH)_y(NO_3)_4]$) with stability constants $\beta_1 = 0.68$, $\beta_2 = 3.0$, and $\beta_4 = 11.93$ in 1 N $H^+$. In contrast to statements by *Hardy et al.*[60], most of these complexes appear to be anionic. Above 2 N $H^+$, Pa(V) is also adsorbed from HBr and HI solutions[92,94]; however, the distribution coefficients are two orders of magnitude smaller than in adsorption from hydrochloric acid, which permits the conclusion that the complex-forming tendency of Pa(V) with $Br^-$ and $I^-$ is smaller.

Small amounts of fluoride ions markedly depress the adsorption of Pa(V) from hydrochloric acid solution on anion exchange resins[95–98], a fact which is frequently used for the separation of Pa (*e.g.* in the separation of

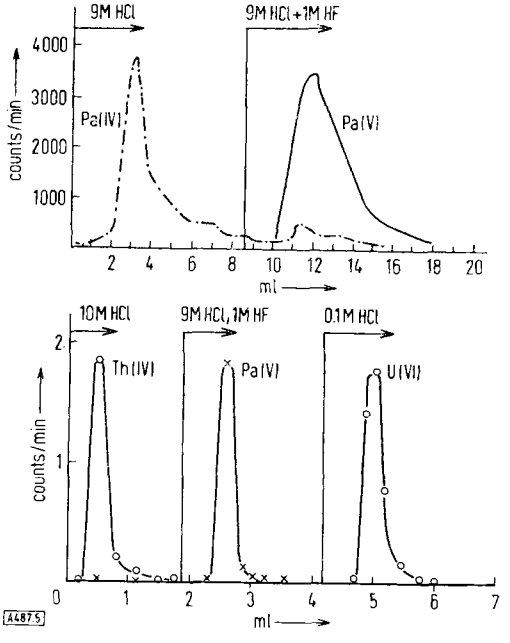


Fig. 5. Ion-exchange separations with Pa.

Top: separation of Pa(IV) and Pa(V) on Dowex 1 anion exchanger. Bottom: separation of Th(IV), Pa(V), and U(VI) on Dowex 1 anion exchanger.

Ordinate: relative activity.
Abscissa: eluate volumes [ml].

Nb, Ta, and Pa or of Pa(IV) and Pa(V), Fig. 5). The distribution coefficients in dilute pure hydrofluoric acid are very high (*ca.* $2\times10^4$ for 0.2 N HF) but decrease markedly with increasing HF concentration (*ca.* $10^2$ in 7 N HF)[92,99].

A similar decrease of $K_D$ with acid concentration is observed in sulfuric acid[71,90–92]. From the shape of the curve it follows that two Pa(V)–$SO_4^{2-}$ complexes exist, namely $[PaO(SO_4)_2]^-$ and $[PaO(SO_4)_3]^{3-}$. The preparation of $H_3PaO(SO_4)_3$ (stable up to about 350 °C, hexagonal with a = 9.743 Å, c = 5.506 Å, Z = 2) by evaporation of a Pa(V) solution containing HF and $H_2SO_4$, and of amorphous $HPaO(SO_4)_2$ and $HPaO_2SO_4$ by thermal decomposition of $H_3PaO(SO_4)_3$, confirms the assumptions on the species in the system Pa(V)-$SO_4^{2-}$[100]. The potassium salt of oxotrisulfatoprotactinic(V) acid, $K_3PaO(SO_4)_3$, had been prepared previously[101]. The corresponding selenato acid $H_3PaO(SeO_4)_3$ (hexagonal with a = 9.743 Å and c = 5.679 Å) has also been isolated[118]. No analogous double sulfates of Nb(V) and Ta(V) are known.

According to *Nowikow* and *Pfrepper*[93], in 1–2 M $H_2SO_4$ a small amount of a 1:1 complex ($[PaO_x(OH)_ySO_4]^-$ with $2x + y = 4$; $\beta_1 = 0.94$ at 1.0 N $H^+$) exists in addition to the Pa(V):$SO_4^-$ 1:2 complex ($\beta_2 = 7.39$ at 1.0 N $H^+$).

Pa(IV) is not adsorbed on anion exchangers from hydrochloric acid solutions[102]. In sulfuric and hydrofluoric acid solutions, too, Pa(IV) has only small $K_D$ values[92], consequently it resembles Th(IV) rather than U(IV).

### 5.3.2. Cation Exchange

The separation of the short-lived $^{234m}Pa$ from its parent $^{234}Th$ – adsorbed on a cation-exchange resin – is possible with the aid of a 5 % citrate solution at pH 2.5[12]. *Moskvin et al.*[103] have determined the stability constants of numerous chelates of Pa(V) with organic acids by ion-exchange processes. On comparing the stability constants of complexes of Pa(V) with inorganic and organic ligands (Tables 3 and 4), it can be seen that most organic complexing agents stabilize Pa(V) to

Table 4. Stability constants of complexes of Pa(V) with some organic acids at 0.25 M ionic strength, calculated from ion-exchange data. An accurate formulation of the individual complexes is not possible and only the Pa(V): complexing agent A ratio can be given [103].

| Acid | Composition Pa(V):A | K |
|---|---|---|
| Lactic | 1:1 | $1.7\times10^2$ |
| α-Hydroxyisobutyric | 1:2 | $3\times10^3$ |
| | 1:3 | $1.0\times10^7$ |
| Mandelic | 1:1 | $1.0\times10^3$ |
| Malic | 1:1 | $8.3\times10^2$ |
| | 1:2 | $5.3\times10^4$ |
| Tartaric | 1:1 | $2.2\times10^2$ |
| | 1:2 | $2.1\times10^4$ |
| Trihydroxyglutaric | 1:1 | $9.1\times10^2$ |
| | 1:2 | $7.7\times10^7$ |
| Oxalic | 1:1 | $3.6\times10^2$ |
| | 1:2 | $8.3\times10^5$ |
| Citric | 1:1 | $4.5\times10^3$ |
| | 1:2 | $8.3\times10^5$ |
| | 1:3 | $6.3\times10^8$ |
| Aconitic | 1:1 | $1.5\times10^2$ |
| Ethylenediaminetetraacetic | 1:1 | $1.5\times10^7$ |
| | 1:2 | $9.1\times10^{11}$ |


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[95] *F. Nelson, R. M. Rush*, and *K. A. Kraus*, J. Amer. chem. Soc. *82*, 339 (1960).

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[100] *K. W. Bagnall, D. Brown*, and *P. J. Jones*, J. chem. Soc. (London) *1965*, 176.

[101] *M. Haissinsky* and *G. Bouissières*, Bull. Soc. chim. France *1957*, 557.

[102] *E. Pluchet* and *R. Muxart*, Bull. Soc. chim. France *1961*, 372.

[103] *A. J. Moskvin, J. Geleceanu*, and *A. V. Lapickij*, Dokl. Akad. Nauk SSSR *149*, 611 (1963).

about the same extent as sulfuric acid, while ethylenediaminetetraacetic acid binds Pa(V) ions in complexes about as strongly as hydrofluoric acid. On the other hand, chloride and nitrate ions are only very weak complexing agents for Pa(V). The stability constants increase with increasing ratio of complexing agent to Pa(V) in the complex, *i.e.* the concentration of free Pa(V) ions in the solution decreases.

### 5.4. Paper Chromatography and Ionophoresis

Paper-chromatographic separation of Pa(V) from other elements is possible practically only with solvents containing HF. Thus *Vernois* [104] obtained a satisfactory separation of Nb, Ta, and Pa with a mixture of HCl, HF, and butanol. In solvents free from hydrofluoric acid, no satisfactory separations are obtained because of hydrolysis of Pa(V) [105, 106]. From the migration of Pa(V) in alkaline solvents, *Jakovac* and *Lederer* [107] have inferred the existence of a protactinate anion. Satisfactory separations can also be obtained on Dowex-50 ion-exchange paper [108].

It follows from ionophoretic investigations [109] that Pa(V) is present completely as an anion in 0.6 N HCl + 2 N HF. On the other hand, in hydrochloric acid both cationic species have been detected [61], the proportion of anions increasing with increasing HCl concentration.

### 5.5. Spectrophotometry of Protactinium

"True" solutions of pentavalent protactinium in hydrochloric acid possess an absorption band at about 210 mμ with $\varepsilon \approx 10^4$ [35, 110–113]. In the course of the ageing process (hydrolysis), this band disappears and simultaneously a new band appears at 260 mμ which is ascribed to hydrolysed species. In sulfuric acid solutions of Pa(V), the absorption band migrates from 206 mμ to 222 mμ with increasing sulfuric acid concentration [71]. From the shift and the change in the intensity of the absorption bands of Pa(V) in dilute hydrofluoric acid, *Mirandi* and *Muxart* [114] deduced the existence of at least four Pa–F species.

The first reliable data on the absorption spectra of Pa(IV) were due to *Fried* and *Hindman* [115]. These authors dissolved pure $PaCl_4$ in oxygen-free 1 N HCl and obtained an absorption spectrum with bands at 276 mμ, 255 mμ, and 223.8 mμ which very closely resembles that of Ce(III). The absorption bands of Pa(IV) in other mineral acids differ from those in hydrochloric acid only by their somewhat different positions and intensities [116–118]. As can be shown spectrophotometrically, aqueous solutions of Pa(IV) are stable only in the presence of an excess of reducing agents. The rate of oxidation of Pa(IV) in hydrofluoric acid solution is first order with respect to Pa(IV). Daylight and particularly ultraviolet light markedly accelerate the oxidation [117].

### 5.6. Electrochemistry of Protactinium

#### 5.6.1. Standard Electrode Potential, Redox Potential

The standard potential of the Pa/Pa(V) electrode has not yet been determined. From measurements of the rate of displacement of metallic protactinium from solutions of various concentrations ($10^{-4}$–$10^{-11}$ M) by various metals – a method first used by *Hevesy* and *Paneth* – it has been concluded [119] that the standard potential of the Pa/Pa(V) couple in hydrofluoric acid solution is about −1.0 v. According to *Haissinsky* and *Pluchet*, the redox potential Pa(IV) → Pa(V) + $e^-$ is 0.25 ± 0.03 v [120].

#### 5.6.2. Electrochemical Deposition on Metals

In trace amounts, Pa deposits spontaneously on numerous metal surfaces and on $PbO_2$, particularly from hydrofluoric and sulfuric acid solutions [121, 122]. On lead its deposition follows a Langmuir isotherm; it is assumed that in deposition from hydrofluoric acid solutions, a layer of $PaF_4$ or $PbPaF_7$ is formed on the lead surface. The diffusion constant of the Pa particles in the deposition process is 0.12 $cm^2$/day [123], whereas a value of 0.62 $cm^2$/day has been found [124] from polarographic investigations.

Quantitative cathodic deposition of trace amounts of Pa on stainless steel plates is possible from solutions in 0.2 M $NH_4F$, 0.015 M $NH_4F$ + 0.25 M $NH_4Cl$, or


[104] *J. Vernois*, J. Chromatogr. *1*, 52 (1958).

[105] *M. Lederer*, J. Chromatogr. *1*, 172 (1958).

[106] *C. Keller*, J. Chromatogr. *7*, 535 (1962).

[107] *Z. Jakovac* and *M. Lederer*, J. Chromatogr. *1*, 291 (1958).

[108] *M. Lederer*, J. Chromatogr. *2*, 210 (1959).

[109] *J. Vernois*, J. Chromatogr. *2*, 155 (1959).

[110] *A. T. Casey* and *A. G. Maddock*, J. inorg. nuclear Chem. *10*, 58 (1959).

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[115] *S. Fried* and *J. C. Hindman*, J. Amer. chem. Soc. *76*, 4863 (1954).

[116] *D. Brown* and *R. G. Wilkins*, J. chem. Soc. (London) *1961*, 3804.

[117] *M. Haissinsky*, *R. Muxart*, and *H. Arapaki*, Bull. Soc. chim. France *1961*, 2248.

[118] *C. F. de Miranda* and *R. Muxart*, Bull. Soc. chim. France *1964*, 2174.

[119] *C. Ferradini*, J. Chim. physique *53*, 714 (1956).

(120] *M. Haissinsky* and *E. Pluchet*, J. Chim. physique *59*, 608 [1962).

[121] *M. Camarcat*, *G. Bouissières*, and *M. Haissinsky*, J. Chim. physique *46*, 153 (1949).

[122] *C. Ferradini* and *M. Haissinsky*, J. Chim. physique *53*, 722 (1956).

[123] *O. Gautsch*, Atompraxis *7*, 101 (1961).

[124] *C. Ferreira de Mirando* and *A. G. Maddock*, J. inorg. nuclear Chem. *24*, 1623 (1962)

0.02 M $H_2C_2O_4$ + 0.06 M $HNO_3$, at a current density of about 160 mA/cm². A firmly adherent layer is formed even with the (recommended) codeposition of 50 μg of $U_{nat}$ [125]. However, other authors [126–128] have obtained deposition yields of only 80–95 % except at the expense of extremely long times of deposition.

#### 5.6.3. Polarography of Protactinium

In 3.8 M fluoride solution (pH 7.2; $10^{-3}$–$10^{-4}$ M Pa) two irreversible polarographic waves at −1.29 v and at −1.56 v (referred to a saturated calomel electrode) have been found [124]. The first can be ascribed to the reduction of the Pa(V)-fluoro complex to the corresponding Pa(IV) complex, and the second to the reduction Pa(IV) → Pa(III). The height of the first wave is proportional to the concentration of Pa. In $F^-$-free Pa(V) solutions, only one irreversible wave is found, which is due to the reduction Pa(V) → Pa(IV).

## 6. Behavior of Protactinium in Molten Salts

In concentrations of 1–2 p.p.b. or 50–75 p.p.m. Pa(V) is precipitated from a LiF–$BeF_2$–$ThF_4$ melt (67:18:15 mole-%) by the addition of 1–2 % of solid BeO or $ThO_2$, respectively. The Pa(V) is adsorbed on the surface of the BeO or $ThO_2$. This method can be used for the separation of $^{233}$Pa and $^{233}$U from the fuel of a two-zone molten salt breeding reactor if it is desired to avoid parasitic neutron absorption by the two nuclides and thus to increase the breeding yield [129]. In the distribution of Pa between fused halides and fused metals [$CaF_2$/Th or Th,U], Pa concentrates in the metallic phase [130]; on the other hand, in systems with uranium as the molten metal and LiCl, LiCl/KCl, $AlCl_3$, or $AlCl_3$/KCl as the halide it concentrates in the chloride melt [131, 132].

## 7. Solid-State Chemistry of Protactinium

### 7.1. Metallic Protactinium

Metallic protactinium was first obtained by *von Grosse* [133] by the bombardment of Pa oxide with 35 kev electrons in high vacuum or by thermal decomposition of $PaCl_5$ on a hot wire. However, he gave no information on the properties of the metal. The pure metal is obtained by the reduction of $PaF_4$ with calcium or barium [134–136] at 1300–1400 °C. It has a tetragonal body-centered lattice with a = 3.929 Å and c = 3.241 Å [135, 137]. Two other modifications probably exist: a body-centered cubic modification above 1170 °C and one of lower symmetry, obtained by rapid quenching from 1580 °C to room temperature. The melting point of 1560 °C lies between the values for the neighboring elements thorium (1750 °C) and uranium (1132 °C). Metallic Pa forms no amalgam [138]. The magnetic susceptibility ($\chi = 270\times10^{-6}$ EMU/g) is – like that of tantalum – practically independent of the temperature. Metallic Pa reacts with 6 N HCl very violently at first, but dissolution ceases after a short time. This behavior is ascribed to the formation of a surface oxide layer [135]. With hydrogen at 250–300 °C, metallic Pa forms a hydride $PaH_3$ (cubic, a = 6.648 Å) which is isostructural with $UH_3$ [134].

### 7.2. Halogen Compounds of Protoactinium

#### 7.2.1. Binary Compounds

The evaporation of a solution of Pa(V) in aqueous hydrofluoric acid of Pa(V) gives $PaF_5 \cdot 2\,H_2O$ [139], which decomposes above 160 °C to give the oxide fluoride $Pa_2OF_8$ (body-centered cubic, a = 8.4065 Å, isotypic with $U_2F_9$) which probably contains $F_4Pa$–O–$PaF_4$ bridges. $Pa_2OF_8$ is also formed by direct fluorination of $Pa_2O_5$ at 550 °C and by hydrolysis of $PaF_5$. Pure $PaF_4$ is obtained only by the fluorination of $PaF_4$ with highest-purity fluorine. $PaF_5$ crystallizes in the tetragonal system with the β-$UF_5$ type of structure (a = 11.53 Å, c = 5.19 Å). It is less volatile than $VF_5$, $NbF_5$, and $TaF_5$, but can be sublimed above 500 °C at $10^{-5}$ to $10^{-6}$ mm. $Pa_4F_{17}$ (body-centered cubic, a = 8.507 Å) and $PaF_4$ (monoclinic, isotypic with $ThF_4$ and $UF_4$) can be prepared by the reaction of $Pa_2O_5$ with $H_2$/HF above 500 °C [139, 140]. In contrast to $PaF_5$, $PaF_4$ is insoluble in dilute hydrofluoric acid but dissolves in 15 M $NH_4F$ [117].

The addition of fluoride ions to a sulfuric acid solution of $Pa^{4+}$ gives $PaF_2SO_4 \cdot 2H_2O$ [140]. The preparation of the corresponding uranium compounds suggests an analogy between the ions $UF_2^{2+}$ and $PaF_2^{2+}$ and the stable $UO_2^{2+}$ ion.

$PaCl_5$ is most simply obtained by the reaction of $Pa_2O_5$ with a stream of chlorine saturated with $CCl_4$ vapor at 300–400 °C [141]. Its melting point is 300 °C, but in

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vacuum it sublimes above 160 °C. The volatility of $PaCl_5$ can be utilized for various separations, *e.g.* for the recovery of $^{233}Pa$ from neutron-irradiated $ThCl_4$ [142]. $PaCl_5$ crystallizes with a monoclinic lattice (a = 10.25 Å, b = 12.31 Å, c = 8.82 Å, β = 111.8 °C) [143] and, like all protactinium pentahalides, exhibits a structure different from that of the corresponding Nb and Ta pentahalides. Orange $PaBr_5$ (m.p. 317 °C) and black $PaI_5$ are obtained by the reaction of $Pa_2O_5$ with $AlBr_3$ and $AlI_3$, respectively. Purification is possible by vacuum sublimation; however, $PaI_5$ decomposes above 300 °C with liberation of iodine. Both salts are orthorhombic ($PaBr_5$: a = 7.25 Å, b = 12.12 Å, c = 9.13 Å; $PaI_5$: a = 7.22 Å, b = 21.2 Å, c = 6.85 Å).

The reaction of $PaO_2$ with $CCl_4$ or the reduction of $PaCl_5$ with hydrogen at 400–500 °C in a closed system gives $PaCl_4$ (tetragonal; a = 8.377 Å, c = 7.482 Å), isotopic with $UCl_4$ [134].

### 7.2.2. Polynary Compounds

The reaction of $PaF_4$ with an excess of $NH_4F$ gives $(NH_4)_4PaF_8$ [147], which is isotypic with the corresponding U, Np, Pu, and Am compounds [144–146]. By solid-state reaction of RbF with $PaF_4$ the compound 7 RbF·6$PaF_4$ (orthorhombic; a = 9.587 Å, α = 107 °9′) is formed [147], which is isotypic with the analogous Th [148], U [149], and Np and Pu [150] compounds.

Double fluorides of quinquevalent protactinium can be prepared both from aqueous solution and by the fluorination of an alkali metal fluoride / $PaF_4$ mixture. The sparingly soluble $K_2PaF_7$ (which incidentally was the first pure compound of protactinium to be prepared) was first obtained by *von Grosse* [151]. Above 130 °C, it decomposes into $KPaF_6$ and KF [152]. $K_2PaF_7$ is monoclinic [152a] with a = 13.94 Å, b = 6.76 Å, c = 8.24 Å, β = 125,5 °, and Z = 4 (space group $C2/c\text{-}C_{2h}^6$). Each Pa is surrounded by 9 fluorines in an arrangement which may be idealized as a trigonal prism with 3 equatorial fluorines added. These $PaF_9$ groups are linked in infinite chains parallel to [001] by 2 fluorine bridges. The interatomic Pa-F-distances are between 2.13 Å and 2.46 Å.

Depending on the $M^I$:Pa ratio, complex fluorides of the compositions $M^IPaF_6$, $M^I_2PaF_7$, and $M^I_3PaF_8$ can be prepared from hydrofluoric acid solutions of Pa(V) [153–158]. The majority of these double fluorides are isotypic with the corresponding uranium compounds, but not with the compounds of niobium and tantalum, which do not form the $M_3XF_8$ type of compound at all. However, for the $M_3PaF_8$ and $MPaF_6$ double fluorides, approximate structural data are known only for $Li_3PaF_8$ (tetragonal, space group $D_{4h}^6$, a = 10.386 Å, c = 10.89 Å, Z = 8), $Na_3PaF_8$ (tetragonal, space group $D_{4h}^{17}$, a = 5.487 Å, c = 10.89 Å, Z = 2) and $MPaF_6$ (orthorhombic for M = K, Rb, Cs; $KPaF_6$: a = 5.64 Å, b = 5.77 Å, and c = 3.99 Å) [155].

Freshly prepared $Pa_2O_5$·aq dissolves in $SOCl_2$ at room temperature. After the excess of $SOCl_2$ has been distilled off, $SO(PaCl_6)_2$ remains, in contrast to Nb and Ta where the anhydrous chlorides are obtained [153, 159]. $SO(PaCl_6)_2$ decomposes in vacuum above 150 °C. By adding MCl ($M^+ = Cs^+$, $[(CH_3)_4N]^+$, or $[(C_6H_5)_4As]^+$) to the solution of $SO(PaCl_6)_2$ in $SOCl_2$, hexachloro complexes $MPaCl_6$ and octachloro complexes $M_3PaCl_8$ are obtained – the last complex not with $[(C_6H_5)_4As]Cl$, however. Analogous double chlorides can be prepared from U(V), but only hexachloro compounds of Nb and Ta exist. When dissolved in acetonitrile + dichloromethane, $PaCl_5$ forms adducts $PaCl_5$·$R_3PO$ with phosphine oxides $R_3PO$ which are considerably more stable than the pentachloride.

If a tetraalkylammonium bromide is added to a solution of $PaBr_5$, $TaBr_5$, or $NbBr_5$ in acetonitrile, evaporation of the solvent gives a double bromide of the type $M^IM^VBr_6$ [153].

## 7.3. Oxygen Compounds of Protactinium

### 7.3.1. The System Pa–O

In addition to the stoichiometric oxides of quadrivalent and quinquevalent protactinium, there are four oxide phases with a variable oxygen content (Table 5) that can be prepared both by the partial oxidation of $PaO_2$ with oxygen and by the partial reduction of $Pa_2O_5$ with hydrogen. The structures of these compounds can be derived substantially from the fluorite structure, which shows the relationship of $PaO_{2+x}$ to the lower oxides of uranium. Because of the relatively large – in comparison to $UO_2$ – unit cell of $PaO_2$, an increased incorporation of oxygen in interstitial sites of the fluorite lattice is possible without change in structure: in the $PaO_2/O_2$ system up to $PaO_{2.50}$, but in the $UO_2/O_2$ system only up to $UO_{2.35}$.

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Table 5. Phase relationships in the Pa—O system.

| Composition | Structure | Lattice parameters | | | | Range of existence [°C] | Ref. |
|---|---|---|---|---|---|---|---|
| | | a [Å] | b [Å] | c [Å] | α | | |
| PaO (?) | cubic (NaCl) | 4.961 | | | | | [153] |
| $PaO_2$ | cubic ($CaF_2$) | 5.505 | | | | | [153] |
| $PaO_{2.18}$—$PaO_{2.21}$ | cubic | 5.473 | | | | | [160] |
| $PaO_{2.33}$ | tetragonal | 5.425 | | 5.568 | | | [160] |
| $PaO_{2.40}$—$PaO_{2.42}$ | tetragonal | 5.480 | | 5.416 | | | [160] |
| $PaO_{2.42}$—$PaO_{2.44}$ | rhombohedral | 5.449 | | | 89.65° | | [160] |
| $Pa_2O_5$ | cubic ($CaF_2$) | 5.446 | | | | 700 | [153, 161] |
| | tetragonal | 5.429 | | 5.503 | | 1000 | [160, 161] |
| | hexagonal | 3.817 | | 13,22 | | 1000—1200 | [160, 161] |
| | rhombohedral | 5.424 | | | 89.76° | 1240—1400 | [160] |
| | orthorhombic | 6.92 | 4.02 | 4.18 | | ? | [153, 160—162] |
| $Pa_2O_5 \cdot H_2O$ | | | | | | 200—280 | [163] |

After the addition of $H_2O_2$ to a solution of Pa(V) in dilute sulfuric acid, a precipitate of amorphous, unstable Pa peroxide $Pa_2O_9 \cdot 3H_2O$ is obtained [136, 164]; below 200 °C it is transformed into protactinium pentoxide monohydrate, which is stable up to 280 °C.

### 7.3.2. Polynary Oxides of Protactinium

$Pa_2O_5$ is amphoteric; like a basic oxide, it dissolves in molten hydrogen sulfates, but it reacts as an acidic oxide with alkali metal and alkaline earth oxides. From the solid-state reactions of $PaO_2$ and $Pa_2O_5$ with oxides of other elements, it may be concluded that protactinium behaves as a "true" actinide element (Table 6). Thus with $GeO_2$ or $SiO_2$, $PaO_2$ forms ternary oxides of the type $Pa^{IV}X^{IV}O_4$, which are also known for other quadrivalent actinide elements but not for Nb(IV) and Ta(IV). Further, $Pa^{V}Nb_3O_{10.67}$ corresponds completely to the compounds $UNb_3O_{10.67}$ and $NpNb_3O_{9.5}$, in spite of the different oxygen numbers. With the sesquioxides of the lanthanides and actinides, $Pa_2O_5$ reacts to give double oxides of the type $(M^{III}_{0.5}, Pa^{V}_{0.5})O_2$ with the fluorite structure and a statistical distribution of the heavy metal ions on the $Ca^{2+}$ sites of the $CaF_2$ lattice. Like all binary actinide oxides with fluorite structure, the M(III)/Pa(V) double oxides take up additional $MO_{1.5}$ or $PaO_{2.5}$ in solid solution, the solubility of $MO_{1.5}$ in the $(M_{0.5},Pa_{0.5})O_2$ lattice being a function of

Table 6. Polynary oxides of quadrivalent and quinquevalent protactinium [165—173].

| Compound | Conditions of formation | Structure | Lattice parameters | | | | Isostructural compounds with |
|---|---|---|---|---|---|---|---|
| | | | a [Å] | b [Å] | c [Å] | β | |
| $LiPaO_3$ | $LiO + Pa_2O_5$/600 °C/2×8 h/$O_2$ | unknown | | | | | |
| $Li_3PaO_4$ | | tetragonal; $Li_3UO_4$ | 4.52 | | 8.48 | | U,Np,Pu,Am |
| $Li_7PaO_6$ | | hexagonal; $Li_7BiO_6$ | 5.55 | | 15.84 | | U,Np,Pu,Am |
| $(2-4)Li_2O \cdot Pa_2O_5$ | $Li_2CO_3 + Pa_2O_5$ | cubic, fluorite phase | | | | | |
| $(2-4)Na_2O \cdot Pa_2O_5$ | $Na_2CO_3 + Pa_2O_5$ | | | | | | |
| $NaPaO_3$ | $Na_2O_2 + Pa_2O_5$/500 °C/2×8 h/Ar | orthorhombic; $GdFeO_3$ | 5.82 | 5.97 | 8.36 | | U |
| $Na_3PaO_4$ | | tetragonal; $Li_3SbO_4$ | 6.68 | | 9.60 | | |
| $KPaO_3$ | $K_2CO_3 + Pa_2O_5$/600 °C/2×8 h/$O_2$ | cubic; $CaTiO_3$ | 4.341 | | | | U |
| $RbPaO_3$ | $Rb_2CO_3 + Pa_2O_5$/500 °C/2×8 h/$O_2$ | | 4.368 | | | | U |
| $CsPaO_3$ | $Cs_2CO_3 + Pa_2O_5$/500 °C/2×8 h/$O_2$ | unknown | | | | | |
| $BaPaO_3$ [a] | $BaO + PaO_2$/1200 °C—8 h/vacuum | cubic; $CaTiO_3$ | 4.45 | | | | U,Np,Pu,Am |
| $SrPaO_3$ [a] | $SrO + PaO_2$/1200 °C/8 h/vacuum | unknown | | | | | |
| $Ba(Ba_{0.5},Pa_{0.5})O_{2.75}$ | $BaO + Pa_2O_5$/1350 °C/2×6 h/$O_2$ | cubic, $Ba_3WO_6$ | 8.932 | | | | Nb,Ta,U |
| $GaPaO_4$ | $Ga_2O_3 + Pa_2O_5$/1200 °C/8 h/$O_2$ | unknown | | | | | $M^{III}$ = rare earths, Y, |
| $(La_{0.5}, Pa_{0.5})O_2$ | $La_2O_3 + Pa_2O_5$/1100 °C/2×8 h/$O_2$ | cubic, $CaF_2$ | 5.525 | | | | Sc,In,Pu,Cm |
| $Ba(La_{0.5}, Pa_{0.5})O_3$ | $BaO + (La_{0.5},Pa_{0.5})O_2$/1350 °C/12 h/$O_2$ | cubic, $Ba_3WO_6$ | 8.885 | | | | $M^{III}$= rare earths,Y,Sc,In,Pu |
| α-$PaGeO_4$ | $PaO_2 + GeO_2$/1100 °C/2×12 h/vacuum | tetragonal, $CaWO_4$ | 5.106 | | 11.38 | | Th,U,Np, Pu, Am |
| β-$PaGeO_4$ [a] | α-$PaGeO_4$ —1200 °C→ hydrothermal/230 °C/5d | tetragonal, $ZrSiO_4$ | 7.068 | | 6.509 | | Th,U,Np |
| α-$PaSiO_4$ [a] | hydrothermal/230d/5d | tetragonal; $ZrSiO_4$ | 7.068 | | 6.288 | | Th,U,Np,Pu,Am |
| β-$PaSiO_4$ [a] | α-$SiO_4$ —1200 °C→ $PaO_2 + SiO_2$/1250 °/8 h/vacuum | monoclinic; $CePO_4$ | 6.76 | 6.92 | 6.45 | 104°50′ | Th |
| $Pa_2O_5/ThO_2$ | $Pa_2O_5 + ThO_2$/1100 °C/8 h/$O_2$ $(Pa, Th)O_2 + O_2$/400 °C | cubic, fluorite phase | | | | | |
| $PaO_2 \cdot 2\,Nb_2O_5$ [a] | $PaO_2 + Nb_2O_5$/1200 °C/20min/vacuum | tetragonal, $Th_{0.25}NbO_3$ | 7.76 | | 7.81 | | U,Np,Pu |
| $PaO_2 \cdot 2\,Ta_2O_5$ [a] | $PaO_2 + Ta_2O_5$/1250 °C/8 h/vacuum | | 7.77 | | 7.79 | | U,Np,Pu |
| $Pa_2O_5 \cdot 3\,Nb_2O_5$ | $Pa_2O_5 + Nb_2O_5$/1150 °C/8 h/$O_2$ | hexagonal, $UTa_3O_{10.67}$ | 7.48 | | 15.81 | | $UNb_3O_{10.67}$; |
| $Pa_2O_5 \cdot 3\,Ta_2O_5$ | $Pa_2O_5 + Ta_2O_5$/1200 °C/8 h/$O_2$ | | 7.425 | | 15.76 | | $NpNbO_{9.5}$ |

[a] Could not be prepared in the pure state, always contained varying amounts of Pa(V).


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the ionic radius of M (Fig. 6). The lattice parameters of the solid solutions change linearly with the amount of $MO_{1.5}$ dissolved in the $(M_{0.5},Pa_{0.5})O_2$. The solubility increases with increasing temperature. As in the $Li_2O/Pa_2O_5$ system [173], a fluorite phase also exists in the $Li_2O/U_2O_5$ system [174, 175]. Only in compounds of

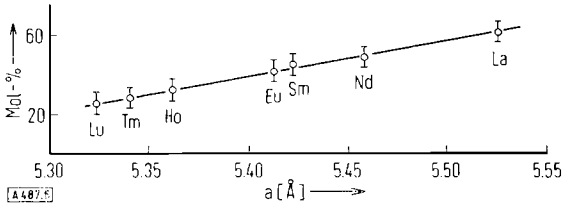


Fig. 6. Solubility of $MO_{1.5}$ in $(M^{III}_{0.5}Pa^{V}_{0.5})O_2$ *versus* lattice parameter.

the type $Ba(M^{II}_{0.5},Pa_{0.5})O_{2.75}$ and $Ba(M^{III}_{0.5},Pa_{0.5})O_3$ with an ordered fluorite structure can a relationship of protactinium to niobium and tantalum be seen; moreover, the uranium compounds of at least the last-mentioned type can also be prepared [176].

### 7.4. Nitrides, Carbides, and Sulfides

Little information is available on the Pa/N, Pa/C, and Pa/S systems [153]. Thermal treatment of $PaCl_5$ with $H_2S/CS_2$ at 900 °C leads to the formation of PaOS, and treatment of $PaCl_5$ or $PaCl_4$ with gaseous $NH_3$ at 800 °C to $PaN_2$. The identification of PaOS and $PaN_2$ was made solely on the basis of their isotypicity with the analogous uranium compounds. PaC can be prepared by the reaction of $PaF_4$ with Ba + C at 1400 °C.

### 7.5. Nitrato Complexes of Pa(V)

The reaction of $N_2O_5$ with $Pa_2O_5$·aq or $PaCl_5$ yields the hexanitrato acid $HPa(NO_3)_6$ [177], whose salts – *e. g.* $CsPa(NO_3)_6$ or $[N(CH_3)_4]Pa(NO_3)_6$ – can also be prepared by the reaction of the hexahaloprotactinates(V) with $N_2O_5$. On the other hand, in the analogous reaction the hexahaloniobates and hexahalotantalates form only oxotetranitro complexes, *e.g.* $CsNbO(NO_3)_4$. All these compounds are very sensitive to hydrolysis, and they were identified mainly on the basis of their infrared spectra.

## 8. Outlook

Within the past few years our knowledge of the chemistry of protactinium has increased to such an extent that many aspects are better known than for the neighboring elements niobium and tantalum. In other fields, however, such as metallurgy, phase diagrams of multi-component systems, and other thermodynamic data, no thorough investigations have yet been carried out. However, this statement applies also to many of the "well-known" elements. If the present interest in protactinium continues and can be increased by the production of a larger amount of $^{231}Pa$, these gaps may rapidly be closed, despite the element's radiotoxicity. Weighable amounts of $^{231}Pa$ can be handled only in airtight glove boxes (the maximum permissible concentration of $^{231}Pa$ in air is $10^{-8}$ mg/m³; that of hydrogen cyanide is 10 mg/m³).

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[172] *C. Keller*, J. inorg. nuclear Chem. *27*, 797 (1965).
[173] *P. N. Iyer* and *A. J. Smith*, see [10].
[174] *W. Rüdorff*, *S. Kemmler*, and *H. Leutner*, Angew. Chem. *74*, 429 (1962).
[175] *L. M. Kovba* and *A. N. Golubenko*, Zh. strukt. Khim. *1*, 390 (1960).
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[177] *P. J. Jones*, see [10].

# Novel Approaches to the Synthesis of Some Heterocycles Containing Nitrogen

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*Some syntheses of heretofore unknown pyrimidines, tetrahydroquinazolines, and quinazolines are described. These methods are uniquely simple one- or two-step reactions, general and versatile in scope, and give high yields. Some interesting chemistry associated with these heterocyclic systems is discussed.*

For a number of years we have been involved in the synthesis of new heterocyclic systems for biological evaluation. This work has led to the preparation of a variety of new heterocycles, amongst which are 5,6,7,8-tetrahydrobenzothiazolin-2-ones [1], 5,6,7,8-tetrahydrobenzoxazoles [2, 3], 1,2,4,5-tetrahydro-1,3-benzodiazepines [4], and pyrazolo[1,5-*c*]quinazolines [5]. Recently we have developed some new synthetic routes to 1,2-disubstituted pyrimidines [6], tetrahydroquinazolines [7,8], and quinazolines [9,10], and it is the purpose of this review to present this work in its entirety.

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[2] *G. deStevens*, US.-Pat. 2 857 394 (Oct. 2nd, 1958).
[3] *G. deStevens* and *R. H. Sprague*, US.-Pat. 2892837 (Sept. 22nd, 1959).
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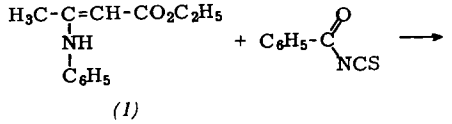
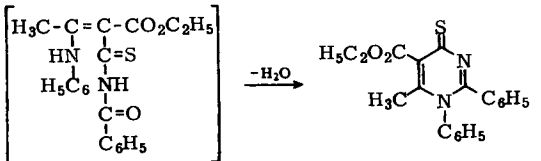
## 1,2-Disubstituted Pyrimidines

In a recent monograph on pyrimidines *Brown*[11] noted that, although many mercaptopyrimidines have been prepared, only the 2-mercaptopyrimidines have been synthesized from a 3-carbon intermediate and an appropriate condensing agent (*e.g.* ethyl cyanoacetate and thiourea). The usual procedure employed to arrive at the 4-mercaptopyrimidines involves the synthesis of the 4-hydroxy- or 4-chloropyrimidines, which are then allowed to react with phosphorus pentasulfide or sodium hydrogen sulfide, respectively. This method has in the past been confined to pyrimidines unsubstituted in the 1-position. 1-Alkyl-4-oxopyrimidines have been prepared in certain cases through alkylation of a 4-aminopyrimidine derivative. The resultant 1-alkyl-4-iminopyrimidine was hydrolysed to the 4-oxo derivative[12]. Thus, a minimum of four steps is required in the preparation of a 1-alkyl-1,4-dihydro-4-thiopyrimidine from the condensation of an appropriate 3-carbon intermediate (*e.g.* malononitrile) with an amidine. The problem becomes even more acute if one considers the synthesis of the previously unknown 1,2-disubstituted 1,4-dihydro-4-thioxopyrimidines and especially the 1,2-diaryl compounds which are not available by conventional routes.

The investigations of *Behrend et al.* during the early part of this century served as a convenient starting point in the preparation of such compounds. *Behrend*[13,14] found that the condensation of ethyl β-aminocrotonate with phenyl isothiocyanate affords not only the anticipated product, 6-methyl-3-phenyl-2-thiouracil, but also ethyl β-amino-α-phenylthiocarbamoylcrotonate. The tendency of ethyl β-aminocrotonate to behave as an enamine towards the isothiocyanate function under certain conditions was thus established. It was with this



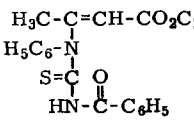
*(1)*



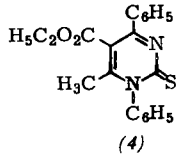
*(2)* *(3)*

observation in mind that we considered the condensation of ethyl β-anilinocrotonate *(1)* with benzoyl isothiocyanate. It was anticipated that the primary product of this condensation reaction would be ethyl β-anilino-α-benzoylthiocarbamoylcrotonate *(2)*. However, when these intermediates were allowed to react in ethyl ether or tetrahydrofuran under mild reflux a bright yellow precipitate was obtained in 60 % yield. The elemental analysis of this compound indicated that the elements of water had been eliminated from the intermediate *(2)*.

The ultraviolet, infrared, and nuclear magnetic resonance spectra along with the elemental analysis strongly supported the assignment of structure *(3)* to this compound. The alternative structure *(4)* was not considered feasible since it required an amide-carbonyl interaction with the carbon bearing the vinyl proton [cf. *(2a)*], a reaction which is not favorable for the elimination of water under the mild reaction conditions described.

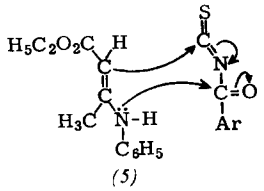


*(2a)*

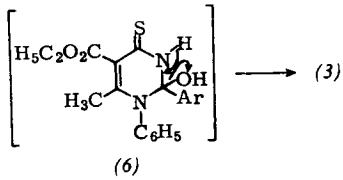


*(4)*

This reaction has been applied to a variety of α,β-unsaturated amino-esters and acyl and aroyl isothiocyanates[6]. Several factors are worthy of note. The reaction conditions are very mild, condensation and ring closure occurring in the absence of an acid or base catalyst and at relatively low temperature (25–50 °C). The reaction seems to be quite general although higher yields of 4-thioxopyrimidines are obtained if the aroyl isothiocyanate is substituted with an electron withdrawing group (*e.g. p*-nitrobenzoyl isothiocyanate). On the other hand, the condensation of ethyl β-anilinocrotonate with *o*-methoxybenzoyl isothiocyanate gives a poor yield and a number of different by-products are formed. These facts suggest the mechanism represented by formulae *(5)–(6)* which requires an electron-deficient carbonyl group to facilitate ring closure and subsequent dehydration.



*(5)*



*(6)*

The isothiocyanate derivatives of aliphatic acids also give good yields. Variations in the structure of the crotonic ester do not significantly affect the course of the reaction. However, condensation of the ethyl β-

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[6] *G. deStevens, B. Smolinsky,* and *L. Dorfman,* J. org. Chemistry *29,* 1115 (1964).

[7] *R. W. J. Carney, J. Wojtkunski,* and *G. deStevens,* J. org. Chemistry *29,* 2887 (1964).

[8] *H. M. Blatter* and *H. Lukaszewski,* J. org. Chemistry, in press.

[9] *H. M. Blatter* and *H. Lukaszewski,* Tetrahedron Letters *1964,* 855.

[10] *H. M. Blatter, H. Lukaszewski,* and *G. deStevens,* J. org. Chemistry *30,* 1020 (1965).

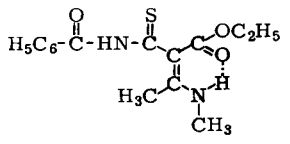
[11] *D. J. Brown*: The Pyrimidines. Wiley, New York 1962.

[12] *D. J. Brown, E. Hoerger,* and *S. F. Mason,* J. chem. Soc. (London) *1955,* 211; cf. also [2].

[13] *R. Behrend, F. Meyer,* and *Y. Buchholz,* Liebigs Ann. Chem. *314,* 200 (1900).

[14] *R. Behrend* and *P. Hesse,* Liebigs Ann. Chem. *329,* 341 (1903).

methylaminocrotonate with benzoyl isothiocyanate in *diethyl ether* results in immediate reaction with precipitation of the uncyclized intermediate ethyl α-*N*-benzoylthiocarbamoyl-β-methylaminocrotonate *(7)*, which dissolves in refluxing ethanol or tetrahydrofuran



*(7)*

to undergo ring closure with water elimination. A similar phenomenon was observed with ethyl β-aminocrotonate. However, this ester reacts with acylisothiocyanates in tetrahydrofuran, to give the corresponding 4-thioxopyrimidines directly. Infrared and NMR spectrocsopy were very useful in determining the stereochemistry of *(7)* and related compounds.

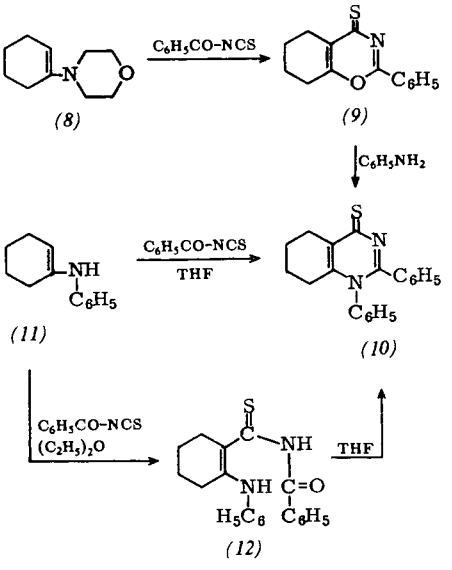
The 1665 $cm^{-1}$ band of ethyl β-aminocrotonate was assigned to the ester carbonyl, and the carbonyl group of the β-anilino derivative absorbs at 1655 $cm^{-1}$. A *cis* relationship between the amino and the ester groups has previously been shown[15]. This assignment is supported by the chemical shifts observed in the NMR spectrum[15]. In addition, ethyl β-diethylaminocrotonate[15] gives two carbonyl bands, 1677 $cm^{-1}$ (strong) and 1655 $cm^{-1}$ (very weak). This fully alkylated amine therefore is a mixture of *cis* and *trans* isomers, with *trans* predominating.

The *cis* stereochemical relationship (*i.e.* the *cis*-orientation of the amino and ester groups) thus apparently holds for the aroylcarbamoyl and thiocarbamoyl derivatives since the ester group absorption is found at 1665–1672 $cm^{-1}$ when the amino group is unsubstituted and at 1657 $cm^{-1}$ when it carries a phenyl substituent. However, this stereochemical assignment has little if any influence on the ring closure reaction since a *cis-trans* equilibrium is feasible in solution. Ring closure could then proceed rapidly through the small amount of *trans* isomer that is always present.

## 1,2-Disubstituted 5,6,7,8-Tetrahydroquinazolines

*Hünig* and *Hübner*[16] reported the formation of 5,6,7,8-tetrahydro-2-phenylbenzoxazine-4-thione *(9)* in 50 % yield from *N*-(1-cyclohexenyl)morpholine *(8)* with benzoyl isothiocyanate. Since 1,3-oxazin-4-ones bear a formal resemblance to 1,4-pyrones with regard to the disposition of the double bonds, and since 1,4-pyrones upon heating with primary amines can readily be transformed into 4-pyridones[17], we explored the reactivity of *(9)* towards such amines.

When *(9)* was refluxed in ethanol with excess aniline, a yellow crystalline material *(10)* was obtained in 59 % yield. Elemental analysis indicated the product to consist of the combined reactants minus water. The ultraviolet absorption spectrum of *(10)* in ethanol shows a shoulder at 254 mμ and a maximum at 342–345 mμ, in marked contrast to that of compound *(9)*, which has



*(8)* *(9)* *(11)* *(10)* *(12)*

maxima at 228–230 mμ, 287 mμ, and 333–335 mμ in dioxane. Evidently the chromophore of the heterocycle *(9)* is substantially altered in this reaction. The absence of NH, OH, or CO bands in the infrared spectrum further suggested that we were dealing with a heterocyclic compound rather than with a ring-opened cyclohexenyl derivative.

To substantiate the structure *(10)*, anilinocyclohexene *(11)* was treated with benzoyl isothiocyanate in tetrahydrofuran. The product was identical with compound *(10)*. However, in diethyl ether the benzoylthiocarbamoyl derivative *(12)* was obtained which, in turn, was converted to *(10)* in refluxing tetrahydrofuran. The isolation of *(12)* and its subsequent conversion to *(10)* relates the mechanism of the formation of *(10)* from *(11)* to the one illustrated for the pyrimidine synthesis.

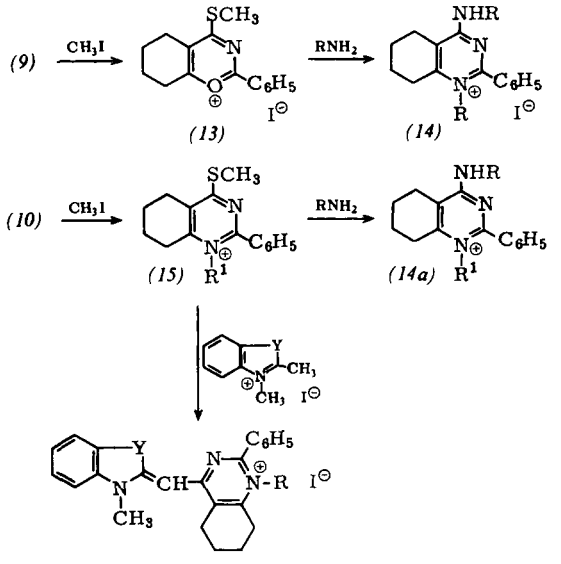
Compound *(9)* reacts with a number of primary amines to afford the previously unknown 1-substituted 5,6,7,8-tetrahydro-2-phenylquinazoline-4-thiones. Treatment of *(9)* with ammonia gives 5,6,7,8-tetrahydro-2-phenylquinazoline-4-thione. These substances are readily converted to the corresponding tetrahydroquinazolin-4-ones with mercuric acetate.

The versatility of *Hünig*'s intermediate benzoxazine *(9)* is illustrated further by its application to the synthesis of tetrahydroquinazolinium salts *(14)* and *(16)*. The reaction of *(9)* with methyl iodide yields the oxonium salt *(13)* which readily condenses with primary amines to form the 1,2-disubstituted tetrahydroquinazolinium iodide in good yields.

The R groups at positions 1 and 4 in these compounds are identical. However, to prepare compounds in which the R groups at positions 1 and 4 are different, it is necessary to treat *N*(1)-substituted 5,6,7,8-tetrahydroquinazolines with methyl iodide. The resulting salts *(15)* are then condensed with a primary amine whose R

[15] *C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson,* and *P. Strachan,* J. org. Chemistry *28*, 3134 (1963).
[16] *S. Hünig* and *K. Hübner,* Chem. Ber. *95*, 937 (1962).
[17] *L. F. Cavalieri,* Chem. Rev. *41*, 525 (1947).

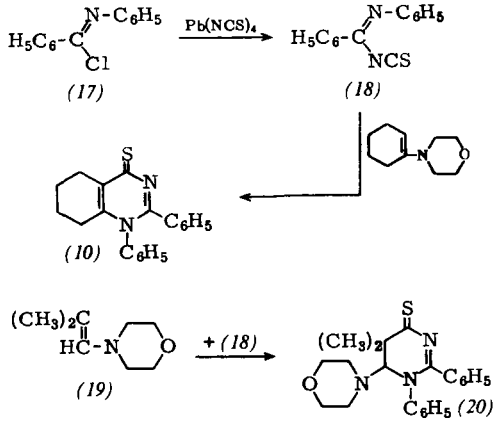
function is different from that already incorporated at the 1-position of the heterocycle. The 4-methylmercapto-5,6,7,8-tetrahydroquinazolinium salts *(15)* also react quite readily with the alkyl iodide salts of 2-methyl-substituted heterocycles, *e.g.* 2-methylbenzothiazole, to afford compounds of the cyanine dye type.



*(16)*, Y = O, S, CH=CH

In the synthesis of compounds related to *(9)* with substituents in the 2-phenyl group, the use of appropriately substituted aroyl isothiocyanates, usually gave intractable tars from which no distinct product could be isolated. This unexpected result limited the utility of the above route to 1-substituted 2-phenyl-5,6,7,8-tetrahydroquinazoline-4-thiones. For this reason it was necessary to devise an alternate route of synthesis of such compounds.

*N*-Arylimidoyl isothiocyanates had already been prepared in our laboratory in connection with another project[9,18]. For example, *N*-phenylbenzimidoylchloride *(17)*, readily obtainable from benzanilide by the



action of thionyl chloride, reacts with lead thiocyanate (in refluxing benzene for 2 h) to afford *N*-phenylbenzimidoyl isothiocyanate *(18)* in good yield.

[18] *H. M. Blatter*, 145th Meeting Amer. Chem. Soc., New York, September 1963; Abstracts of Papers 89 Q.

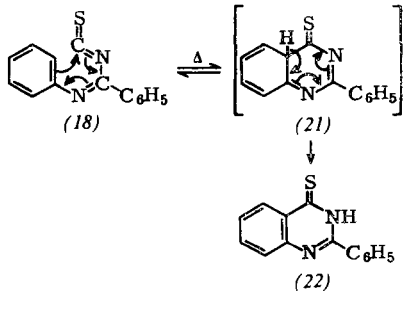
This readily condenses with *N*-(1-cyclohexenyl)morpholine to give *(10)* in fair yield[8]. In fact, this was then found to be a general reaction regardless of the nature of the substituent on the benzene ring. In this way a number of 1,2-disubstituted 1,4,5,6,7,8-hexahydroquinazoline-4-thiones were prepared, which were unobtainable by other routes. These substituted imidoyl isothiocyanates also react with other enamines, *e.g.* *N*-(2-methylprop-1-enyl)morpholine *(19)*, to form dihydropyrimidine-4-thiones *(20)*[8].

## 2-Substituted Quinazolines

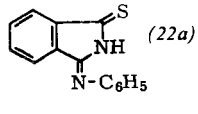
*N*-Phenylbenzimidoyl isothiocyanate *(18)* readily cyclizes to 2-phenyl-3,4-dihydroquinazoline-4-thione *(22)* at temperatures as low as 80 °C (refluxing benzene[9]). This ring closure was carried out with a variety of imidoyl isothiocyanates and represents a general synthesis of 3,4-dihydroquinazoline-4-thiones that enables one to circumvent the use of the often difficultly accessible anthranilic acid derivatives. The reaction occurs regardless of the presence of electron-withdrawing (*e.g.* $NO_2$) or electron-releasing substituents (*e.g.* $OCH_3$) in either benzene ring and particularly in the ring directly involved[19].

It seems likely, therefore, that *cis*-imidoyl isothiocyanates such as *(18)* undergo ring closure by a cyclic, concerted, thermally induced reorganization of the σ- and π-electrons. This would reversibly yield the less stable valence isomer (in brackets) which could stabilize itself through irreversible prototropic shift to form the aromatic 3,4-dihydroquinazoline-4-thione.

Reactions of this type, which includes both the Claisen and Cope rearrangements, have been designated as "no mechanism reactions"[21]; referring to the difficulty, if not impossibility, of describing precisely the transition state or states of such reactions. Such multicenter processes[22] are neither ionic nor free-radical. They are thermally induced,



[19] The alternative possibility that monothioimides such as *(22a)* are formed was ruled out by independent synthesis and



by the fact that such compounds are obtainable only in the presence of Friedel-Crafts catalysts [20].

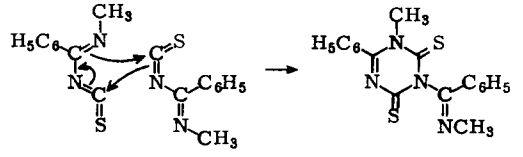
[20] *P. A. S. Smith*, J. Amer. chem. Soc. *82*, 4753 (1960).

[21] *W. v. E. Doering* and *W. R. Roth*, Tetrahedron *18*, 67 (1962).

[22] Review: *S. J. Rhoads* in *P. de Mayo*: Molecular Rearrangements. Interscience, New York, London 1963, Vol. I, p. 655.

are independent of the extramolecular environment, and are often insensitive to internal structural variation. These criteria are fulfilled in the present case.

Usually a red, crystalline imidoyl isothiocyanate dimer can also be isolated, albeit in poor yield. Structure determination by means of analytical and spectral data

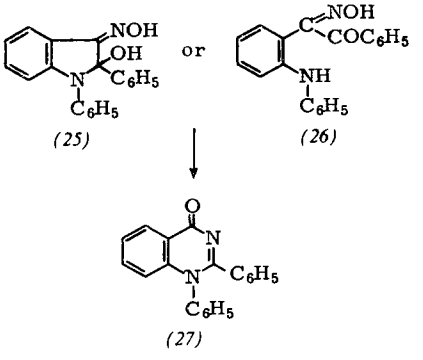


(23) (24)

as well as independent synthesis has established the dimer formed from *N*-methylbenzimidoyl isothiocyanate *(23)* to be the triazine *(24)* [23]. Thus, all the red, crystalline dimers have been assigned the corresponding triazine structures.

## 1,2-Disubstituted 1,4-Dihydroquinazolin-4-ones and their 4-Thioxo Derivatives

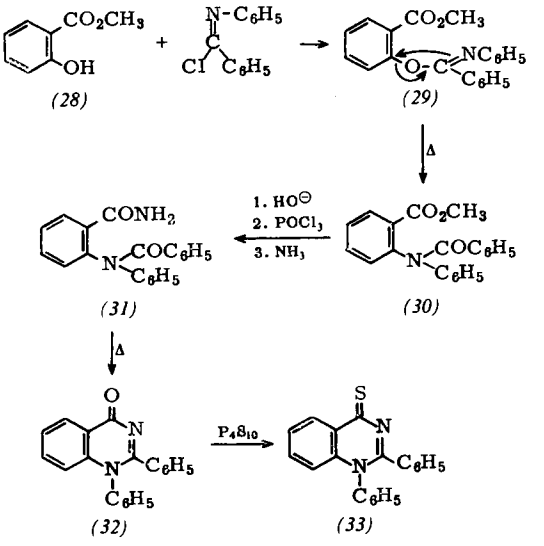
Finally our attention was directed to the synthesis of 1,2-disubstituted 1,4-dihydroquinazoline-4-thiones and their 4-oxo derivatives. A survey of the literature surprisingly revealed that compounds of this type have received little attention. *Huang-Hsinman* and *Mann* [24] reported that 2-hydroxy-3-oximino-1,2-diphenylindoline *(25)*, obtained from 3-amino-1,2-diphenylindole through atmospheric oxidation, is converted by means of ethanolic hydrogen chloride, aqueous sodium hydroxide, or heat alone to a colorless, crystalline substance, m.p. 280–281 °C, whose molecular formula, $C_{20}H_{14}N_2O$, corresponds to that of the quinazolinone *(27)*. These authors acknowledged the tenuity of their structural assignments, and suggested the oxime *(26)* as an alternative to *(25)*.



(25) or (26)

(27)

After a variety of methods to prepare *(27)* and related substances was explored with little success, *e.g.* condensation of *N*-phenylanthranilic acid with benzonitrile [25] or ethyl iminobenzoate [25,26], dehydrogenation of 1,2-diphenyl-1,4,5,6,7,8-hexahydroquinazolin-4-one and -thione with palladium on carbon in cymene, it was decided that the least complicated and most unambigous route to these compounds would be *via* the imido ester *(29)* prepared by condensing methyl salicylate with *N*-phenylbenzimidoyl chloride. Chapman rearrangement [27] of compound *(29)* according to



(28) (29) (30) (31) (32) (33)

the prodecure of *Jamison* and *Turner* [28] yields methyl 2-(*N*-benzoyl-*N*-phenylamino)benzoate *(30)*. Saponification of the ester, followed by conversion to the acid chloride and subsequent amination, gives *(31)* [29]. Heating of this compound for a few minutes at 300 °C gives almost quantitatively the desired 1,2-diphenyl-1,4-dihydroquinazolin-4-one *(32)* [10]; its conversion into the thione *(33)* can be carried out by the conventional method.

Each of these steps gives high yields and is free from complicating side reactions. The method is general and versatile since the nature of the substituents on the benzene rings of the quinazoline ring system and of the 1,2-diphenyl groups is governed by the starting materials, which are readily available commercially or through synthesis.

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German version: Angew. Chem. *78*, 125 (1966)

[23] *H. M. Blatter* and *H. Lukaszewski*, Tetrahedron Letters *1964*, 1087.

[24] *Huang-Hsinman* and *F. G. Mann*, J. chem. Soc. (London) *1949*, 2903.

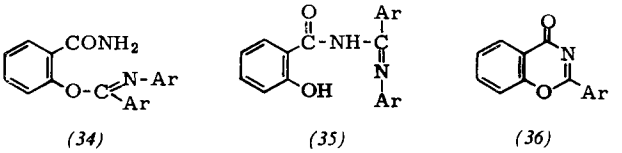
[25] *W. Ried* and *W. Stephan*, Chem. Ber. *95*, 3042 (1962).

[26] *W. Ried* and *W. Stephan*, Chem. Ber. *96*, 1218 (1963).

[27] *P. G. Stecher*: The Merck Index. 7th Edit., Merck, Rahway 1960.

[28] *M. M. Jamison* and *E. H. Turner*, J. chem. Soc. (London) *1937*, 1954.

[29] The preparation of other substituted anthranilamides through the application of the Chapman rearrangement to the



(34) (35) (36)

imido ester *(34)* is difficult since other products such as *(35)* and *(36)* are sometimes also formed.

# The Modifications of Niobium Pentoxide [1]

BY PROF. DR. HARALD SCHÄFER, DR. R. GRUEHN, AND DR. F. SCHULTE

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*Dedicated with sincere good wishes to Professor Wilhelm Klemm on his 70th birthday*

*Niobium pentoxide crystallizes in numerous modifications. The present paper describes their mode of formation, structures, and thermal properties.*

## 1. Introduction

In his fundamental work on the oxides of niobium [2], *Brauer* distinguished three modifications of niobium pentoxide which, according to their appearance at low, medium, and high temperatures, are denoted by the letters T, M, and H. In the last few years other modifications have been found, and numerous observations have been made on the modes of formation, the structural principles, and the stabilities of these materials. The abundance of observations makes it desirable to subject the available material to a critical review and classification, and thus simultaneously to create a basis for further investigations.

## 2. What is a "Modification"?

The classical concept of polymorphism and its definition of modifications appears unambiguous when we think of, for example, sulfur or phosphorus, but its clarity diminishes when closely related structures are present between which transitions are possible. In such cases a discussion of whether particular modifications exist is not of fundamental importance, since it would be sufficient to characterize the materials by an accurate description of their structure. However, such characterization is still not possible for many substances, and the convenient concept of polymorphism will be abandoned only with reluctance. We must therefore attempt to obtain a more precise definition.

As an example, consider a material MX which – like ZnS – can be prepared in a cubic sequence ABC ABC ABC ... and also in a hexagonal sequence AB, AB, AB .... It is then correct to speak of cubic and hexagonal modifications. Assume now that it is possible to link these two modifications in some way through a region of homogeneity with a statistical distribution of ABC and AB sequences. Even then it appears meaningful to speak of the limiting forms with purely cubic or purely hexagonal structure as modifications, although thermodynamically they belong to the same phase. Obviously, however, it is no longer meaningful to regard any particular compositions $(ABC)_x(AB)_y$ within the range of homogeneity as modifications. However, a *regular* sequence such as ABC AB ABC AB ... must be described as another modification.

In this sense, a modification merely requires an ordered structure: *a corresponding ideal structure can be given for a modification.* It is immaterial for this definition that the actual crystal possesses structure defects. It is equally immaterial whether homogeneity regions or considerable concentrations of vacancies occur (in unordered distribution).

It should be particularly noted that the frequently coincident terms "modification" and "thermodynamic phase" are independent of one another. The definition does not exclude the possibility that – as discussed – several modifications may occur in one phase, or several phases may belong to the same modification. Obviously, however, this will not usually occur.

The above indicates how the concept of modification is to be understood in what follows. Frequently, the structurally less definite symbolism $Nb_2O_5$ in the X-form, *e.g.* in the M-form (or M–$Nb_2O_5$) is to be preferred because of insufficient knowledge of the structure.

## 3. Designation and Characterization of the Modifications (Forms) of Niobium Pentoxide

If all the phases (or modifications) occurring in a chemical system are known, it is convenient to denote these by a sequence of letters $\alpha, \beta, \gamma, \ldots$ which simultaneously gives a sequence in stability or in composition. Such knowledge is still lacking in the case of niobium pentoxide, and for this reason nomenclature proposals of this type are premature and confusing (Table 1). We prefer the neutral symbols given in the first column of Table 1. In almost all cases, these were used also by the authors who first observed the corresponding modification.

The form $Nb_2O_5$-II observed by *Shafer* and *Roy* [3] and identified with *Brauer*'s M–$Nb_2O_5$ [2] is mentioned with the M-form. However, $Nb_2O_5$-II is, according to the interplanar

[1] 49th Communication on "Contributions to the Chemistry of Niobium and Tantalum". 48th Communication: *H. Schäfer* and *D. Bauer*, Z. anorg. allg. Chem., in press.

[2] *G. Brauer*, Z. anorg. allg. Chem. *248*, 1 (1941).

[3] *M. W. Shafer* and *R. Roy*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *110*, 241 (1958).

Table 1. Designations of the forms of $Nb_2O_5$. The authors mentioned at the head of each column use the symbols given in that column.

| This paper (deriviation) | *Brauer* [2] | *Frevel* and *Rinn* [5] | *Holtzberg et al.* [4,6] *Laves* [7,8] *Zvinchuk* [9] | *Terao* [10,11] | *Gold-schmidt* [12] | *Nowotny* [13] | *Shafer* and *Roy* [3] | *Schäfer et al.* |
|---|---|---|---|---|---|---|---|---|
| TT(tief-tief) (low-low) | | pseudo-hexagonal modific.[5] | δ [6] (γ′ [6]) | δ | | diffuse α-form | | TT [14,15] |
| T (tief) (low) | T [2] | | γ [6] | γ | α [12] | α | III [3] | |
| B (Blätter) (plates) | | | ζ [7] | γ′ [11] | | | | B [15] |
| M (medium) | M [2] | | β [6] (α′ [6]) | β | precursor of β | β | II [3] | |
| H (high) | H [2] | | α [6] | α | β [12] | β′ [13] | I [3] | |
| N (needles) | | | | | | | | N [15,16] |
| P (prisms) | | | η [8] | | | | | P [15] |
| ε | | | ε [4] | | | | | |
| I-high | | | | | | | I-high [3] | |
| II | | | | | | | II [3] | |
| ox I to ox VI (oxidation) | | | | | | | | ox I to ox VI [18] |

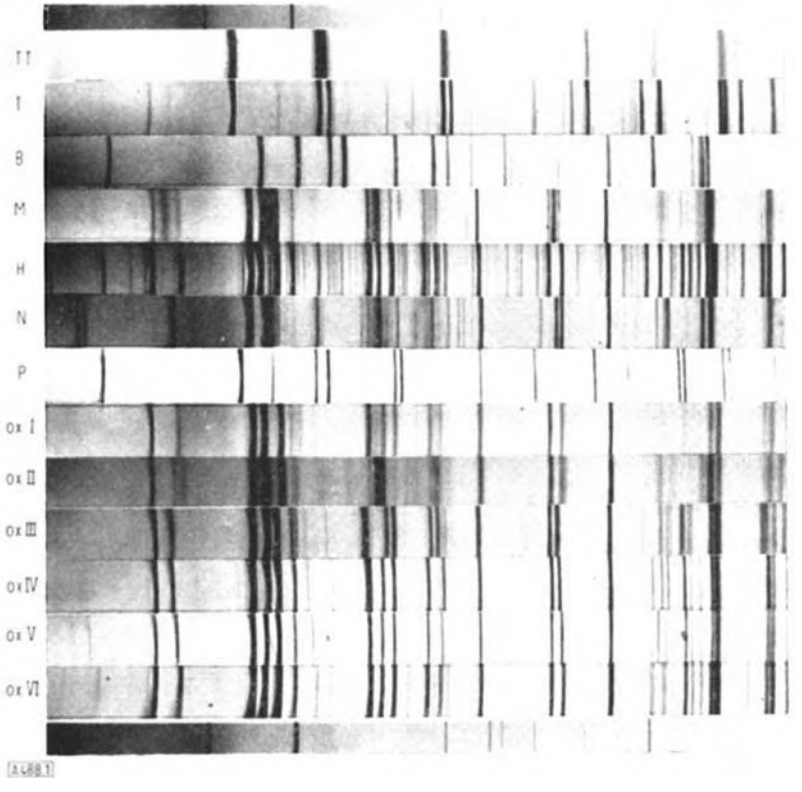


Fig. 1. Guinier photographs of the $Nb_2O_5$-forms TT, T, B, M, H, N, P, and oxI to $ox_{VI}$. Cu—$K\alpha_1$ radiation. Top and bottom: α-quartz for comparison. Range of angles: $\Theta$ = 5 to 30°.

spacings reported[3], different from all known forms of niobium pentoxide[4] and has therefore also been cited as a new phase.

In the X-ray characterization of $Nb_2O_5$ samples, the large number of lines in the powder diagram and the often slight difference between the X-ray patterns of related modifications must be borne in mind. Guinier photographs with Cu-$K\alpha_1$ radiation are particularly suitable because of the high resolution possible (Fig. 1). The X-ray patterns of the T-, B-, M-, N-, and P-forms are derived from samples prepared by chemical transport (cf. Section 4) in crystals of millimeter size. Interplanar spacings (d values) for most of the observed forms of $Nb_2O_5$ are given in the literature (Table 2). The table also indicates those literature data which agree particularly well with our own observations. Numerical values will therefore be given below only for the M-form.

[4] *A. Reisman* and *F. Holtzberg*, J. Amer. chem. Soc. *81*, 3182 (1959).

[5] *L. K. Frevel* and *H. W. Rinn*, Analytic. Chem. *27*, 1329 (1955).

[6] *F. Holtzberg*, *A. Reisman*, *M. Berry*, and *M. Berkenblit*, J. Amer. chem. Soc. *79*, 2039 (1957).

[7] *F. Laves*, *R. Moser*, and *W. Petter*, Naturwissenschaften *51*, 356 (1964).

[8] *F. Laves*, *W. Petter*, and *H. Wulf*, Naturwissenschaften *51*, 633 (1964).

[9] *R. A. Zvinchuk*, Soviet Physics Crystallogr. *3*, 750 (1959).

[10] *N. Terao*, Japan. J. appl. Physics *2*, 156 (1963).

[11] *N. Terao*, Japan. J. appl. Physics *4*, 8 (1965).

[12] *H. J. Goldschmidt*, J. Inst. Metals *87*, 235 (1958/59).

[13] *H. Nowotny*, *F. Benesovsky*, *E. Rudy*, and *A. Wittmann*, Mh. Chem. *91*, 975 (1960).

[14] *F. Schulte*, Thesis, Universität Münster, 1962.

[15] *H. Schäfer*, *F. Schulte*, and *R. Gruehn*, Angew. Chem. *76*, 536 (1964); Angew. Chem. internat. Edit. *3*, 511 (1964).

[16] This notation is also used by *Andersson* [17].

[17] *S. Andersson*, International Conference on Electron Diffraction and Crystal Defects, Melbourne 1965, II D-2.

[18] *R. Gruehn* and *D. Bergner*, unpublished work.

The selection of an X-ray pattern of the M-form suitable as a "standard" for this form presents difficulties: some preparations [25–27] have given Guinier photographs differing clearly from *Brauer*'s M–$Nb_2O_5$ diagram [2]. Other data [9, 11, 22] differ from those of *Brauer* [2] and also to some extent from our own values. In order to be able to describe the X-ray pattern of the M-form, taking into account its variability [11, 13] (which we have also observed), it is convenient to distinguish between two groups of reflections (Table 3):

1. Diffuse reflections with d values (*e.g.* 4.88, 3.57, 2.05 Å) for which no lines of the H-form exist. These diffuse reflections disappear in the M → H conversion by a decrease in their intensity without any observed splitting.

2. Some sharp and some diffuse reflections, whose lines can be assigned to H–$Nb_2O_5$ with the same or almost the same value of d.

*Brauer*'s M–$Nb_2O_5$ diagram [2] contains all the lines of group 1 and also all the diffuse and some sharp reflections of group 2; Guinier photographs of our preparations, however, show other sharp reflections of group 2, which we have denoted in Table 3 by 2+. If the different resolving power of the Guinier compared with the Debye method is taken into account, it would be conceivable that the additional reflections (2+) were unobservable on Debye photographs [2]. However, we cannot exclude the possibility that these reflections arise from a partial M → H–$Nb_2O_5$ conversion and therefore cannot be ascribed to pure M–$Nb_2O_5$. Since, however, our preparations, which were obtained in various ways (cf. Section 4) as powders or needle-like crystals, all give the (2+) reflections, we consider it likely that sufficiently ordered M–$Nb_2O_5$ preparations give all the reflections mentioned (Table 3) [28]. The ratio of the intensities of the diffuse and the sharp reflections depends on the degree of order of the preparations; variations in the literature data are thus understandable.

Table 2. List of references on interplanar spacings (d or Θ values) and on intensities of X-ray reflections. The references in braces give results which are in best agreement with our own observations. The references in parentheses do not give d values but, for example, line diagrams.

| | | | |
|---|---|---|---|
| TT | {[5]} | ([6, 13]) | [10] |
| T [19] | {[12]} | ([6, 13, 22]) | [2, 5, 10, 20, 21, 23] |
| B | {[7, 15]} | | [11] |
| M | | ([22]) | [2, 9, 11] |
| H | {[10, 12, 24]} | ([22]) | [2, 6, 9, 21] |
| N | {[15]} | | |
| P | {[15]} | | |
| I-high | | | [3] Not repeated by |
| II | | | [3] the present authors |
| oxI-oxVI | Not yet published [18]. | | |

Table 3. Interplanar spacings (d) and estimated intensities (I) of the M-form of $Nb_2O_5$. The diffuse reflections (I in parentheses) are decisive for the detection of M–$Nb_2O_5$.

| d [Å] | I | Group (cf. text) | d [Å] | I | Group (cf. text) |
|---|---|---|---|---|---|
| 5.12 | 2 | 2 | 2.54 | 5 | 2 |
| 4.88 | (1) | 1 | 2.49 | 4 | 2+ |
| 4.63 | 2 | 2 | 2.31 | 6 | 2 |
| 3.86 | 1 | 2 | 2.07 | 3 | 2+ |
| 3.75 | 10 | 2 | 2.05 | (4) | 1 |
| 3.64 | 6 | 2 | 2.04 | 3 | 2+ |
| 3.57 | (8) | 1 | 1.91 | 8 | 2 |
| 3.49 | 6 | 2 | 1.78 | (3) | 2 |
| 3.36 | 3 | 2 | 1.70 | 1 | 2 |
| 3.16 | 1 | 2 | 1.69 | 4 | 2+ |
| 2.83 | 5 | 2 | 1.68 | (5) | 2 |
| 2.77 | (6) | 2 | 1.67 | 4 | 2+ |
| 2.70 | 3 | 2 | | | |

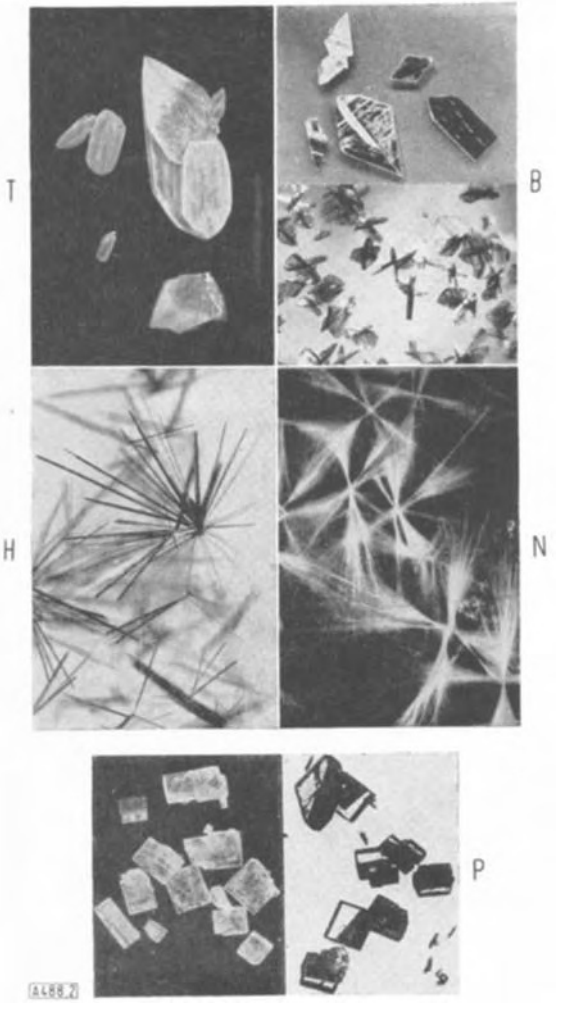


Fig. 2. Crystals of the T-, B-, H-, N-, and P-forms of $Nb_2O_5$. The lengths of the needle-shaped crystals shown (H, N) are 4 to 8 mm, the size of the prisms (P) is 1 to 2 mm, while T- and B–$Nb_2O_5$ form 5 to 10 mm single crystals. The crystals of the T-form are optically turbid but behave as single crystals to X-rays.

[19] The data of *R. B. Hahn* [20] have been ascribed by *Nowotny et al.* [13] to the TT-form.

[20] *R. B. Hahn*, J. Amer. chem. Soc. *73*, 5091 (1951).

[21] *H. Inouye*, U.S. Atomic Energy Comission Publ. 1953 (ORNL-156).

[22] *H. Schäfer, A. Dürkop*, and *M. Jori*, Z. anorg. allg. Chem. *275*, 289 (1954).

[23] *D. W. Bridges* and *W. M. Fassell*, J. electrochem. Soc. *103*, 326 (1956).

[24] *A. Magnéli* and *S. Lagergren*, A.S.T.M. Index-Card 5-0379/80. These lattice constants, however, are incorrect (personal communication from *R. Norin*). Correct data: a = 21.23 Å; b = 3.824 Å; c = 19.43 Å; β = 120°10′; cf. [52].

[25] *H. Schäfer, R. Gruehn*, and *M. Hüesker*, unpublished work.

[26] *H. Schäfer, R. Gruehn*, and *M. Rönspiess*, unpublished work.

[27] *R. Gruehn* and *M. Görbing*, unpublished work.

[28] Single-crystal investigations on this subject are in progress (*W. Mertin*, Münster).

[29] Calculated by us from the lattice constants [5].

[30] For these measurements we are obliged to Miss *M. Rönspiess*.

Table 4 gives lattice constants, X-ray densities, and molar volumes calculated from these data, together with pycnometrically determined densities. In addition, the following densities have been measured pycnometrically: amorphous $Nb_2O_5$ obtained from "chloride niobic acid": 4.36 g/cm³ [6], amorphous $Nb_2O_5$ (from $NbO_2$): 5.12 g/cm³ [41]; N–$Nb_2O_5$: 4.59 g/cm³ [30]; P–$Nb_2O_5$: 4.50 g/cm³ [30].

Fig. 2 shows crystal photographs of the T-, B-, H-, N-, and P-forms of $Nb_2O_5$. The crystals were prepared by the chemical transport of $Nb_2O_5$ (see below). An illustration of the M-form is not given, since it crystallizes in needles like the H-form.

Table 4. Lattice parameters and densities of some forms of $Nb_2O_5$.

| Form of $Nb_2O_5$ | Lattice constants [Å] | Space group or crystal system | Formula units $Nb_2O_5$/cell | Density [g/cm³] $D_{X\text{-ray}}$ | Density [g/cm³] $D_{pyk}$ | Molar volume [cm³] $M(Nb_2O_5)$ (from $D_{X\text{-ray}}$) | References and Remarks |
|---|---|---|---|---|---|---|---|
| TT | a 3.607; c 3.925 | "pseudohexagonal" | 0.5 | 4.99 [29] | — | 53.3 | [5] similar data for "hexag." unit cell in [10] |
| | — | — | — | — | 4.86 | — | [30] |
| T | a 6.19; b 3.65; c = 3.94 | orthorhombic | — | — | — | — | [31]; similar data in [10, 32] |
| | a 6.24; b 43.79; c 3.92 | orthorhombic | 12 | 4.94 | - | 53.8 | [9] |
| | a 7.31; b 15.72; c = 10.75; β = 120°42' | monoclinic | 12 | 4.99 [33] | — | 53.3 | [5]; similar data for monoclinic unit cell in [10] |
| | — | — | — | — | 5.17 | — | [6] |
| | — | — | — | — | 5.04 | — | [30] |
| B | a 12.73; b = 5.56; c = 4.88; γ = 105°05' | B 2/c | 4 | 5.29 | — | 50.2 | [8]; structure investigated on single crystals |
| | a = 7.348; b = 5.962; c = 13.646; β = 115°30' | monoclinic | — | — | — | — | [11] |
| | — | — | — | — | 5.19 | — | [14] |
| M | a = 20.28; b = 3.83; c 20.28; β = 120° | monoclinic | 15 | 3.84 | — | 54.8 | [9] |
| | a = 22.10; b = 7.638; c 19.52; β = 118°15' | monoclinic | — | — | — | — | [11] |
| | — | — | — | — | 4.3–4.4 | (62–60) [34] | [30] |
| H | a = 21.50; b = 3.825; c 20.60; β = 121°45' | monoclinic | 14 | 4.29 | — | — | [24]; lattice constants do not correspond to the indices given [6, 24a] |
| | a 21.34; b = 3.816; c = 19.47; β = 120°20' | monoclinic | 14 | 4.52 | 4.55 | 58.8 | [6]; similar data in [10, 32] |
| | a 19.63; b = 3.835; c = 20.93; β = 120° | monoclinic | 14 | 4.53 | 4.46 | 58.7 | [3] |
| | a = 20.39; b = 3.82; c = 19.47; β = 115°39' | monoclinic | 14 | 4.51 | — | 58.9 | [9] |
| | a = 21.16; b = 3.822; c 19.35; β = 119°50' | P 2 | 14 | 4.55 | 4.55 [6] | 58.4 | [35]; structure investigated with single crystals |

## 4. Modes of Formation

Niobium pentoxide can be obtained in many different ways. If the solid oxide is heated for some time at temperatures above 1000 to 1200 °C, the H-form, which is stable under these conditions, is always produced.

The forms of $Nb_2O_5$ prepared at lower temperatures are mostly metastable (cf. Section 7). The method of preparation then also plays a decisive part. If the $Nb_2O_5$ is obtained, for example by oxidation, the resulting form may depend on the nature of the starting material. Moreover, small amounts of impurities may have a stabilizing or directing effect. If the starting material used is "niobic acid" separated from aqueous solution, then in addition to the presence of water, the presence of foreign ions is also of importance. In this connection, we call the niobic acid precipitated from a pyrosulfate digestion "sulfate niobic acid". These preparations of "sulfate niobic acid" (or "chloride niobic acid", *etc.*) are carefully washed and have only a small (but detectable) content of sulfate (or chloride, *etc.*), which cannot be reduced by further washing.

The chemical transport [36] of niobium pentoxide is of particular importance; the reversible formation of gaseous oxide halides $NbOX_3$ (with X = Cl, Br, I) is utilized [37]. For the chloride system, used most frequently, we have

$$Nb_2O_5 + 3\ NbCl_5\ (g) = 5\ NbOCl_3\ (g) \quad (1)$$

This transporting reaction is endothermic, so that $Nb_2O_5$ is consumed in the hot zone ($T_2$) of the reaction tube and deposited in the less hot zone ($T_1$) [37a]. The

[31] *W. T. Holser*, Acta crystallogr. *9*, 196 (1956).

[32] *O. Kubaschewski* and *B. E. Hopkins*, J. less-common Metals *2*, 172 (1960).

[33] Calculated [6] from the lattice constants [5].

[34] Calculated by us from the pycnometric density [30].

[35] *B. M. Gatehouse* and *A. D. Wadsley*, Acta crystallogr. *17*, 1545 (1964).

[36] *H. Schäfer*: Chemische Transportreaktionen. Verlag Chemie, Weinheim 1962.

[37] *H. Schäfer* and *M. Hüesker*, Z. anorg. allg. Chem. *317*, 321 (1962).

[37a] Under somewhat modified conditions, the transport can also take place exothermally, *i.e.* into the hotter zone, in accordance with the scheme $Nb_2O_5 + 3\ NbX_4\ (g) + 3\ X_g = 5\ NbOX_3\ (g)$. This is important particularly in the preparation of NbOx phases (x < 2.5) [25].

transport is carried out in the presence of free chlorine [$p(Cl_2)$ = 1 atm, 20 °C], so that the appearance of reduced $NbO_x$ phases ($x < 2.50$) is suppressed. The procedure followed in the transport experiments will be described below using H–$Nb_2O_5$ as an example. Fig. 3 shows a transport tube before charging.

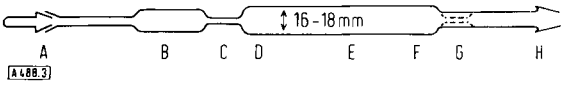


Fig. 3. Charging of a transport tube (fused silica). Length DEF: 12 to 13 cm.

A known amount of $Nb_2O_5$ (250–700 mg) is introduced into the reaction tube at D from H, and subsequently a capillary is drawn at G. After part B of the tube has been charged with the calculated amount of Nb, and A has been closed, the tube is evacuated from H and the section of the tube C–G is heated with a bunsen flame. After cooling, a stream of purified $Cl_2$ is passed through the tube from A. When the air has been displaced, the Nb at B is ignited and $NbCl_5$ is condensed at DEF. The cooled tube, filled with $Cl_2$ at 1 atm (room temperature) is sealed off at C and G. The transport tube C–G has then been charged.

It is then introduced into the predetermined temperature gradient in a horizontal or, if desired, in a sloping position (convection) where it remains for from 3 to 8 days. Under these conditions, the transport of $Nb_2O_5$ from $T_2$ to $T_1$ takes place with the aid of the reversible establishment of the equilibrium (1). If heating is to be discontinued, first only Section D of the tube is removed from the oven, so that the contents of the gas phase deposit there and do not contaminate the transported crystals that have already deposited at EF.

Fig. 4 shows a transport tube with H–$Nb_2O_5$ crystals. The white substance on the left-hand side of the tube consists of the condensed contents of the gas phase (essentially $NbOCl_3$).

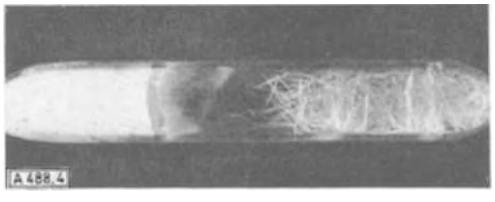


Fig. 4. Transport tube with crystals of H–$Nb_2O_5$. Left: $NbOCl_3$ condensate.

The occurrence of oxygen-poorer $NbO_x$ phases, which is observed, for example, during chemical transport in the absence of $Cl_2$, has also been studied [26, 37–39]. It is important in connection with the forms of $Nb_2O_5$ oxI to oxVI, and it may be mentioned that the O:Nb ratio can be obtained very accurately *via* determination of the $Nb^{4+}$ content.

For a direct determination of small contents of $Nb^{4+}$ [40], samples of 3–15 mg are introduced under vacuum into a degassed KOH–KBr melt, whereupon all the substance dissolves in the form of niobate(V) and an amount of hydrogen equivalent to the content of $Nb^{4+}$ is liberated. The gas evolved is pumped off, compressed with a Töpler pump, and its volume measured in a mercury gas buret; it can also be identified by combustion over CuO. The limits of error may be characterized by the analytical compositions $NbO_{2.420 \pm 0.004}$ and $NbO_{2.480 \pm 0.001}$.

Preparations of all modifications investigated so far with the composition $NbO_{2.49}$ already have a definite blue color. An oxygen deficiency cannot, therefore, be made responsible for the occurrence of numerous colorless forms of $Nb_2O_5$. Contrary assumptions [11, 13] are incorrect.

### TT—$Nb_2O_5$

This form, first described by *Frevel* and *Rinn* [5], was produced as the first state crystalline to X-rays [6] from "sulfate niobic acid" and "chloride niobic acid" on heating at 500 to 600 °C [3, 6, 14]; with longer times of heating, amorphous niobic acid is converted into TT-$Nb_2O_5$ at even lower temperature (*e.g.* 440 °C [6]) [41]. Different samples of niobic acid prepared in the same way may exhibit different rates of conversion, so that an X-ray check is always necessary.

The TT-oxide is also formed when $NbO_2$ is oxidized in air at 320 to 350 °C [41a], amorphous $Nb_2O_5$ being observed as an intermediate [41]. If the oxidation is carried out at higher temperatures (350 to 500 °C), TT–$Nb_2O_5$ is obtained only with very short reaction times [41]. In the reaction of $NbO_2$ with $Cl_2$, in accordance with the equation

$$3\ NbO_2 + {}^3/_2\ Cl_2 = Nb_2O_5 + NbOCl_3\ (g) \quad (2)$$

at 270 to 320 °C, we again obtained the TT-form [41]. The TT-form can also be obtained by oxidation of niobium alloys in air at, for instance, 800 °C [13], as well as by the slow oxidation of Nb or lower oxides arising from it under special conditions [10]. Moreover, TT-$Nb_2O_5$ (together with $Nb_3O_7Cl$) has been observed in the chemical transport of $Nb_2O_5$ in accordance with Eq. (1) for $T_1$ = 350 °C and $T_2$ = 450 °C [15, 26].

The 24-hour oxidation of $Nb_2O_5$ with air at 320 °C is to be recommended as a method of preparing pure TT-$Nb_2O_5$.

### T—$Nb_2O_5$

This form, described by *Brauer* [2], appears when "sulfate niobic acid" or "chloride niobic acid" is heated at 600 to 800 °C [3, 6, 41]. Prolonged heating at, for example, 400 °C (3 days) also leads to the T form [41]. In addition, it can be obtained from TT-$Nb_2O_5$, which changes almost continuously into T-$Nb_2O_5$ on being heated at 600 to 800 °C [41]. The T-form arises in a short time already at temperatures over 400 °C from TT-$Nb_2O_5$ obtained by the oxidation of $NbO_2$ in air at 320 to 350 °C [41]. If $NbO_2$ is oxidized in air at 600 to 800 °C, T-$Nb_2O_5$ is produced after a short time [41]. It is also produced in the oxidation of Nb or Nb alloys below 1000 °C [13]. Under hydrothermal conditions (P = 170 atm, T = 330–380 °C), amorphous "niobic acid"

[38] *R. Gruehn* and *H. Schäfer*, Naturwissenschaften *50*, 642 (1963).

[39] *R. Gruehn*, *D. Bergner*, and *H. Schäfer*, Lecture, Clausthal 1965. Summary: Angew. Chem. *77*, 1082 (1965); Angew. Chem. internat. Edit. *4*, 1087 (1965).

[40] *R. Gruehn*, unpublished work.

[41] *C. Brendel*, Münster, unpublished work.

[41a] TT-$Nb_2O_5$ produced in this way may still contain some amorphous $Nb_2O_5$.

also changes into T-$Nb_2O_5$ [3]. We have now obtained the T-form in single crystals by quenching supercooled $Nb_2O_5$ melts [42] and also by the chemical transport of $Nb_2O_5$ in accordance with Eq. (1) [26, 43].

For crystal formation by means of chemical transport a device has proved satisfactory which permits nucleation and crystal growth to be observed visually at the experimental temperature. A "fused silica oven" constructed for this purpose simultaneously permits a favorable rate of nucleation to be established by varying $T_2$-$T_1$ at constant $T_1$.

In principle, the following arrangement has been used [43]: a fused silica transport tube is fixed centrally in a horizontal silica tube of correspondingly larger cross-section, which carries the two heating coils for establishing the temperatures $T_1$ and $T_2$. The outer cladding of this oven has openings which permit nucleation and the growth of crystals to be observed between the windings of the heating coil. For example, for the preparation of T–$Nb_2O_5$, the temperature is first controlled such that $T_2$ = 890 °C and $T_1$ = 835 °C. Under these conditions, nuclei of T–$Nb_2O_5$ (and of B- and N–$Nb_2O_5$) can be formed. If it can be seen from the shape of the crystals (and from the color, which is yellowish at high temperatures for all $Nb_2O_5$ modifications except B–$Nb_2O_5$) that only T–$Nb_2O_5$ has been produced at $T_1$, $T_2$–$T_1$ is reduced by lowering $T_2$ to 875 °C. This prevents the formation of new nuclei, while the crystals which are already present grow further. The subsequent time of transport is, for example, 5 days. If unwanted crystals of other forms are formed, all nuclei can be removed again by interchanging $T_1$ and $T_2$.

The following procedures are recommended for the preparation of T-$Nb_2O_5$ *powder*:

1. Dehydration of substantially chloride-free washed "chloride niobic acid" at 400 °C (2 hours) with subsequent heating to 600 to 800 °C (10 hours).

2. Oxidation of $NbO_2$ in air at 400 °C for 4 to 5 hours, Samples of T-$Nb_2O_5$ prepared by methods 1 and 2. which cannot be distinguished by their Guinier diagrams, nevertheless show different transformation behavior on further heating [41] (cf. Section 5).

### B–$Nb_2O_5$

This form was first observed in the chemical transport of $Nb_2O_5$ in accordance with Eq. (1) when the deposition temperature $T_1$ was 750 to 850 °C and $T_2$–$T_1$ 100 °C [14, 15] (cf. also [7]). Under these conditions, N-$Nb_2O_5$ and P-$Nb_2O_5$ are formed in addition to B-$Nb_2O_5$, but the characteristic plate-like crystals of the B-form can easily be sorted out. Fig. 5 shows crystals of B- and N-$Nb_2O_5$ that have deposited together in the transport tube. Growth of large untwinned single crystals (cf. Fig. 2) can be achieved in the fused silica oven in the manner described for T-$Nb_2O_5$. Here again, by selection of nuclei, it is possible to obtain B-$Nb_2O_5$ alone, without contamination by other forms of $Nb_2O_5$ [43].

If $Nb_2O_5$ is transported in accordance with Eq. (1) (or by means of the analogous bromide or iodide systems), all the forms of $Nb_2O_5$ obtainable in this way (T, M, H, N, P, B) can be obtained with a blue color, *i.e.* with a low content of $Nb^{4+}$ [25, 26]. However, colorless crystals of stoichiometric composition are obtained when the transport according to Eq. (1) is carried out in an oxidizing atmosphere produced by the introduction of chlorine into the transport tube [$P(Cl_2)$ = 1 atm, 20 °C]. Even under these conditions, however, the B-form – and only this – is usually produced with light blue color [15] (composition, for example, $Nb_2O_{4.994}$). This color further facilitates hand-sorting of crystals of the B-form from mixtures; at higher temperatures it changes to pale green.

Fig. 5. Transport tube with crystals of B- and N–$Nb_2O_5$ deposited together.

The $Nb^{4+}$ content of the blue B-crystals was hardly lowered on ignition (800 °C) in air for several hours [44]. After 80 hours, however, appreciable decoloration had occurred, and after 800 hours the crystals became practically colorless [40].

Crystals of B-$Nb_2O_5$ obtained by the transport method contained less than 0.01 % of Cl [14]. However, this Cl content is not characteristic of the B-modification, since the latter can also be obtained free from chlorine by the oxidation of $NbO_2$.

During transport in the temperature gradient, the nature of the $Nb_2O_5$ added at $T_2$ does not affect the form of $Nb_2O_5$ depositing at $T_1$. Usually H-$Nb_2O_5$ was used as the starting material.

On prolonged isothermal heating at 750 °C in the presence of $NbOCl_3$ as transporting agent, we obtained [26] the pure B-form from T-$Nb_2O_5$ and P-$Nb_2O_5$ [45]. If H-nuclei are also present under these conditions, B-$Nb_2O_5$ is converted into the H-form already at 750 °C [26]; cf. Section 7.

TT-$Nb_2O_5$ and T-$Nb_2O_5$ prepared by the oxidation of $NbO_2$ in air are converted into the B-form [11, 41] by further heating in air (*e.g.* for a few hours at 800 °C; 180 hours at 500 °C) [41]. It is also possible, although less convenient, to start from metallic Nb.

The oxidation of $NbO_2$ in air (24 hours at 320 °C and 24 hours at 850 °C for the subsequent TT → T → B conversion) may be recommended for the preparation of pure B-$Nb_2O_5$ powder.

[42] *W. Mertin*, Münster, unpublished work.

[43] *W. Jagusch*, Münster, unpublished work.

[44] *R. Gruehn, F. Schulte*, and *H. Schäfer*, Angew. Chem. *76*, 685 (1964); Angew. Chem. internat. Edit. *3*, 634 (1964).

[45] All T-$Nb_2O_5$ preparations undergo this T → B conversion, regardless of their history.

M—$Nb_2O_5$

This form, first observed by *Brauer* [2], arises when "sulfate niobic acid" or "chloride niobic acid", or the T-form obtained from "sulfate" or "chloride" niobic acid is heated for some hours at 900 to 950 °C [14,27] (or possibly a shorter time at a higher temperature [2,6]). The M-form has also been observed in the oxidation of Nb and Nb alloys at 1000 °C in air [13] and in the chemical transport of $Nb_2O_5$ *via* $NbOCl_3$ or $NbOBr_3$, with $T_1$ = 850 to 900 °C and $T_2-T_1$ = 100 °C [14,25,26].

It is difficult to prepare pure M-$Nb_2O_5$, since considerable amounts of H-$Nb_2O_5$ are frequently produced together with the M-form (cf. Section 3). In transport experiments, moreover, M-$Nb_2O_5$ and N-$Nb_2O_5$ may be deposited together. There is as yet no reliable method of preparation of the pure M-form.

H—$Nb_2O_5$

This modification of niobium pentoxide is particularly easy to obtain. As far as is known, H-$Nb_2O_5$ arises from any other form on heating in air to about 1100 °C. The same result is obtained when precipitates of niobic acid, *e.g.* from solutions containing sulfate, chloride, bromide, iodide, or fluoride, are heated at 1100 °C or when metallic niobium or lower oxides (NbO, $NbO_2$, $NbO_x$) are oxidized in air at this temperature to $Nb_2O_5$. If single crystals of the M-form are heated at 1100 °C, the single-crystal nature is retained in the transformation to the H-form, while crystals of all other forms of $Nb_2O_5$ are converted into polycrystalline H-$Nb_2O_5$ [44].

The H-form is also produced under hydrothermal conditions (P = 170 atm, T = 1075 °C) [3] and from a melt when, to avoid separation of T-$Nb_2O_5$, it is seeded with H-$Nb_2O_5$ or is cooled very slowly [42] (cf. also [4]). By chemical transport in accordance with Eq. (1), the pure H-form deposits [14] when the lower temperature $T_1$ of the transport tube is at least 950 °C [26]; cf. Fig. 4. In the presence of H-nuclei (cf. B-$Nb_2O_5$) or in the presence of HCl as transporting agent [P(HCl) = 1atm, 20 °C] we obtained H-$Nb_2O_5$ even at 750 °C [26].

N—$Nb_2O_5$

This form arose first in the chemical transport of $Nb_2O_5$ [14,15] in accordance with Eq. (1), the temperature of separation $T_1$ being 830 to 840 °C and $T_2-T_1$ 90 to 100 °C [26]. Under these conditions, often mixtures of N- with M- or H-$Nb_2O_5$ and also some B-$Nb_2O_5$ were obtained. The bundles of needles of N-$Nb_2O_5$ (Figs. 2 and 5) can, however, easily be distinguished.

The formation of the N-form is promoted by the presence of small amounts of fluoride [17,26]. Thus by chemical transport we obtained only the N-form when the quartz tube had been cleaned with dilute hydrofluoric acid (subsequently rinsed with water and heated in vacuum) or when the transport tube contained a little fluoride, *e.g.* 5 mg of $NbO_2F$ per 500 mg $Nb_2O_5$, in addition to the other materials. The N-$Nb_2O_5$ obtained in this way contained $<0.1$ % of F [26,46]. However, even when F was rigorously excluded, crystals of the N-form could be produced by chemical transport, particularly by the selection of nuclei in the fused silica oven ($T_1$ = 840 °C; $T_2$ = 900 °C; cf. T-$Nb_2O_5$) [43]. The N-form has also been obtained under hydrothermal conditions (2000 atm, 900 °C) [17], where OH probably plays the role of F.

*Andersson* and *Åström* [47] obtained N-$Nb_2O_5$ by thermal decomposition of $NbO_2F$; N-$Nb_2O_5$ obtained in this way contains about 0.2 % of F [48]. This method of preparation has been confirmed in our laboratory [49].

The order of magnitude of the F content of preparations of $Nb_2O_5$ has been determined by mass spectrometry. The samples were heated in a graphite crucible to incipient decomposition, and the ion currents corresponding to the gaseous fluorides produced were measured and integrated over time [48]. The limit of detection was 0.05 to 0.1 % of F. The compound $Nb_{31}O_{77}F$ [17,50] was used as an F standard. The mass-spectrometric determination therefore is based on the F-content proposed by structural analysis.

Thermal decomposition of $NbO_2F$ can be recommended for the preparation of pulverulent N-$Nb_2O_5$ (containing about 0.2 % of F): $NbO_2F$ is heated for some hours at 1000 °C in a high vacuum (with the pump running) [49]. Different preparations of $NbO_2F$ can behave somewhat differently with respect to the decomposition temperature (see under P-$Nb_2O_5$). The course of the decomposition should be checked by X-ray analysis, since $Nb_3O_7F$ [47,70] may arise when the time of heating is too short and H-$Nb_2O_5$ when it is too long.

P—$Nb_2O_5$

This form first arose in the chemical transport of $Nb_2O_5$ in the chloride system [Eq. (1)], with $T_1$ = 750 °C and $T_2-T_1$ = 100 °C [14,15]. Meanwhile it has also been prepared by the transport method by *Laves et al.* [8]. Analogous transport in the bromide and iodide systems also gives the P-form in admixture with T- and B-$Nb_2O_5$ at $T_1$ = 650 to 750 °C [25]. The experimental conditions and the specific formation of nuclei play a decisive part. This goes so far that in an earlier stage of the investigations [14] we thought that the P-form was thermodynamically stable over a certain range of temperatures and was obtainable from all other modifications. However, this view was not confirmed, and it is actually very difficult in some cases to obtain P-$Nb_2O_5$ by transport in the presence of $NbOCl_3$ and $Cl_2$.

New experiments have shown that the formation of P-$Nb_2O_5$ is promoted when the transport tube is filled, not with $NbOCl_3$ + $Cl_2$, but with $Cl_2$ (1 atm/20 °C) and small amounts of water, *e.g.* 0.04 to 0.12 mg of $H_2O$/ml of tube volume ($T_1$ = 600, $T_2$ = 800 °C). At present this appears to be the most satisfactory method for the preparation of P-$Nb_2O_5$ [26]. Possibly the formation of P-$Nb_2O_5$ observed previously in transport with $NbOCl_3$ + $Cl_2$ without the addition of water [14] should be ascribed to the water content of the silica.

[46] In the presence of fluorides, $SiO_2$ can be transported from the quartz wall onto the deposited N-$Nb_2O_5$ crystals; the amorphous $SiO_2$ adhering to the surface simulates a high $SiO_2$-content [15] of the $Nb_2O_5$ [27].

[47] *S. Andersson* and *A. Åström*, Acta chem. scand., in press.

[48] *K. Rinke*, Münster; unpublished mass-spectrometric investigation.

[49] *D. Giegling*, Münster, unpublished work.

[50] We are obliged to Dr. *S. Andersson* for the sample.

We obtained the P-form in admixture with T-$Nb_2O_5$ by heating "chloride niobic acid" with a high content of HCl (*e.g.* 8%) to 650–800 °C (in air [15] or in a stream of moist HCl) [26]. The decomposition of $Nb_3O_7Cl$ (in air or in vacuum) at 700 to 800 °C yielded corresponding polycrystalline mixtures of P-$Nb_2O_5$ and T-$Nb_2O_5$ [42].

The use of HCl-containing starting materials obviously has a promoting effect on the formation of P-$Nb_2O_5$. Nevertheless, analyses of P-$Nb_2O_5$ crystals obtained by chemical transport and of precipitates heated to 750 °C gave a Cl content of less than 0.01 % [14].

The P-form also arises during the very slow thermal decomposition (heating from room temperature to 740 °C over 5 days) [41] of $NbO_2F$, which can easily be obtained from $Nb_2O_5$ and hydrofluoric acid.

### ε—$Nb_2O_5$

*Reisman* and *Holtzberg* [4] found a freezing point (1435 °C) corresponding to a metastable phase when an $Nb_2O_5$ melt was supercooled. The ε-$Nb_2O_5$ crystallizing under these conditions remained stable for a few hours above 1400 °C, but was converted exothermally into H-$Nb_2O_5$ on further cooling or on seeding with the latter material. Since it has so far been impossible to investigate this substance by X-rays, the possibility cannot be excluded that one of the known forms of $Nb_2O_5$ crystallized in a metastable state from the melt and caused the observed phenomenon.

### $Nb_2O_5$-I-high

This modification was described by *Shafer* and *Roy* [3] as a stable high-temperature form. According to differential thermal analysis and high-temperature X-ray photographs taken by these authors, at 1285 °C H-$Nb_2O_5$ is converted endothermally and reversibly into $Nb_2O_5$-I-high. The occurrence of this new stable form above 1250 °C has been queried by *Reisman* and *Holtzberg* [4], particularly since the d-values given for $Nb_2O_5$-I-high differ only slightly from those of H-$Nb_2O_5$. The substance observed [3] may have been an $NbO_x$ phase with $x < 2.5$. More accurate investigations on this point should be carried out.

### $Nb_2O_5$-II

This form was reported by *Shafer* and *Roy* [3], who obtained poorly crystalline $Nb_2O_5$-II by heating amorphous "niobic acid" to 880 to 950 °C in air; particularly well crystallized samples were obtained under hydrothermal conditions (P = 170 atm, T = 390 to 1060 °C).

*Shafer* and *Roy* considered their $Nb_2O_5$-II to be identical with *Brauer*'s M-$Nb_2O_5$ [2], but the d values they give for $Nb_2O_5$-II can be assigned neither to the M-form nor to any other form of niobium pentoxide [4]. The behavior of $Nb_2O_5$ under hydrothermal conditions should be investigated further (cf. also the hydrothermal production of N-$Nb_2O_5$).

### The oxI to oxVI Forms of $Nb_2O_5$ [18]

Closely similar $NbO_x$ phases separated by heterogeneous regions [38, 39] can be prepared by chemical transport under reducing conditions [26] and by the reduction of $Nb_2O_5$ (or the oxidation of $NbO_2$) in an $H_2/H_2O$ atmosphere, *e.g.* at 1300 °C [51]. Some of them have also been obtained by tempering oxide mixtures [52–54]. All these deep blue materials correspond to definite structures (Table 5) [35, 53–56]; there are two modifications of the compound $NbO_{2.417}$, corresponding to $Nb_{12}O_{29}$.

The oxidation of this material at 1100 °C in air leads to H-$Nb_2O_5$. A 4-hour oxidation at 650 °C, however, yields other colorless $Nb_2O_5$ preparations that we denote by oxI to oxVI. Their Guinier diagrams are related to those of the initial $NbO_x$ phases, but differ from one another and from that of H-$Nb_2O_5$ (Fig. 1). On subsequent ignition (1100 °C), all these preparations change into the H-form.

Table 5. The $Nb_2O_5$ forms oxI to oxVI [18] and their origin.

| Composition $NbO_x$ by chemical analysis | $NbO_{2.417}$ (I) [55a] | $NbO_{2.417}$ (II) [55a] | $NbO_{2.453}$ [55a] | $NbO_{2.46}$ [39] | $NbO_{2.467}$ to $_{2.480}$ [38, 39] | $NbO_{2.483}$ [39] |
|---|---|---|---|---|---|---|
| Formula corr. to structural analysis | $Nb_{12}O_{29}$ (I) [53, 55] | $Nb_{12}O_{29}$ (II) [53] | $Nb_{22}O_{54}$ [52, 55] | | $Nb_{25}O_{62}$ (upper limit of the phase) [54] | |
| Designation of the 650 °C oxidation product | oxI | oxII | oxIII | oxIV | oxV | oxVI |

The $Nb_2O_5$-forms oxI to oxVI are preparatively and X-radiographically defined. They are undoubtedly closely related. All (or some of them) might belong to the same mixed-crystal phase. Information on whether these materials are to be regarded as modifications in the sense of Section 2 can be given only by structural investigations.

### Other Forms of $Nb_2O_5$

The multiplicity of the forms of $Nb_2O_5$ is not exhausted by those described above. At any rate, we possess some preparations of $Nb_2O_5$ with a different X-ray pattern, which have not yet been investigated further [26, 57].


[51] *D. Bergner*, Münster, unpublished work.

[52] *R. Norin* and *A. Magnéli*, Naturwissenschaften *47*, 354 (1960).

[53] *R. Norin*, Acta chem. scand. *17*, 1391 (1963).

[54] *R. Norin*, Naturwissenschaften *52*, 300 (1965).

[55] *R. Norin*, personal communication.

[55a] For the assignments see *R. Gruehn* and *H. Schäfer*, J. less-common Metals, in press.

[56] *S. Andersson*, Bull. Soc. chim. France *1965*, 1088.

[57] *L. Zylka*, Münster, unpublished work.

## 5. "Memory" of Solids

Niobium pentoxide provides a fine example of this term, introduced by *Hüttig*[58]: T-$Nb_2O_5$ can be prepared in three ways; the resulting samples are not distinguishable by X-rays:

a) By oxidation of $NbO_2$ (4-5 h in air) at 500 to 600 °C.
b) By reaction of $NbO_2$ with $Cl_2$; 9–10 h, 270 to 300 °C; [cf. the formation of TT-$Nb_2O_5$ according to Eq. (2)]. Further heating (15 min at 500 °C in air).

c) By heating "sulfate" or "chloride" niobic acid (2 h, 600 °C in air).

However, the preparations "remember" their different origins, and behave differently on further heating[41]: $Nb_2O_5$ (a) is converted into B-$Nb_2O_5$ sharply at 817 °C (differential thermals analysis)

$Nb_2O_5$ (b) changes into B-$Nb_2O_5$ so slowly that the conversion is not complete even after 165 hours at 850 °C.

$Nb_2O_5$ (c) is converted into the forms M-$Nb_2O_5$ + H-$Nb_2O_5$ after heating for 16 hours at 800 °C. Here, therefore, the B-form has been passed over.

The basis of the "memory" of the three $NbO_2$ preparations has not yet been investigated. The first interpretation that comes to mind is incorporation of impurities or the presence of specific structural defects.

## 6. Structures

The crystal structures of the various forms of $Nb_2O_5$ are complicated. Accurate investigations of even the long-known forms have been undertaken only recently.

Octahedral elements are the decisive factor for the structure of the pentoxides. The stoichiometric O/Nb ratio of 2.5 can be achieved by the combination of various octahedral linkages, and this is the reason for the multiplicity of the $Nb_2O_5$ structures.

The situation is even more complicated, as in addition to crystal structures with all metal ions coordinated in a similar manner (a), there are also those containing cations of different coordination (type b; *e.g.* octahedral and tetrahedral coordination occur together). Type (a) includes a structure in which all the cations are surrounded octahedrally by $O^{2-}$ particles. Under these conditions, in addition to a structure of similarly linked octahedra (*e.g.* the $ReO_3$ lattice), modifications are conceivable in which several types of $O^{2-}$ octahedra can be distinguished by the distinct natures of their linkage in the lattice. The various ways of linking the $O^{2-}$ octahedra are expressed formally by the extent to which the $O^{2-}$ ions belonging to an octahedron must be ascribed to the corresponding cation[59]. In this way, for example, the $O^{2-}$ octahedra from which a hypothetical $M_3O_8$ structure[60] could be constructed are divided into two types: (1) octahedra which are joined by corners to all surrounding octahedra, so that each $O^{2-}$ is to be reckoned as belonging to two octahedra. This type of linkage, which is present in $ReO_3$, is designated $[MO_{6/2}]$ or $MO_{3.0}$. In addition, (2) octahedra joined by three corners (3 $O^{2-}$) and two edges (3 $O^{2-}$; here with two other octahedra in each case), are necessary. They are symbolized by $[MO_{3/2}\,O_{3/3}]$ or $MO_{2.50}$ (cf. Fig. 6). $MO_{3.0} + 2\,MO_{2.50}$ give $M_3O_8$.

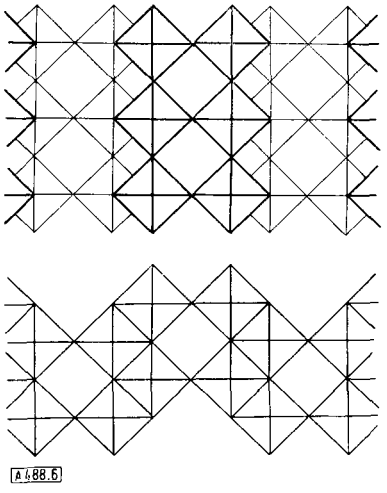

Fig. 6. A particularly simple $M_2O_5$ structure: $V_2O_5$ (highly idealized, after [56]).

Such a notation proves to be expedient for understanding structures in which the unit cell contains a multiplicity of $O^{2-}$ octahedra[40]. It can also be used correspondingly for a structure composed of different $O^{2-}$ coordination polyhedra (type b), particularly octahedra and tetrahedra. If a geometrically simple principle of construction from $O^{2-}$ coordination polyhedra, all possessing the same type of linkage, is required for $Nb_2O_5$, $5/2$ $O^{2-}$ must be assigned to each metal ion; this condition can be realized, for example, by a structure composed of $[MO_{3/2}\,O_{3/3}]$ octahedra. Such $MO_{2.5}$ octahedra exist with various types of linkage; one of these possibilities is observed in the case of B-$Nb_2O_5$. Here $O^{2-}$ octahedra form pairs through a common edge; the linkage *via* $O_{3/3}$ corresponds to that in the rutile lattice[8]; cf. Fig. 7b.

Another geometrically simple arrangement (two $Nb_2O_5$ per cell) is that in which $[MO_{3/2}\,O_{3/3}]$ octahedra are joined by two perpendicular edges with the neighboring octahedra in such a way that a zigzag chain of octahedra is produced. These chains arranged in paralle would be linked to one another by sharing corners. The resulting constructional principle corresponds to that of the highly idealized[56] structure of $V_2O_5$[62] (Fig. 6). A variation of this principle is found in the structure of P-$Nb_2O_5$[62a]. It is worth noting that the chains of octahedra mentioned, with O/Nb = 2.5, occur widely as an *additional* constructional element in several forms of $Nb_2O_5$ and related compounds ($Nb_{12}O_{29}$[53],

[58] *G. F. Hüttig, E. Zeidler,* and *E. Franz,* Z. anorg. allg. Chem. *231*, 104 (1937).

[59] This notation is not completely unambiguous but is adequate to characterize the types of linkage that occur frequently.

[60] This corresponds to the $Nb_3O_7F$ structure [61].

[61] *S. Andersson,* Acta chem. scand. *18*, 2339 (1964).

[62] *H. G. Bachmann, F. R. Ahmed,* and *W. H. Barnes,* Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *115*, 110 (1961).

[62a] *F. Laves* and *W. Petter,* 8th Discussion Meeting of the Sektion für Kristallkunde, Marburg 1965.

$Nb_{25}O_{62}$ [54,63]; $Nb_{31}O_{77}F$ [17], $Nb_{17}O_{42}F$ [17], $Nb_3O_7F$ [61], and $Nb_3O_7Cl$ [64]). In the majority of such cases (although the X/Nb ratio is close to 2.5) a structure in which "$MO_{2.5}$" octahedra predominate is avoided, and an arrangement is preferred in which these $MO_{2.5}$ octahedra are "diluted" to a considerable extent by $MO_3$ and $MO_{<2.5}$ octahedra. From another point of view, this means that "block structures" [35] occur. Within the blocks, $MO_3$ octahedra are joined in the manner of $ReO_3$ by corners, while the blocks are bound to one another by edge sharing of octahedra ($MO_{2.5}$ and $MO_{2.5}$) (cf. also Table 6).

The occurrence of different linkage regions can be regarded to a certain extent as "internal disproportionation" of the structural elements (octahedra), while an actual disproportionation into separated phases is excluded, since the Nb already possesses its maximum charge. If we pass to ternary systems with an X/M ratio of 2.5, there is an additional possibility of an actual disproportionation into phases with simpler structures.

The principle of the structure composed of octahedra with various O/Nb ratios (above, below, and equal to $MO_{2.5}$) makes it clear that the stoichiometric ratio O/M = 2.5 has no particular structural significance. Consequently, slightly different O/M values near 2.5 can be realized whenever the charge of the lattice units permits such deviations. Related to this is the fact that numerous phases differing from the stoichiometry O/Nb = 2.5 occur in the reduction of $Nb_2O_5$ [38,39,51–54] and that forms of $Nb_2O_5$ (H [35], N [65]) belong to "structure-related series" [35,56] whose members have different O/M values. Finally, the O/M ratio can also be varied by passing to ternary compounds rich in $Nb_2O_5$ [38,39,63,66]. In this way, a direct structural relationship is obtained between the forms of $Nb_2O_5$ and the related ternary oxides [35,56,63,67].

A discussion of the $Nb_2O_5$ structures from these idealized geometrical points of view provides information on the possible structure variants and on relationships between them, but permits not statements to be made about the thermodynamic stability of the existing arrangements. However, it should be mentioned that the absolute value of the enthalpy of formation of the $Nb_2O_5$ modifications decreases in the sequence B > T > H, while the molar volume increases in that sequence (cf. Section 7). Such a relationship has been observed frequently with other classes of compounds [68].

### B-$Nb_2O_5$

The crystal structure of this modification has been investigated by *Laves et al.* [8]. It belongs to space group B 2/b, and possesses the smallest molar volume (50.2 cm³) of all known forms of $Nb_2O_5$. The anionic lattice consists of a slightly deformed hexagonal close packing of $O^{2-}$; the hexagonal layers run parallel to $(2\bar{1}0)$, with an a-axis in (001). The octahedral cavities of this packing are two-fifths occupied by Nb. The monoclinic cell contains eight $[MO_{3/2}O_{3/3}]$ octahedra occupied by Nb, every two octahedra being linked through an edge to form a pair. Each of the two $O^{2-}$ belonging to a common edge are simultaneously corners of two more octahedra (Fig. 7b); the same type of linkage occurs in the rutile structure (Fig. 7a).

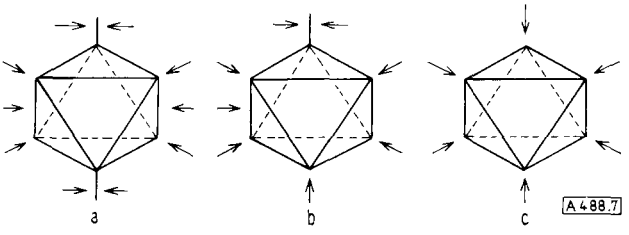


Fig. 7. Types of linkage of $O^{2-}$ octahedra, according to *F. Laves* [8]. a: Rutile $[MO_{6/3}]$. b: B—$Nb_2O_5$ $[MO_{3/3}O_{3/2}]$. c: $ReO_3$ $[MO_{6/2}]$.

Of the other four $O^{2-}$ of the octahedra under consideration, three are joined by corners (cf. $ReO_3$, Fig. 7c) to neighboring octahedra, while one belongs simultaneously to the common edge of another pair of octahedra. The pairs mentioned are arranged parallel to $(2\bar{1}0)$; they are mutually displaced by the width of an octahedron and engage with one another, forming in this way a common "sheet" parallel to (100) with a depth of about a/2 (Fig. 8). These sheets are bound to one another only by sharing corners ($O_{1/2}$). Edge linkages in which $O_{1/3}$ participate occur only within the sheets.

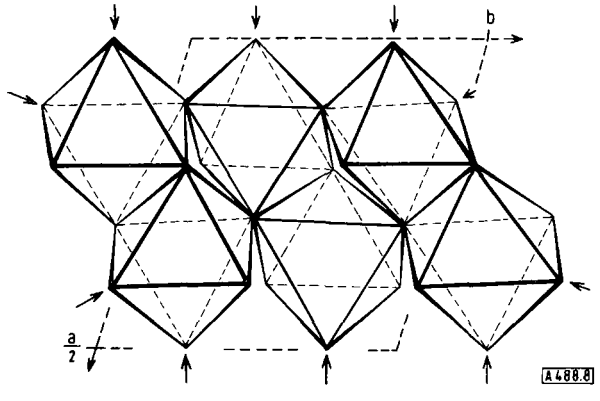


Fig. 8. Structure of B—$Nb_2O_5$. Schematic section of the skeleton of $O^{2-}$ octahedra. ↑ : corner linkage corresponding to $ReO_3$.

The numerous unoccupied octahedral sites present in the B-$Nb_2O_5$ structure obviously offer good possibilities for the incorporation of further metal cations, and this is probably responsible for the fact that B-$Nb_2O_5$ also incorporates additional Nb under extreme conditions, as follows from the blue color of the preparations (cf. Section 4).

### T-$Nb_2O_5$

The crystal structure of this modification, which has the smallest molar volume (about 53 cm³) apart from B-$Nb_2O_5$, is still unknown. Powder photographs by

[63] Cf. also *R. S. Roth* and *A. D. Wadsley*, Acta crystallogr. *18*, 724 (1965).

[64] *H. G. Schnering* and *W. Mertin*, Naturwissenschaften *51*, 552 (1964).

[65] *S. Andersson*, personal communication.

[66] *A. D. Wadsley*, Acta crystallogr. *14*, 660 (a), 664 (b) (1961).

[67] *R. S. Roth*, *A. D. Wadsley*, and *S. Andersson*, Acta crystallogr. *18*, 643 (1965).

[68] Cf. *H. Biltz*: Raumchemie der festen Stoffe. Leopold Voss; Leipzig 1934.

the Guinier method show a great similarity to T-$Ta_2O_5$, which, however, in contrast to T-$Nb_2O_5$, occurs in several variants [40,69], and also a particular similarity to $Nb_5O_{12}F$ [70]. Other relationships exist with $U_3O_8$ and $\alpha$-$UO_3$. It is possible that the compounds mentioned have an almost hexagonal cationic lattice [71]. Single crystals of T-$Nb_2O_5$ have been prepared only recently, and are now being investigated [42].

The crystal structure of the "pseudohexagonal" [5] TT-$Nb_2O_5$ is perhaps closely related to the structure of T-$Nb_2O_5$. Since a continuous conversion into the T-form seems to occur when TT-$Nb_2O_5$ is heated, with some strong reflections being split and many very weak ones being added, the TT-form should probably be regarded as a less ordered precursor of the T-form [3,6].

### H–$Nb_2O_5$

The crystal structure of this relatively open monoclinic modification (molar volume 58.4 $cm^3$) has recently been determined by *Gatehouse* and *Wadsley* [35]. According to these authors, the structure of the H-form (space group P 2), which contains 28 Nb in the unit cell, is characterized by the occurrence of structural groups related to $ReO_3$. The idealized H-$Nb_2O_5$ structure contains two different structural elements which can be regarded as $ReO_3$-lattice sections of different sizes (and are therefore called "$ReO_3$ blocks"). Within each of these blocks, the corner linkage of the oxygen octahedra continues uninterrupted ($\infty$) in the direction of growth of the needle (b-axis [35]); in both directions perpendicular to b, the extension of the blocks is limited to a typical number of octahedra. The two types of blocks occurring can be formulated as $[3\times4\times\infty]$ and $[3\times5\times\infty]$ [35], the number of octahedra in each edge of a block being given. A section in the b-direction of the length of one octahedron diagonal is sufficient to describe the H-$Nb_2O_5$ structure (and all crystal structures built up correspondingly, cf. N-$Nb_2O_5$) while the characteristics of the structure are represented by a picture of the extension of the blocks in the (010) plane (Fig. 9). It can be seen that the $[3\times5\times\infty]$ blocks are displaced with respect to one another and are bound through the narrow sides into "obliquely running chains" of blocks. The spaces between each two of these parallel series of blocks are filled with $[3\times4\times\infty]$ blocks, the position of which is shifted by b/2 as compared with the $[3\times5\times\infty]$ blocks. This block skeleton, with 27 octahedrally surrounded niobium cations per cell, contains an additional 4/4 Nb in tetrahedral cavities, half of these cavities being occupied by Nb. Here Nb occurs both in octahedral and in tetrahedral coordination.

The shear planes [72] envisaged between the $ReO_3$ blocks are therefore characterized by the fact that here

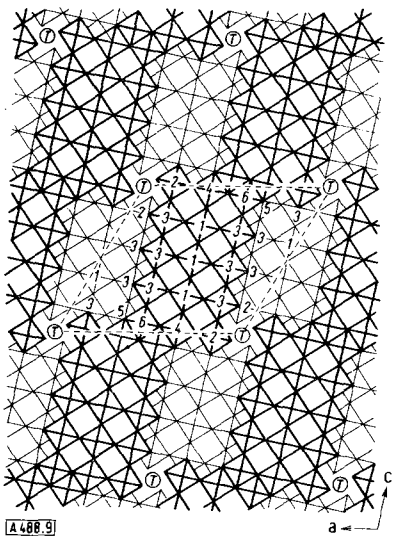


Fig. 9. Structure of H–$Nb_2O_5$, idealized [35]. For the numering of the octahedra, see Table 6. The unit cell is indicated by the broken lines.

the oxygen octahedra of adjacent blocks are bound to one another by sharing edges. At these positions, some of the octahedra possess a formal O/M ratio of less than 2.5, so that the stoichiometry $M_2O_5$ arises from the combination of a total of six types of octahedra differing in their O/M ratio (Table 6).

Table 6. Structure of H–$Nb_2O_5$.

| Linkage symbol | O/Nb | Octahedra per cell | Contribution to the cell content | No. in Fig. 9 |
|---|---|---|---|---|
| $[NbO_{6/2}]$ | 3.00 | 5 | $Nb_5O_{15}$ | 1 |
| $[NbO_{1/1}\ O_{2/2}\ O_{3/3}]$ | 3.00 [73] | 4 | $Nb_4O_{12}$ | 2 |
| $[NbO_{3/2}\ O_{3/3}]$ | 2.50 | 12 | $Nb_{12}O_{30}$ | 3 |
| $[NbO_{2/2}\ O_{3/3}\ O_{1/4}]$ | 2.25 | 2 | $Nb_2O_{4,5}$ | 4 |
| $[NbO_{2/2}\ O_{2/3}\ O_{2/4}]$ | $2.16_7$ | 2 | $Nb_2O_{4,33}$ | 5 |
| $[NbO_{1/2}\ O_{4/3}\ O_{1/4}]$ | $2.08_3$ | 2 | $Nb_2O_{4,167}$ | 6 |
| (a) Nb participating in octahedra + total O skeleton | | | $= Nb_{27}O_{70}$ | |
| (b) Nb present in tetrahedra | | | $- Nb$ | |
| Sum formula | | | $Nb_{28}O_{70}$ ($Nb_2O_5$) | |

### M–$Nb_2O_5$

The crystal structure of this form is still unknown. The close relationship of the powder diagrams of the M- and H-forms, which agree in a large number of reflections, permits the assumption of a considerable similarity between the two crystal structures. Since, on heating, the M-form apparently changes continuously into the H-form, the diffuse reflections characteristic for M-$Nb_2O_5$ gradually disappearing, the M-form should perhaps be regarded as a less ordered precursor of the H-form. This is supported by the observation that single

[69] *Yu. P. Simanov, A. V. Lapitskii,* and *E. P. Artemonova,* Izv. Mosk. Univ., Ser. fiz.-mat. Nauk. *6*, 109 (1954).

[70] *S. Andersson* and *A. Åström,* Acta chem. scand. *18*, 2233 (1964).

[71] *A. F. Wells*: Structural Inorganic Chemistry. Oxford University Press, Oxford 1962.

[72] *A. D. Wadsley,* Proc. Roy. Soc. New South Wales *92*, 25 (1958), cf. [66b].

[73] Since in the calculation (Table 6), all $O^{2-}$ were formally reckoned in the octahedron skeleton (a), one type of $O^{2-}$ was considered as belonging only to the octahedron ($O_{1/1}$) although this $O^{2-}$ simultaneously forms a corner of the neighboring Nb-occupied tetrahedron and therefore would also be counted partially with this Nb. The simplified distribution used here makes it possible to introduce the Nb contained in tetrahedral cavities in the calculation without reference to its environment (b).

crystals of M-$Nb_2O_5$ change into single crystals of H-$Nb_2O_5$ on heating [44]. X-Ray investigations with single crystals are in progress [28].

A structure in which the arrangement of H-$Nb_2O_5$ already exists in two dimensions while there is defective order in the third has been considered by *Holtzberg et al.* [6].

### N—$Nb_2O_5$

The crystal structure of this form has been investigated by *S. Andersson* [74]. According to this work, the structure of the monoclinic N-form can be related to the $ReO_3$ lattice in a similar manner to that of the H-form. The N-structure contains only *one* type of $ReO_3$ block: $[4\times4\times\infty]$; these (like the $[3\times5\times\infty]$ blocks of the H-form) are displaced with respect to one another and are linked to form obliquely running chains of blocks (Fig. 10). The positions of neighboring chains of blocks

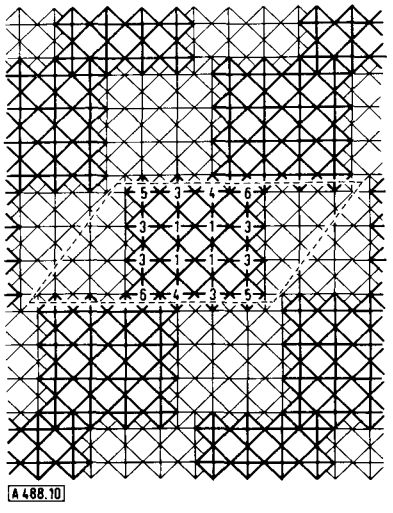


Fig. 10. Structure of N—$Nb_2O_5$. Shown in an idealized manner according to *S. Andersson* [74].

differ in the direction perpendicular to the plane of the figure by half an octahedron diagonal, so that edge sharing can occur at each surface of contact between two blocks. Here the stoichiometry is derived by combination of five types of octahedra differing in their formal O/M ratio (numbers 1, 3, 4, 5, and 6 in Fig. 10; cf. Table 6).

[74] These data were kindly made available by Dr. *S. Andersson* [65].

The lattice of N-$Nb_2O_5$ is closely related to the crystal structures of the compounds $TiNb_2O_7$ [66a], $Ti_2Nb_{10}O_{29}$ (I) (monoclinic) [66b], and $Nb_{12}O_{29}$ (I) (monoclinic) [53,55] and, like these, contains no tetrahedrally coordinated Nb cations.

### P—$Nb_2O_5$

The structure of this form has been investigated by *Laves et al.* [8,62a]. The P-structure contains zigzag chains of $MO_{2.5}$ octahedra like the idealized $V_2O_5$-structure, the zigzag chains being parallel and forming sheets. The chains of neighboring sheets, however, in contrast to idealized $V_2O_5$, are perpendicular to one another. The lattice constants for the tetragonal P-form (from Guinier photographs) [42] are: a = 3.90 Å; c = 25.5 Å; $D_{x\text{-ray}} = 4.54$ g/cm³ (cell content z = 4 $Nb_2O_5$); molar volume: 58.5 cm³.

## 7. Thermal and Thermochemical Behavior

Fig. 11 shows the thermal transformations observed so far [76]. The influence of the history of the preparations can be clearly observed. All the conversions mentioned in the figure take place monotropically, and the transition temperatures are therefore due to kinetics.

Consequently, the time of heating is of great importance as follows, for example, from Fig. 12. On the basis of differential thermal analyses, the signs of the heats of transformation are as follows:

amorphous → T, exothermic [6, 75, 77, 78]
T → B, exothermic [75]
T → H, endothermic [75]
B → H, endothermic [75]
P → H, endothermic [75]

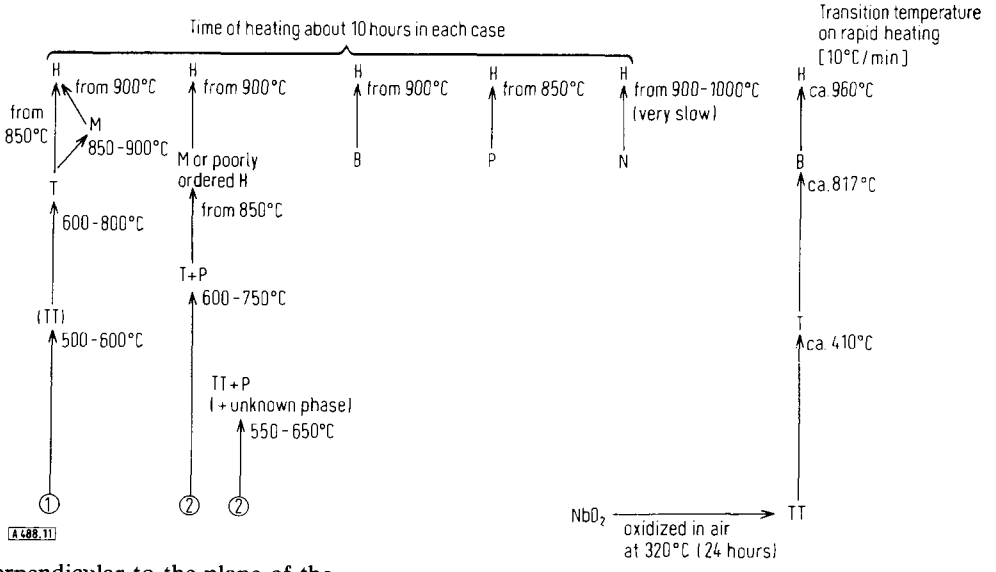


Fig. 11. Conversions of the forms of $Nb_2O_5$ on heating in air [75]. ① = amorphous "chloride niobic acid" or "sulfate niobic acid", thoroughly washed. ② = amorphous "chloride niobic acid" with a high content of HCl.

[75] Unpublished observations in these laboratories.

[76] The H → I-high transformation described by *Shafer* and *Roy* [3], upon which doubt has been cast by *Reisman* and *Holtzberg* [4], is not included.

[77] *J. Böhm*, Z. anorg. allg. Chem. *149*, 217 (1925).

Fig. 13 shows an example of a typical thermogram. The enthalpies of transformation are of the order of one to a few kcal/mole [78].

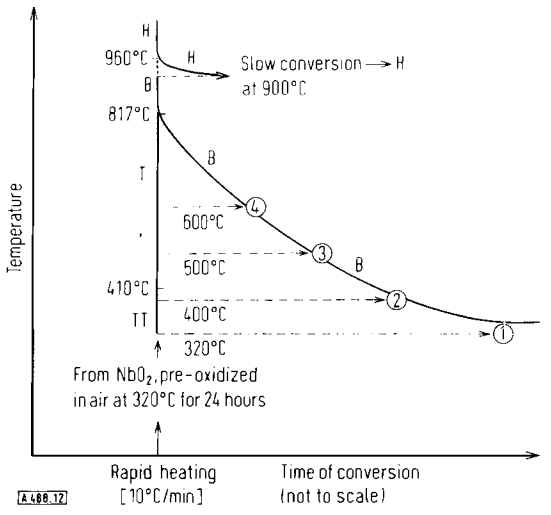


Fig. 12. Influence of time on the conversion of the $Nb_2O_5$ forms TT → T → B [75]. Initial preparation: $NbO_2$ oxidized in air at 320 °C; ① = no conversion into B—$Nb_2O_5$ in 46 days; ② = predominantly B—$Nb_2O_5$ after 14 days; ③ = predominantly B—$Nb_2O_5$ after 90 hours, pure B—$Nb_2O_5$ after 180 hours; ④ = predominantly B—$Nb_2O_5$ after 2 hours.

No indications have so far been found of thermal effects in the TT → T and M → H transformations.

It is significant for thermodynamic stability that on isothermal heating [750 °C, $P(NbOCl_3)$ = 5 atm and $P(Cl_2)$ = 3.5 atm] tablets of mixtures of the P- and B-forms, or of the T- and B-forms, are converted into the pure B-form [26,45]. In contrast to transport in a temperature gradient, no new formation of nuclei was necessary in this case. It is also important that mixtures of the B- and H-forms are converted into the B-form on isothermal heating [650 °C, $P(NbOCl_3)$ = 5 atm and $P(Cl_2)$ = 3.1 atm] [26]. The reversibility of the B → H transformation was first observed in this way.

The thermodynamic data given in the literature ($\Delta H°$ [79]; $S°$ [80]; $C_p°$ [81]) refer to the H-form.

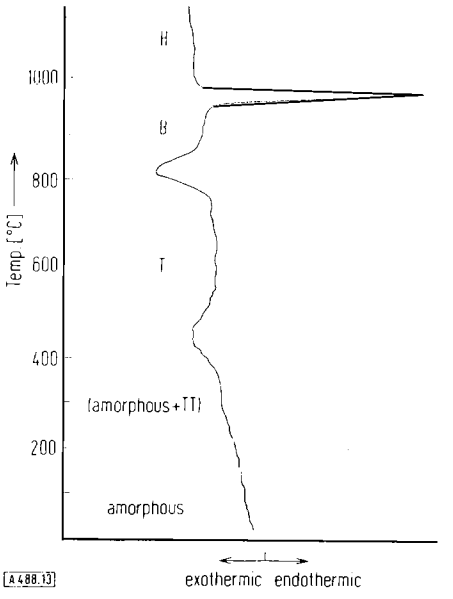


Fig. 13. Differential thermal analysis of the conversions of the $Nb_2O_5$ forms amorphous → T → B → H. Rate of heating: 10 °C/min. Starting material: $Nb_2O_5$ from $NbO_2$ oxidized in air at 320 °C for a short time.

The observations so far available support the assumption that of all the forms, B-$Nb_2O_5$ has the highest absolute value of the enthalpy of formation. Consequently, B-$Nb_2O_5$ is thermodynamically stable at low temperatures. As described, the conversion B → H could be observed at 750 °C, while the reverse conversion is realized at 650 °C. If the mean (700 °C) is taken to be the equilibrium temperature, and if in addition an enthalpy of transformation of 2 kcal/mole is assumed [41], we obtain for the B → H transformation an entropy increase of 2 cal. The increase in entropy can be understood on the basis of the structure.

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# Compounds of Phosphorus with Silicon and Aluminum

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BASED ON INVESTIGATIONS CARRIED OUT WITH DIPL.-CHEM. G. BECKER, DR. G. POPPENBURG, DR. M. ROCHOLL, AND DR. G. TRENCZECK

*Dedicated to Prof. W. Klemm on the occasion of his 70th birthday*

*The formation and properties of silicon-phosphorus and aluminum-phosphorus compounds are described. Silylphosphines are decomposed solvolytically by $H_2O$, $C_2H_5OH$, $NH_3$, hydrogen halides, $C_2H_5I$, and boron halides at the Si–P bond; decomposition may be preceded by formation of an addition compound. Extensive side reactions during the reaction of halogenosilanes with $LiPEt_2$ [1] (formation of $Et_2P–PEt_2$, $HPEt_2$, Si-rich residues) are due to an excess of $LiPEt_2$ in the reaction mixture. The reaction of $LiPEt_2$ with $AlCl_3$, $AlHCl_2$, and $AlH_2Cl$ leads to definite aluminum-phosphorus compounds if only one $PEt_2$ group is present per Al atom, e.g. in $(Cl_2Al–PEt_2)_3$ and $(H_2Al–PEt_2)_3$, or if salts such as $Li[Al(PEt_2)_4]$ and $Li[AlH_2(PEt_2)_2]$ can be formed with an excess of $LiPEt_2$.*

## A. Silylphosphines

The first hydrides containing an Si–P bond were prepared in 1953 by two groups of workers. While *Aylett, Emeléus*, and *Maddock* [2] found the compounds $SiH_3PI_2$, $(SiH_3)_2PI$, and $(SiH_3)_3P$ by the action of $SiH_3I$ on white phosphorus, *G. Fritz* [3] obtained $SiH_3PH_2$ by the reaction of $SiH_4$ with $PH_3$.

$SiH_4$ decomposes at about 400 °C *via* intermediate products into hydrogen and silicon, whereas appreciable thermal decomposition of $PH_3$ takes place only above 550 °C. Equation (1) shows the first step in the decomposition of $SiH_4$ [4].

$$SiH_4 \rightarrow \dot{S}iH_3 + \dot{H} \qquad (1)$$

The following free-radical reactions must be assumed in connection with Equation (1) for the pyrochemical formation of $SiH_3PH_2$ (450 °C, gas phase, reduced pressure)

$$\dot{H} + PH_3 \rightarrow \dot{P}H_2 + H_2 \qquad (2)$$

$$\dot{S}iH_3 + \dot{P}H_2 \rightarrow SiH_3PH_2 \qquad (3)$$

$SiH_3PH_2$ (b.p. 12.7 °C) can be distilled off from less volatile silicon-phosphorus compounds such as $SiH_2(PH_2)_2$ [5]. A blue-black substance of composition $Si_2P$ and amorphous to X-rays, which decomposes at about 600 °C into Si and SiP [6], remains behind. $Si_3PH_2$ is also formed by an electric discharge in mixtures of gaseous $SiH_4$ and $PH_3$, as shown by mass-spectrometric investigation of the products [7]. An electric discharge in mixtures of $SiH_3PH_2$ and $SiH_4$ or of $Si_2H_6$ and $PH_3$ gives $(SiH_3)_2PH$ [8], $Si_2H_5PH_2$, and other products.

### 1. Reactions of Silylphosphine, $SiH_3PH_2$

$SiH_3PH_2$ ignites spontaneously in air [9]. In alkaline solution, the compound is hydrolysed quantitatively in accordance with Equation (4).

$$SiH_3PH_2 + 4\,H_2O \xrightarrow{HO^-} \{Si(OH)_4\} + 3\,H_2 + PH_3 \qquad (4)$$

In an acidic medium the hydrolysis is substantially more complicated. With dilute hydrochloric acid, evolution of $H_2$, $PH_3$, and $SiH_4$ (traces) sets in even below 0 °C, solid silicon oxyhydrides [*] being formed. All of the phosphorus of the $SiH_3PH_2$ is evolved as $PH_3$. Treatment of these decomposition products with alkali liberates the same amount of hydrogen as the alkaline hydrolysis of the $SiH_3PH_2$, namely three moles per mole of $Si_3PH_2$. Consequently, in acid hydrolysis cleavage of the $Si_3PH_2$ molecule begins at the Si–P bond:

$$SiH_3PH_2 + H_2O \xrightarrow{H^+} H_3SiOH + PH_3 \qquad (5)$$

[1] The following abbreviations are used in this paper: Et = $C_2H_5$; Me = $CH_3$; M = alkali metal.

[2] *B. J. Aylett, H. J. Emeléus*, and *A. G. Maddock*, Research (London) *6*, 30 (1953); J. inorg. nuclear Chem. *1*, 187 (1955).

[3] *G. Fritz*, Z. Naturforsch. *8b*, 776 (1953).

[4] *K. Stockland*, Trans. Faraday Soc. *44*, 545 (1948); *H. J. Emeléus* and *C. Ried*, J. chem. Soc. (London) *1939*, 1021; *G. Fritz*, Z. Naturforsch. *7b*, 507 (1952).

[5] *G. Fritz*, Z. anorg. allg. Chem. *280*, 332 (1955).

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[9] *G. Fritz* and *H. O. Berkenhoff*, Z. anorg. allg. Chem. *289*, 250 (1957).

[*] Silicon oxyhydrides are high-molecular weight silicon compounds of uncertain composition, containing SiH, SiO, and SiOH groups.

followed with rising temperature by the decomposition of the silanol according to:

$$n\ H_3SiOH \rightarrow H_2 + \text{silicon oxyhydrides} + \text{traces of } SiH_4 \quad (6)$$

On solvolysis with $C_2H_5OH$, it is possible by working at two temperatures to cause the evolution of $PH_3$ and the formation of $H_2$ from the SiH groups to take place successively [9]. Cleavage of the Si–P bond with $C_2H_5OH$ (anhydrous, saturated with gaseous HCl), in which 1 mole of $PH_3$ is formed according to Equation (7), begins at temperatures as low as about −80 °C.

$$SiH_3PH_2 + EtOH \rightarrow H_3SiOEt + PH_3 \quad (7)$$

If the alcoholic solution is now allowed to warm up slowly to room temperature, evolution of $H_2$ sets in, at first slowly and then more vigorously, according to Equation (8).

$$n\ H_3SiOEt \rightarrow H_2 + \text{traces of } SiH_4 + \text{SiH-containing esters of polysilicic acid} \quad (8)$$

When the reactions (5) and (7) are carried out in the presence of dissolved HCl, $H_3SiCl$ could be formed first, which would then react with $H_2O$ or $C_2H_5OH$ to give $H_3SiOH$ or $H_3SiOC_2H_5$, respectively.

In liquid ammonia the Si–P bond of the $SiH_3PH_2$ is split primarily in accordance with Equation (9).

$$SiH_3PH_2 + NH_3 \rightarrow SiH_3NH_2 + PH_3 \quad (9)$$

The $SiH_3NH_2$ produced gives rise to subsequent reactions leading to high-molecular SiH-containing silicon-nitrogen compounds and $H_2$. $SiH_3PH_2$ reacts with HBr at temperatures as low as about −80 °C:

$$SiH_3PH_2 + HBr \rightarrow H_3SiBr + PH_3 \quad (10)$$

## 2. Syntheses of Organo-Substituted Silylphosphines

The pyrochemical reaction of $SiH_4$ with $PH_3$ yields $SiH_3PH_2$ and some other compounds of this type which have not been investigated; however, the preparation of relatively large amounts in this way is very laborious. We therefore attempted to make polar Si and P compounds react with one another [Eq. (11)] in order to facilitate formation of the Si–P bond by the formation of the salt MX.

$$\equiv SiX + MP= \rightarrow \equiv Si-P= + MX \quad (11)$$

(X = Cl, Br, I; M = alkali metal)

The reaction of $LiPH_2$ with $H_3SiBr$, $H_3SiI$, or $SiH_2I_2$ (in diethyl ether) has so far not led to the desired silylphosphines. Instead, sublimable products of as yet unknown composition are formed. Similar results were obtained [10] in the reaction of $H_3SiI$ with the ether-soluble $LiPEt_2$. *Amberger* and *Boeters* [11] obtained $(SiH_3)_3P$ from $KPH_2$ and $H_3SiBr$ at a low temperature, but the formation of this compound indicates a series of parallel and/or subsequent reactions. In order to reduce the likelihood of side reactions, compounds were used which have no or only a few SiH groups, and in which the other valences of the silicon and phosphorus atoms are substantially blocked by unreactive groups (alkyl groups). The simplest reaction is that of $Me_3SiCl$ with $LiPEt_2$, which gives $Me_3Si–PEt_2$ [12] and $Et_2P–PEt_2$ simultaneously.

Some silylphosphines have been prepared by the reaction of $LiPEt_2$ with methylchlorosilanes and $SiCl_4$. These preparations are always accompanied by side reactions. Thus large amounts of diethylphosphine were produced in reactions which were intended to give SiH-containing substituted silylphosphines, and in reactions with SiH-free chlorosilanes – $SiCl_4$ and $Me_3SiCl$ – tetraethyldiphosphine and silicon-rich residues were formed. The yields of the desired products were correspondingly low [10, 13]. The initial assumption that silylphosphines are transformed into these by-products at higher temperatures can be dismissed, since $MeHSi–PEt_2$ undergoes no change on heating to 80 °C (with the exclusion of air and moisture) [14].

In the reaction of chlorosilanes with $LiPEt_2$, it was observed that the side reactions leading to $HPEt_2$ and $Et_2P–PEt_2$ occur to a smaller extent or not at all when an excess of the halogenosilane is maintained in the mixture during the whole reaction. Side reactions are always favored when the chlorosilane is added in drops to the $LiPEt_2$ solution. In this case, moreover, a red color of the solution is generally observed, which is absent in the presence of an excess of the chlorosilane (addition of $LiPEt_2$ solution in drops to the chlorosilane) [14]. Under these conditions, it was possible to obtain $Me_2HSi–PEt_2$ (b.p. 58.5 °C/25 mm Hg) in accordance with Equation (12).

$$Me_2HSiCl + LiPEt_2 \rightarrow Me_2HSi–PEt_2 + LiCl \quad (12)$$

This compound reacts further with an ethereal solution of $LiPEt_2$ [Equation (13)], as NMR investigations and the isolation of the product have shown.

$$Me_2HSi–PEt_2 + LiPEt_2 \rightarrow Me_2Si(PEt_2)_2 + LiH \quad (13)$$

$Me_2Si(PEt_2)_2$ (b.p. 83 °C/3 mm Hg) is also formed from $Me_2SiCl_2$ and $LiPEt_2$.

With an excess of $H_3SiBr$, $LiPEt_2$ reacts primarily as follows:

$$H_3SiBr + LiPEt_2 \rightarrow H_3Si–PEt_2 + LiBr \quad (14)$$

In spite of the excess of $H_3SiBr$ the compounds $H_2Si(PEt_2)_2$ and $HSi(PEt_2)_3$ arise as by-products [Equations (15) and (16)] as shown by proton resonance investigations [15].

$$H_3Si–PEt_2 + LiPEt_2 \rightarrow H_2Si(PEt_2)_2 + LiH \quad (15)$$

$$H_2Si(PEt_2)_2 + LiPEt_2 \rightarrow HSi(PEt_2)_3 + LiH \quad (16)$$

Subsequently the LiH gives LiBr and $SiH_4$ with the excess of $H_3SiBr$.

$HSiCl_3$ reacts with $LiPEt_2$ with the formation of SiH-containing silylphosphines only if the trichlorosilane is

[10] *G. Fritz, G. Poppenburg*, and *M. G. Rocholl*, Naturwissenschaften *49*, 255 (1962).

[11] *E. Amberger* and *H. Boeters*, Angew. Chem. *74*, 32 (1962) Angew. Chem. internat. Edit. *1*, 52 (1962).

[12] *G. Fritz* and *G. Poppenburg*, Angew. Chem. *72*, 208 (1960).

[13] *G. Fritz* and *G. Poppenburg*, Angew. Chem. *75*, 297 (1963); Angew. Chem. internat. Edit. *2*, 262 (1963).

[14] *G. Fritz* and *G. Becker*, unpublished work.

[15] *G. Fritz, G. Becker*, and *D. Kummer*, unpublished work.

permanently in excess[14]. However, even from such mixtures it is impossible to isolate pure $HSi(PEt_2)_3$, since chlorine-containing silylphosphines are formed simultaneously. Thus $ClHSi(PEt_2)_2$ is formed in addition to $HSi(PEt_2)_3$, but rearranges in accordance with Equation (17), as seen from NMR investigations[15].

$$2\ ClHSi(PEt_2)_2 \rightarrow Cl_2Si(PEt_2)_2 + H_2Si(PEt_2)_2 \quad (17)$$

The reaction of $HSiCl_3$ with $LiPEt_2$ (molar ratio 1:3) at room temperature, or more rapidly on slow heating to 100 °C, leads to a red-brown solution from which diethylphosphine and a red-brown solid of unknown constitution can be isolated.

The compounds obtained are summarized in Table 1. The investigations described give the following picture:

Table 1. Silylphosphines formed by the reaction of $LiPEt_2$ or $LiPMe_2$ with silicon halides. Me = $CH_3$, Et = $C_2H_5$.

| Silicon halide | Silylphosphine | B.p. (°C/mm Hg) | Ref. |
|---|---|---|---|
| $Me_3SiCl$ | $Me_3Si-PEt_2$ | 71–72/20 | [12] |
| $Me_2SiCl_2$ | $Me_2ClSi-PEt_2$ | 53–54/5 | [12] |
| $Me_2HSiCl$ | $Me_2HSi-PEt_2$ | 58,5/25 | [14] |
| $Me_2SiCl_2$ | $Me_2Si(PEt_2)_2$ | 83/3 | [12] |
| $Me_2HSiCl$ | $Me_2Si(PEt_2)_2$ | 83/3 | [14] |
| $SiCl_4$ | $Cl_3Si-PMe_2$ | 50/25 | [12] |
| $SiCl_4$ | $Cl_2Si(PMe_2)_2$ | 47/5 | [12] |
| $SiHCl_3$ | $Cl_2Si(PEt_2)_2$ | | [14] |
| $SiCl_4$ | $ClSi(PMe_2)_3$ | 120/>1 | [12] |
| $SiCl_4$ | $ClSi(PEt_2)_3$ | 138/142/>1 | [10] |
| $SiCl_4$ | $Si(PEt_2)_4$ | 160/1 | [13] |
| $C_6H_5SiH_2Cl$ | $C_6H_5SiH_2-PEt_2$ | 60–61/>1 | [10] |
| $H_3SiBr$ | $H_3Si-PEt_2$ | 53.5/79 | [14] |
| $H_3SiBr$ | $H_2Si(PEt_2)_2$ | *ca.* 110/13 | [14] |
| $SiHCl_3$ | $H_2Si(PEt_2)_2$ | *ca.* 110/13 | [14] |
| $H_3SiBr$ | $HSi(PEt_2)_3$ | | [14] |
| $SiHCl_3$ | $HSi(PEt_2)_3$ | | [14] |
| $SiHCl_3$ | $ClHSi(PEt_2)_2$ | | [14] |

Alkyl-substituted and SiH-containing silylphosphines such as $Me_2HSi-PEt_2$ and $H_3Si-PEt_2$ are stable when atmospheric moisture is excluded, and do not decompose on heating into $HPEt_2$ and compounds of higher molecular weight with Si–Si bonds.

Tetraethyldiphosphine and diethylphosphine are formed in relatively large amounts in the reaction of halogenosilanes with $LiPEt_2$ only if an excess of $LiPEt_2$ is present in the reaction mixture. If, on the other hand, an excess of halogenosilane is maintained, this side reaction is suppressed.

SiH-containing silylphosphines, such as $Me_2HSi-PEt_2$, react further with $LiPEt_2$, the SiH group being converted into an $Si-PEt_2$ group. Even fully alkylated silylphosphines react slowly with $LiPEt_2$.

The side reactions probably can be explained by a first reaction step involving a metal-halogen or metal-hydrogen exchange between silylphosphines containing SiCl or SiH groups [Equations (18) and (19)]; the starting materials and products then react further according to Equations (20) and (21) (in the reaction of $(R_2P)_3SiCl$).

$$(R_2P)_3SiCl + LiPR_2 \rightarrow (R_2P)_3SiLi + ClPR_2 \quad (18)$$

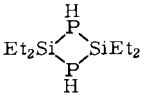
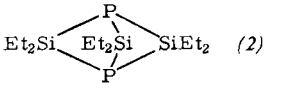
$$(R_2P)_3SiH + LiPR_2 \rightarrow (R_2P)_3SiLi + HPR_2 \quad (19)$$

$$LiPR_2 + ClPR_2 \rightarrow LiCl + R_2P-PR_2 \quad (20)$$

$$(R_2P)_3SiCl + LiSi(PR_2)_3 \rightarrow LiCl + (R_2P)_3Si-Si(PR_2)_3 \quad (21)$$

In addition, a secondary reaction of $LiPR_2$ with the Si–P bond must be considered. Final proof of the reactions represented by Equations (18)–(21) has not yet been obtained.

The reaction of alkali-metal phosphides with silicon halides gives compounds which contain several $SiR_3$ groups on the same phosphorus atom. Thus the reaction of $Me_3SiF$ and $KPH_2$ at low temperatures leads to $(Me_3Si)_2PH$ and $(Me_3Si)_3P$[16]. The same products are formed, together with $Me_3SiPH_2$, in the reaction of a mixture of $LiPH_2$, $Li_2PH$, and $Li_3P$ with $Me_3SiCl$[17,18]. A mixture of $Li_2PH$ and $Li_3P$ reacts with $Et_2SiCl_2$ with the formation of cyclic compounds for which *Parshall* and *Lindsey*[17] propose formulae *(1)* and *(2)*.

*(1)*  *(2)* 

$Me_3Si-P(C_6H_5)_2$ has been obtained by cleavage of tetraphenyldiphosphine with sodium and the subsequent reaction of the $(C_6H_5)_2PNa$ formed with $Me_3SiCl$[19].

Compounds of the type of $Et_3Si-PO(OEt)_2$ and $(EtO)_3Si-PO(OEt)_2$ have been obtained, with other products, from the reaction of $Et_3SiBr$ and $(EtO)_3SiCl$, respectively, with $P(OEt)_3$ or $[(EtO)_2PO]Na$[20–22].

### 3. Reactions of Organo-Substituted Silylphosphines

In distinction to $SiH_3PH_2$, organo-substituted silylphosphines have only one reactive position in the molecule: the Si–P bond. Thus $Me_3Si-PEt_2$ is hydrolysed quantitatively[23] in accordance with Equation (22).

$$Me_3Si-PEt_2 + H_2O \rightarrow Me_3SiOH + HPEt_2 \quad (22)$$

With an excess of EtI or EtBr (or with HI), $Me_3Si-PEt_2$ is split according to Equation (23).

$$Me_3Si-PEt_2 + 2\ EtX \rightarrow Me_3SiX + [Et_4P]X \quad (23)$$
$$X = I, Br$$

In the reaction of equivalent amounts at −78 °C, the stable addition product $Me_3Si-PEt_2 \cdot EtI$ (m.p. 122 °C) is formed, and with the equivalent amount of HI the colorless, crystalline $Me_3Si-PEt_2 \cdot HI$, which is stable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[20] *B. A. Arbuzov* and *A. N. Pudovik,* Dokl. Akad. Nauk SSSR *59*, 1435 (1948); Chem. Abstr. *47*, 4281 (1953).

[21] *F. Fehér, G. Kuhlbörsch, A. Blümcke, H. Keller,* and *K. Lippert,* Chem. Ber. *90*, 134 (1957); *N. W. Newlands,* Proc. chem. Soc. (London) *1960*, 123.

[22] *W. H. Keeber* and *H. W. Post,* J. org. Chemistry *21*, 509 (1956).

[23] *G. Fritz* and *G. Poppenburg,* Z. anorg. allg. Chem. *331*, 147 (1964).

only at −78 °C [24]. The adduct with ethyl iodide reacts further with an excess of ethyl iodide, giving the products of Equation (23).

Investigations of *Nöth* and *Schrägle* [25] have also shown the existence of addition compounds of $Me_3Si-PEt_2$ with $(BH_3)_2$, $BF_3$, $BCl_3$, and $BBr_3$. These addition compounds – $Me_3Si-PEt_2{\cdot}BH_3$ (m.p. 12 °C), $Me_3Si-PEt_2{\cdot}BF_3$ (decomposition at room temperature), $Me_3Si-PEt_2{\cdot}BCl_3$ (stable for short periods at room temperature), and $Me_3Si-PEt_2{\cdot}BBr_3$ (m.p. ≈ 5 °C) – decompose as follows:

$$3\ Me_3Si-PEt_2{\cdot}BH_3 \rightarrow 3\ Me_3SiH + (Et_2P-BH_2)_3 \quad (24)$$

$$Me_3Si-PEt_2{\cdot}BF_3 \rightarrow Me_3SiF + Et_2P-BF_2 \quad (25)$$

$$2\ Me_3Si-PEt_2{\cdot}BX_3 \rightarrow Me_3SiX + (Et_2P-BX_2)_2 \quad (26)$$

(X = Cl, Br).

Cleavage in accordance with Equation (24) sets in only above 80 °C, while with the chlorine and bromine compounds it begins already at room temperature. Silylphosphines containing SiCl and SiH groups, such as $Cl_3Si-PEt_2$ or $H_3Si-PEt_2$, are more sensitive to oxidation and hydrolysis than the completely alkylated compounds. The influence of the substituents on the Si–P bond cannot yet be reviewed.

## B. Aluminum-Phosphorus Compounds

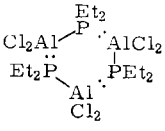
Whereas substitution predominates in reactions between compounds of elements of groups IV and V of the periodic systems, with compounds of elements of groups III and V the formation of adducts is preferred because of their electronic structure. Interesting compounds can sometimes be formed from the adducts by elimination of atoms or groups. The best known example is borazole, which is formed from the adduct $H_3B{\cdot}NH_3$ by the elimination of $H_2$.

The thermal treatment of addition compounds derived from aluminum and phosphorus compounds, however, leads only in a few cases to definite compounds, and is much less productive preparatively than the corresponding treatment of adducts of the compounds of boron and nitrogen. *Davidson* and *Brown* [26] obtained $(Me_2Al-PMe_2)_3$ from $Me_3Al$: $PHMe_2$ [*] by elimination of $CH_4$ at 215 °C. *Burg* and *Mödritzer* [27] obtained aluminum-phosphorus compounds by heating mixtures of aluminum-hydrogen compounds and $HPMe_2$. In the reaction of $ClPMe_2$ with $LiAlH_4$ in liquid $HPMe_2$, they obtained a solid of composition $Me_2PAlH_2$: $PHMe_2$, which could not be separated from the lithium chloride formed at the same time. In the treatment of $HPMe_2$ with $LiAlH_4$ (three weeks, 50 °C), these authors observed the formation of $LiAlH_{0.95}(PMe_2)_{2.93}$ with evolution of $H_2$. Similarly, with $HPMe_2$ they obtained substances of the composition $(Me_2P)_2AlCl$ and $Me_2PAlCl_2$ from $H_2AlCl$ and $HAlCl_2$, respectively (two weeks, 60 °C). A substance $LiAl(PH_2)_4$, formed from $LiAlH_4$ and $PH_3$ on prolonged heating, has also been reported [28].

These investigations show that the formation of definite aluminum-phosphorus compounds by thermal decomposition of the adducts is very complicated, and unsatisfactory from the preparative point of view. Consequently, attempts have been made to convert polar compounds of the two elements (aluminum halides and alkali-metal phosphides) into substances containing the Al–P bond, since the formation of LiCl favors this route. $LiPEt_2$ and $AlCl_3$ (molar ratio 1:1) react quantitatively in ether according to

$$LiPEt_2 + AlCl_3 \rightarrow LiCl + Cl_2Al-PEt_2 \quad (27)$$

After the bulk of the LiCl has precipitated, a clear ethereal solution is obtained, which separates into two layers when most of the ether is distilled off. White crystals of composition $Cl_2Al-PEt_2$ separate from the lower layer on cooling, and these do not redissolve in an excess of hot ether [29]. As is evident from the change in solubility, the substance is no longer monomeric. According to cryoscopic molecular weight determinations in $POCl_3$, $(Cl_2Al-PEt_2)_3$ *(3)* is present.



*(3)*

The trimerization is understandable because it leads to a six-membered ring in which the electron pair of the phosphorus atoms occupy the octet vacancies of the aluminum atoms. The solution of *(3)* in $POCl_3$ is stable for only a short time, as can be seen both from the yellow coloration and from the change in the freezing point depression with time. The decomposition takes the course (28).

$$(Cl_2Al-PEt_2)_3 + 3\ POCl_3 \rightarrow 3\ Et_2P-AlCl_2{:}OPCl_3 \quad (28)$$
*(3)*

The breakdown of the cyclic compound *(3)* is to be expected when a reactant with a lone electron pair displaces the phosphorus from its coordination position with respect to the aluminum. $POCl_3$ evidently is such a reagent. The reaction of 1 mole of $AlCl_3$ with 3 moles of $LiPEt_2$ in ether is also quantitative. Highly viscous products are formed, which contain aluminum and phosphorus in the expected ratio of 1:3 but which can hardly be regarded as compounds of definite molecular weight [30,31]. These products contain $[Al(PEt_2)_3]_n$ units with $n > 3$, and probably also the ether adduct $(Et_2P)_3Al{:}OEt_2$.

$[Al(PEt_2)_3]_n$ is also obtained by the reaction of crystalline $(Cl_2Al-PEt_2)_3$ *(3)* with 6 moles of $LiPEt_2$, a reaction in which one had hoped to obtain $[Al(PEt_2)_3]_3$. It must be assumed that the appearance of oligomers

[24] *G. Fritz* and *G. Poppenburg*, Naturwissenschaften *49*, 449 (1962).

[25] *H. Nöth* and *W. Schrägle*, Chem. Ber. *98*, 352 (1965).

[26] *N. Davidson* and *H. C. Brown*, J. Amer. chem. Soc. *64*, 316 (1942).

[*] The colon denotes the lone electron pair of the phosphorus, to which the aluminum compound adds.

[27] *A. B. Burg* and *K. Mödritzer*, J. inorg. nuclear Chem. *13*, 318 (1960).

[28] *A. E. Finkelt, C. Helling, V. Imhof, L. Nielsen*, and *E. Jacobsen*, Inorg. Chem. *2*, 504 (1963).

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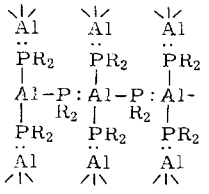
[31] *G. Fritz* and *G. Trenczek*, Z. anorg. allg. Chem. *331*, 206 (1964).

with $n > 3$ is based on the same principle as the formation of $[Cl_2Al{-}PEt_2]_3$ *(3)*. However, when several $PR_2$ groups are attached to the aluminum, these can form cross-links, as shown in Scheme 1.



Scheme 1.

The reaction of $HAlCl_2$ with 2 moles of $LiPEt_2$ also gives a highly viscous product of indefinite molecular size.

Aluminum-phosphorus compounds of definite molecular weight are formed when cross-linking is suppressed by limiting the number of coordinating groups on the Al atom to one [31]. Thus the reaction

$$3\ H_2AlCl + 3\ LiPEt_2 \rightarrow (H_2Al{-}PEt_2)_3 + 3\ LiCl \qquad (29)$$

leads to the compound $(H_2Al{-}PEt_2)_3$, which melts at 1–2 °C and spontaneously ignites in air but which can be distilled without decomposition [32].

Aluminum-phosphorus compounds prepared in this way have a pronounced tendency to form salt-like compounds with an excess of $LiPEt_2$ [33]. Thus the viscous $[Al(PEt_2)_3]_n$ obtained from 1 mole of $AlCl_3$ and 3 moles of $LiPEt_2$ reacts with further $LiPEt_2$:

$$[Al(PEt_2)_3]_n + n\ LiPEt_2 \rightarrow n\ Li[Al(PEt_2)_4] \qquad (30)$$

to give a compound of m.p. 224–226 °C. This compound is also formed directly from $AlCl_3$ and the stoichiometric amount of $LiPEt_2$ [Equation (31)].

$$AlCl_3 + 4\ LiPEt_2 \rightarrow Li[Al(PEt_2)_4] + 3\ LiCl \qquad (31)$$

The colorless, crystalline $Li[AlH_2(PEt_2)_2]$, which ignites spontaneously in air, is formed by the following reactions:

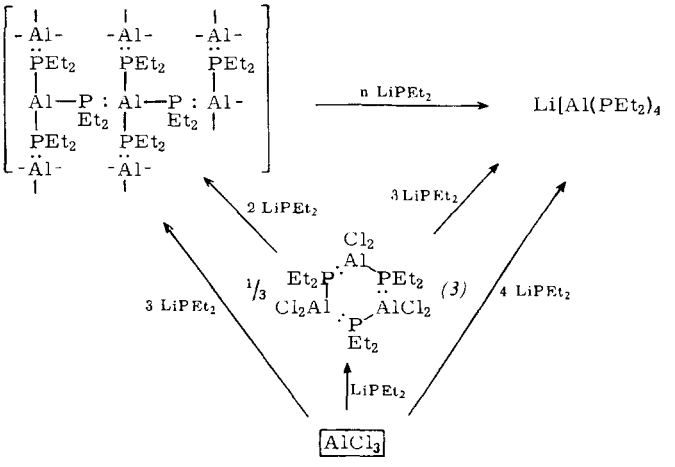
$$H_2AlCl + 2\ LiPEt_2 \rightarrow Li[AlH_2(PEt_2)_2] + LiCl \qquad (32)$$

$$(H_2Al{-}PEt_2)_3 + 3\ LiPEt_2 \rightarrow 3\ Li[AlH_2(PEt_2)_2] \qquad (33)$$

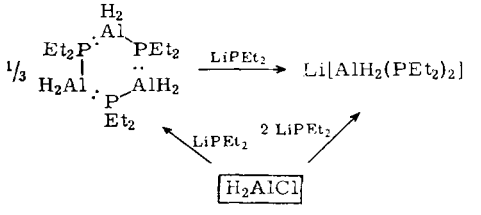
Evidently the formation of salt-like compounds is favored over that of the trimeric and higher-molecular-weight compounds [31]. $Li[AlH_3PEt_2]$ can be obtained directly from freshly-prepared $AlH_3$ [Equation (34)].

$$AlH_3 + LiPEt_2 \rightarrow Li[AlH_3PEt_2] \qquad (34)$$

The reactions of $AlCl_3$ and $H_2AlCl$ with $LiPEt_2$ are summarized in Schemes 2 and 3.




Scheme 2. Reactions of $AlCl_3$ with $LiPEt_2$.




Scheme 3. Reactions of $AlH_2Cl$ with $LiPEt_2$.

According to investigations by *Issleib et al.* [34], tetraalkyldiphosphines are cleaved by $LiAlH_4$, $Li[AlH(PR_2)_3]$ being formed *via* intermediate stages.

The compounds formed in accordance with Equations (30), (32), and (34) are very sensitive to hydrolysis and oxidation. Hydrolysis yields LiOH, $Al(OH)_3$, $HPEt_2$ and – except in the first example – $H_2$.

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Translated by Express Translation Service, London

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[33] *G. Fritz* and *G. Trenczek*, Angew. Chem. *74*, 942 (1962); Angew. Chem. internat. Edit. *1*, 663 (1962).

[34] *K. Issleib, A. Tzschach*, and *R. Schwarzer*, Z. anorg. allg. Chem. *338*, 141 (1965).

# Contributions to the Chemistry of the Binary Compounds of the Transition Elements

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*Dedicated to Professor W. Klemm on the occasion of his 70th birthday*

*Phase and structural relationships of the sulfur, selenium, and tellurium compounds of the 4d and 5d transition elements of groups IV to VII of the periodic system are discussed. Homologous elements behave very similarly with respect to the chalcogens, and this is particularly the case for niobium and tantalum, and for molybdenum and tungsten. However, zirconium, niobium, and molybdenum have a greater tendency towards formation of chalcogen-poor phases than their homologues hafnium, tantalum, and tungsten. Subchalcogenides are known only for zirconium and niobium. The number of phases and the tendency towards formation of solid solutions are considerably smaller among the tellurides than among the sulfides and selenides. The crystal structures of the telluride phases also differ from those of the sulfide and selenide phases of analogous composition. In addition, a review of the phase and structural relationships of the arsenic and antimony compounds of the 4d and 5d transition elements of groups V to VII is given.*

## I. Introduction

Previous investigations on the compounds of the transition elements with the chalcogens sulfur, selenium, and tellurium have shown that these substances show a very complex and, in many respects, unique behavior. Most thoroughly investigated are the chalcogenides of the 3d transition elements. Among them there exist, in addition to compounds of simple stoichiometric composition such as AX, $A_2X_3$, and $AX_2$, phases with extensive regions of homogeneity and compositions that can be expressed either by the formula $A_{1-x}X$ ($0 \leqslant x \leqslant 0.5$) or $A_{1+x}X_2$ ($0 \leqslant x \leqslant 1$).

Phases corresponding to various values of x have, in general, structures which can be derived from the NiAs or $Cd(OH)_2$ structure types by subtraction or addition of metal atoms, respectively. In the first-mentioned case, the composition of the phase can preferably be expressed by the formula $A_{1-x}X$, in the second by $A_{1+x}X_2$. The subtraction or addition of metal atoms is often accompanied by a lowering of crystal symmetry, leading to the formation of superstructures and structures in which the resulting vacancies or the additional metal atoms are distributed more or less regularly in the lattice.

More detailed investigations have shown that compounds with the exact stoichiometric composition AX are present only in a few cases. Thus a structure of the true NiAs-type rarely appears. This type of structure is, in a more or less modified form, usually associated either with a subtractive phase, as already mentioned, or, if an excess of metal atoms is present, with an interstitial phase $A_{1+x}X$.

Among the chalcogenides of the 3d transition elements structures of the $Cd(OH)_2$-type have been found mainly for the di-compounds of titanium and vanadium. Here again small deviations from the stoichiometric composition $AX_2$ apparently occur in most cases, corresponding to a slight excess of metal atoms. Of the remaining dichalcogenides of the 3d transition elements only the ditellurides of cobalt and nickel crystallize with the $Cd(OH)_2$ structure type. The other dichalcogenides of cobalt and nickel, and the dichalcogenides of manganese and iron, have structures either of the pyrite or the marcasite type. Chromium is exceptional as far as it does not form any di-compound with sulfur, selenium, or tellurium. For further details about the chalcogenides of the 3d transition elements, reference may be made to the comprehensive reviews [1–5].

Among the 4d and 5d transition elements, the platinum metals in many respects behave somewhat differently from the 3d transition elements towards the chalcogens, although many similarities can be found [11]. Just like the 3d transition elements, the platinum metals form relatively few compounds with the stoichiometric composition AX. The only compounds of this composition are two sulfides, PdS and PtS, one selenide, PdSe [6], and three tellurides, RhTe, PdTe, and PtTe. Only RhTe and PdTe possess structures of the NiAs-type. PdS, PdSe, and PtS have structures of tetragonal symmetry; PtTe crystallizes in the orthorhombic system.

[1] *H. Haraldsen*, Experientia Suppl. VII, 165 (1957).

[2] *H. Hahn*, Chemical Society Symposia, Bristol 1958 (chem. Soc., London), Special Publication No. *12*, 263 (1958).

[3] *J. Flahaut*, Bull. Soc. chim. France *1960*, 1282.

[4] *F. Jellinek*, Ark. Kemi *20*, 447 (1963).

[5] *A. Kjekshus* and *W. B. Pearson*, Solid State Chem. *1*, 83 (1964).

[6] *K. Schubert, H. Breimer, W. Burkhardt, E. Günzel, R. Haufler, H. L. Lukas, H. Vetter, J. Wegst*, and *M. Wilkens*, Naturwissenschaften *44*, 229 (1957).

The platinum metals form di-compounds with all three chalcogens sulfur, selenium, and tellurium. Only three platinum dichalcogenides, $PtS_2$, $PtSe_2$, and $PtTe_2$, and the ditellurides of palladium, rhodium, and iridium ($PdTe_2$, $RhTe_2$, and $IrTe_2$) possess structures of the $Cd(OH)_2$-type. Most of the other di-compounds of the platinum metals have structures of the pyrite type; a few of them have orthorhombic structures closely related to the pyrite or the marcasite type. Apparently no rhodium disulfide and no iridium diselenide with stoichiometric composition exist. Rhodium and iridium do, however, form compounds richer in chalcogen than the di-compounds. In the case of iridium the existence of even a triselenide ($IrSe_3$) has been shown [1,7]. These chalcogen-rich phases have, as already found by *Biltz et al.* [8], pyrite-like structures of low symmetry.

The platinum metal/chalcogen systems differ also from corresponding systems of the 3d transition elements in that phases with composition intermediate between AX and $AX_2$ exist only in the rhodium and iridium systems with sulfur and selenium. The structures of these phases are still unknown.

above 640 °C PdTe changes continuously into $PdTe_2$ [9–11].

With respect to their magnetic properties, the platinum metal chalcogenides differ considerably from the chalcogenides of the 3d transition elements. In the last-mentioned compounds, paramagnetism, ferromagnetism, antiferromagnetism, or ferrimagnetism is found, depending on composition and temperature. The platinum metal compounds are generally diamagnetic or only weakly paramagnetic.

## II. Chalcogenides of the 4d and 5d Transition Elements of Groups IV to VII

### 1. Sulfides

The chalcogenides of the 4d and 5d transition elements of groups IV to VII of the periodic system have recently been the object of several investigations. A survey of the phase and structural relationships in the sulfide systems is given in Table 1. The data originate mainly from *Jellinek*'s review [4].

Table 1. Sulfides of the 4d and 5d transition elements.

| Elements | Subsulfides $A_{1-x}S$ | Monosulfides $A_{1-x}S$ | Sesquisulfides $A_{1+x}S_2$-Phases | | | Disulfides $AS_2$ | Trisulfides $AS_3$ | Heptasulfides $A_2S_7$ |
|---|---|---|---|---|---|---|---|---|
| Zr | $ZrS_{0.5-0.8}$<br>WC- or<br>≈NiAs-type | $ZrS_{0.9-1.5}$<br>≈NaCl-type | | | | $ZrS_{1.7-2.0}$<br>$Cd(OH)_2$-type | $ZrS_3$<br>$ZrSe_3$-type | |
| Nb | $NbS_{0.9}$<br>>850 °C<br>NiAs-type | $NbS_{1.0-1.2}$<br><800 °C<br>NbS-type | $NbS_{1.40-1.54}$<br>>1000 °C<br>2s-$Nb_{1+x}S_2$-type | $NbS_{1.33-1.8}$<br>800 °C<br>3s-$Nb_{1+x}S_2$-type | $NbS_{1.6-1.8}$<br>1100 °C | $NbS_2$<br>>850 °C<br>2s-$NbS_2$-type<br><800 °C | $NbS_3$<br>$ZrSe_3$-type (?) | |
| Mo | | | | $MoS_{1.5}$<br>$Mo_2S_3$-type | | 3s-$NbS_2$-type<br>$MoS_2$<br>$MoS_2$-type | $MoS_3$ [a]<br>amorphous | |
| Tc | | | | | | 3s-$NbS_2$-type<br>$TcS_2$<br>$MoS_2$-type | | $Tc_2S_7$<br>Type? |
| Hf | | HfS<br>Type? | | $HfS_{1.5}$<br>$Cd(OH)_2$/NiAs-type | | $HfS_2$<br>$Cd(OH)_2$-type | $HfS_3$<br>$ZrSe_3$-type | |
| Ta | | | $TaS_{1.48-1.67}$<br>2s-$Nb_{1+x}S_2$-type | $TaS_{1.67}$<br>6s-$Ta_{1+x}S_2$-type | $TaS_{1.75}$<br>3s-$Nb_{1+x}S_2$-type | $TaS_2$<br>$Cd(OH)_2$-type<br>2s-$NbS_2$-type<br>3s-$NbS_2$-type | $TaS_3$<br>orthorhomb. | |
| W | | | | | | 6s-$TaS_2$-type<br>$WS_2$<br>$MoS_2$-type | $WS_3$<br>amorphous | |
| Re | | | | | | 3s-$NbS_2$-type<br>$ReS_2$<br>$MoS_2$-type<br>3s-$NbS_2$-type | $ReS_3$ (?) | $Re_2S_7$ [a]<br>amorphous |

[a] *Jellinek* [4] also assumes the existence of phases of the approximate composition $MoS_{2.0-2.4}$ and $ReS_{2.0-2.4}$.

Moreover, no pronounced tendency towards the formation of phases with extended regions of homogeneity is found among the chalcogenides of the platinum metals. The same applies even to the rhodium/tellurium and the palladium/tellurium systems, in which phases both with NiAs-like and $Cd(OH)_2$-like structures are present. More recent investigations have shown, however, that

Many of the phases have extended regions of homogeneity, and some of them exhibit structures derivable from certain basic types in similar ways as for the chalcogenides of the 3d transition elements. Only in the zirconium/sulfur system, however, does a solid solution phase exist with a structure derived from a $Cd(OH)_2$-

[7] *L. Søvold*, Thesis, University of Oslo, 1954.

[8] *R. Juza, O. Hülsmann, K. Meisel*, and *W. Biltz*, Z. anorg. allg. Chem. *225*, 369 (1935); *W. Biltz, J. Laar, P. Ehrlich*, and *K. Meisel, ibid. 233*, 257 (1937); *W. Biltz, ibid. 233*, 282 (1937).

[9] *Z. S. Medvedeva, M. A. Klochko, V. G. Kuznetsov*, and *S. N. Andreeva*, Russ. J. inorg. Chem. (Engl. Transl.) *6*, 886 (1961).

[10] *J. Guggenheim, F. Hulliger*, and *J. Müller*, Helv. physica Acta *34*, 408 (1961).

[11] *A. Kjekshus* and *W. B. Pearson*, Canad. J. Physics *43*, 438 (1965).

type structure by addition of metal atoms [12]. There are no definite data on solid-solubility ranges in the hafnium/sulfur system [13]. The different lattice constants of hafnium disulfide found by *Haraldsen, Kjekshus, Røst,* and *Steffensen* [14] (a = 3.633 Å, c = 5.862 Å) on the one hand, and by *McTaggart* and *Wadsley* [13] (a = 3.635 Å, c = 5.837 Å) on the other may, however, indicate that hafnium disulfide is a phase of variable composition. The presence of a structure of the $Cd(OH)_2$-type for $HfS_2$ and of a $Cd(OH)_2$/NiAs-type structure in the case of hafnium sesquisulfide [13] supports this assumption.

The addition of metal atoms, which in hafnium sesquisulfide leads to a structure of the $Cd(OH)_2$/NiAs-type, does not proceed to the stage where all octahedral holes between the $AX_2$ layers in the $Cd(OH)_2$-type structure are occupied by metal atoms, resulting in a compound with composition HfS and a structure of NiAs-type. However, hafnium monosulfide has a different structure which is presently unknown [13].

So far no structure of the NiAs-type has been found in the zirconium/sulfur system. Instead, zirconium monosulfide belongs to a single-phase region which also includes the composition $Zr_2S_3$ and to which a cubic superstructure of the NaCl-type has been attributed [12]. For the subsulfide phase $ZrS_{0.5-0.8}$ *Hahn et al.* [12] proposed a structure of the WC-type. *Jellinek* [4], however, does not exclude the possibility that the phase has a disordered NiAs-like structure.

A structure of the NiAs-type has been found with certainty only for niobium subsulfide $NbS_{0.9}$ [4, 15]. This is another example of the tendency of the NiAs-type structure to occur with a somewhat lower chalcogen (X) content than required by the stoichiometric formula AX.

The structures of the $A_{1+x}X_2$ phases found in the niobium/sulfur and the tantalum/sulfur systems are derived not from the $Cd(OH)_2$ structure but from structure types designated by *Jellinek* [4] as the 2s-$Nb_{1+x}S_2$-type, the 3s-$Nb_{1+x}S_2$-type, and the 6s-$Ta_{1+x}S_2$-type. They are all typical layer structures and differ from the $Cd(OH)_2$-type mainly in that the six sulfur atoms surrounding each metal atom form a trigonal prism instead of an octahedron. The three structure types differ from each other in the stacking of the $AX_2$ layers in the direction of the c-axis. According to the way the layers are stacked upon each other, different structure types may arise [4, 16].

The disulfides are polytypic with exception of those of zirconium, hafnium, and technetium. *Jellinek* [4] reports five different structures for tantalum disulfide, of which one is of the $Cd(OH)_2$-type. In addition to the four structures in Table 1 there is also one in which the $TaS_2$ layers are stacked at random. For molybdenum, tungsten, and rhenium disulfides a rhombohedral structure of the 3s-$NbS_2$-type is known [15, 17–19] in addition to the hexagonal structure of the $MoS_2$-type (called the 2s-$MoS_2$-type by *Jellinek* [4]) which has been known for a long time. The former structure has recently also been observed in naturally occurring molybdenum disulfide [20–22].

Excepting technetium and possibly rhenium, all the metals mentioned in Table 1 form trisulfides. The trisulfides of molybdenum and tungsten have so far, however, been obtained only in X-ray amorphous form [4, 19]. The existence of rhenium trisulfide has not yet been ascertained.

Although no complete structure determination has been carried out, it is suggested that zirconium trisulfide [12] and hafnium trisulfide [13] are isostructural with monoclinic $ZrSe_3$, the structure of which has been determined by *Krönert* and *Plieth* [23]. Whether or not niobium trisulfide possesses this structure remains doubtful [24]. Tantalum trisulfide has a structure of orthorhombic symmetry [25]. The fact that rhenium forms a heptasulfide ($Re_2S_7$) was already recognized by *Biltz* and *Weibke* [26]. In the case of technetium, a disulfide of the $MoS_2$-type and a heptasulfide ($Tc_2S_7$) have been described [27].

Among the 3d transition elements titanium and vanadium form only sulfur-rich compounds. Thus a trisulfide of titanium, $TiS_3$, and a tetrasulfide of vanadium, $VS_4$, and possibly also a pentasulfide, $VS_5$ [28], are known. The structure of vanadium tetrasulfide has been determined by *Hellner et al.* [29]; it contains groups of two and two sulfur atoms, corresponding to a formula $V(S_2)_2$ with tetravalent vanadium.

### 2. Selenides

The selenides of the 4d and 5d transition elements of groups IV to VII of the periodic system have not been investigated in such detail as the sulfides. The results obtained so far are summarized in Table 2.


[12] *H. Hahn, B. Harder, U. Mutschke,* and *P. Ness,* Z. anorg. allg. Chem. *292,* 82 (1957).

[13] *F. K. McTaggart* and *A. D. Wadsley,* Austral. J. Chem. *11,* 445 (1958).

[14] *H. Haraldsen, A. Kjekshus, E. Rost,* u. *A. Steffensen,* Acta chem. scand. *17,* 1283 (1963).

[15] *F. Jellinek, G. Brauer,* and *H. Müller,* Nature (London) *185,* 376 (1960).

[16] *B. E. Brown* and *D. J. Beerntsen,* Acta crystallogr. *18,* 31 (1965).

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[19] *J. C. Wildervanck* and *F. Jellinek,* Z. anorg. allg. Chem. *328,* 309 (1964).

[20] *S. Graeser,* Schweiz. mineralog. petrogr. Mitt. *44,* 121 (1964).

[21] *R. J. Traill,* Canad. Mineralogist *7,* 524 (1963).

[22] *J. Takéuchi* and *W. Nowacki,* Schweiz. mineralog. petrogr. Mitt. *44,* 105 (1964).

[23] *W. Krönert* and *K. Plieth,* Naturwissenschaften *45,* 416 (1958); Z. anorg. allg. Chem. *336,* 207 (1965).

[24] *S. Furuseth* and *A. Kjekshus,* personal communication.

[25] *E. Bjerkelund* and *A. Kjekshus,* Z. anorg. allg. Chem. *328,* 235 (1964).

[26] *W. Biltz* and *F. Weibke,* Z. anorg. allg. Chem. *203,* 3 (1932).

[27] *R. Colton* and *R. D. Peacock,* Quart. Rev. (chem. Soc. London) *16,* 299 (1962).

[28] *G. Gaudefroy,* C. R. hebd. Séances Acad. Sci. *237,* 1705 (1953).

[29] *R. Allmann, J. Baumann, A. Kutoglu, H. Rösch,* and *E. Hellner,* Naturwissenschaften *51,* 263 (1964).

Table 2. Selenides of the 4d and 5d transition elements.

| Elements | Subselenides $A_{1+x}Se$ | Monoselenides $A_{1-x}Se$ | Sesquiselenides $A_{1+x}Se_2$-phases | | Diselenides $ASe_2$ | Pentaselenides $A_2Se_5$ | Triselenides $ASe_3$ | Heptaselenides $A_2Se_7$ | Tetraselenides $ASe_4$ |
|---|---|---|---|---|---|---|---|---|---|
| Zr | $ZrSe_{0.6-0.8}$ WC-type | $ZrSe_{1.0-1.4}$ NaCl-type | | | $ZrSe_{1.7-2.0}$ $Cd(OH)_2$-type | | $ZrSe_3$ $ZrSe_3$-type | | |
| Nb | $NbSe_{0.80}$ $Ti_5Te_4$-type | | $NbSe_{1.33}$ $Nb_3Se_4$-type | $NbSe_{1.55-2.00}$ 2s-$Nb_{1+x}S_2$-type 3s-$Nb_{1+x}S_2$-type 4s-$Nb_{1+x}Se_2$-type | | | | | $\approx NbSe_4$ $\alpha,\beta,\gamma$ Type? |
| Mo | | | | $MoSe_{1.5}$ (?) | $MoSe_2$ $MoS_2$-type | $Mo_2Se_5$ (?) | $MoSe_3$ amorphous | | |
| Hf | | HfSe Type? | | $HfSe_{1.5}$ Type? | $HfSe_2$ $Cd(OH)_2$-type | | $HfSe_3$ $ZrSe_3$-type | | |
| Ta | | | $TaSe_{1.22-1.60}$ 2s-$Nb_{1+x}S_2$-type | $TaSe_{1.60-1.95}$ 6s-$Ta_{1+x}S_2$-type | $TaSe_{2.00}$ $Cd(OH)_2$-type 2s-$NbS_2$-type 3s-$NbS_2$-type 4s-$TaSe_2$-type 6s-$TaS_2$-type | | $TaSe_{3.00}$ $TaSe_3$-type | | |
| W | | | | | $WSe_2$ $MoS_2$-type | | $WSe_3$ amorphous | | |
| Re | | | | | $ReSe_2$ $ReSe_2$-type | | | $Re_2Se_7$ (?) | |

The picture is on the whole similar to that of the sulfides. It is particularly worth noting that no structure of NiAs or a related type seems to occur, unless zirconium subselenide $ZrSe_{0.6-0.8}$ possesses such a structure, in analogy with *Jellinek*'s proposal [4] for the corresponding sulfide. The WC-type given in Table 2 and the other data on the zirconium/selenium system are due to *Hahn* and *Ness* [30].

Niobium subselenide, $NbSe_{0.80}$, crystallizes in the tetragonal $Ti_5Te_4$-type [31]. The structure of $Ti_5Te_4$ itself was first determined by *Grønvold*, *Kjekshus*, and *Raaum* [32] and is shown in Fig. 1 in [001]-projection. The titanium and tellurium atoms are arranged in chains in the direction of the c-axis. The tellurium chains form square groups, with four chains in each. The titanium atoms form groups each containing five chains, one chain being surrounded by the four others at the corners of a square.

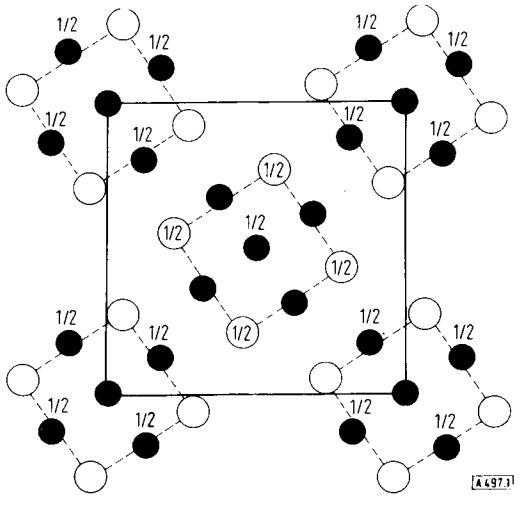


Fig. 1. [001] projection of the $Ti_5Te_4$ structure [32].
● Ti; ○ Te.

It is interesting to compare this structure with a NiAs-structure of the composition TiTe. Fig. 2 shows such a TiTe structure in [010]-projection. It follows from Figs. 1 and 2 that, apart from slight changes in the positions of the atoms, the most striking difference between the two structures is that the tellurium atoms

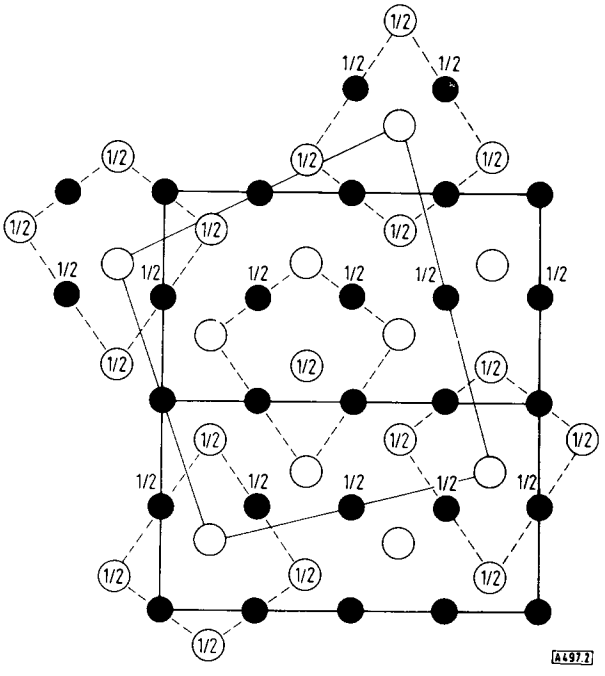


Fig. 2. [010] projection of the NiAs-type structure of TiTe [32].
● Ti; ○ Te.

within the quadrilateral of the TiTe structure (shown in broken lines) have been replaced by titanium atoms in the $Ti_5Te_4$ structure [32].

Not only the chalcogenides $Ti_5Te_4$, $V_5S_4$ [33], $V_5Se_4$ [34], $Nb_5Se_4$ [31], and $Nb_5Te_4$ [31] crystallize with the $Ti_5Te_4$-

[30] *H. Hahn* and *P. Ness*, Z. anorg. allg. Chem. *302*, 37 (1959).
[31] *K. Selte* and *A. Kjekshus*, Acta chem. scand. *17*, 2560 (1963).
[32] *F. Grønvold*, *A. Kjekshus*, and *R. Raaum*, Acta crystallogr. *14*, 930 (1961).
[33] *F. Grønvold*, *H. Haraldsen*, *B. Pedersen*, and *T. Tufte*, Contract AF 61 (052)–178, United States Air Force 1962.
[34] *E. Rost* and *L. Gjertsen*, Z. anorg. allg. Chem. *328*, 299 (1964).

type structure, but also the antimonides $Nb_5Sb_4$ [35, 36] and $Ta_5Sb_4$ [36, 37], as well as the arsenides $Mo_5As_4$ [36, 38] and $(W, Ti)_5As_4$ [36].

The diselenides of zirconium [30] and hafnium [13] have structures of the $Cd(OH)_2$-type, just like the corresponding sulfides. One of the five modifications of tantalum diselenide also belongs to this type of structure [39]. The other modifications of tantalum diselenide, the modifications of niobium diselenide, and the solid solutions derivable from the disulfides have structures corresponding to those of the analogous sulfides [16, 39–41]. Only the structures of the 4s-type are new. The compositions of the phases differ, however, to some extent.

More recent investigations indicate that the 2s-$NbS_2$-type is the only structure present in the $NbSe_{\approx 1.9-2.0}$ region, and that the other two structures occur only at still lower selenium concentrations [42]. It is therefore open to question whether the three structures given for the diselenide actually are polytypes of the same phase, or belong to phases of different composition.

A similar situation occurs in case of tantalum diselenides [39]. The only structures present for tantalum diselenide of stoichiometric composition apparently belong to the $Cd(OH)_2$- and the 4s-$NbSe_2$-types. Further structures given by *Kadijk*, *Huisman*, and *Jellinek* [41] and by *Brown* and *Beerntsen* [16] obviously appear only at lower concentrations of selenium. Thus, the 2s-$Nb_{1+x}S_2$-type has been found in the regions $TaSe_{\approx 1.22-1.60}$ and $TaSe_{\approx 1.95-2.00}$, and the 6s-$TaS_2$-type in the region $TaSe_{\approx 1.60-1.95}$. These results indicate that the solid solubility regions $NbSe_{1.55-2.00}$ and $TaSe_{1.22-2.00}$ given in Table 2 actually include several phases.

The molybdenum and tungsten diselenides have hexagonal structures of the $MoS_2$-type [43–45].

Rhenium diselenide has a structure of triclinic symmetry [46]. The similarity with the $Cd(OH)_2$ structure can be seen clearly from Fig. 3: both are typical layer structures. Each rhenium atom is surrounded by six selenium atoms at the corners of a somewhat distorted octahedron. Unlike the cadmium atoms in the $Cd(OH)_2$ structure the rhenium atoms are not situated exactly in the center of the octahedron, but are shifted towards one face leading to the presence of three shorter and three longer rhenium-selenium distances, and three significantly shorter rhenium-rhenium distances of 2.646,

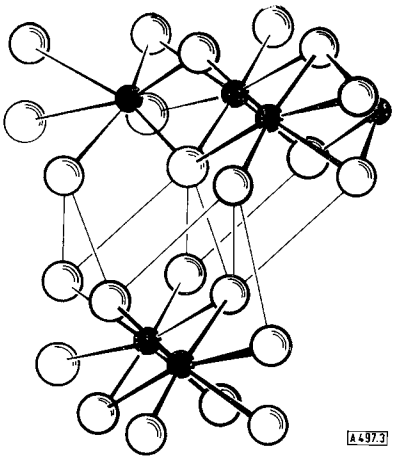

Fig. 3. The $ReSe_2$ structure [46].
● Re; ○ Se.

2.837, and 2.927 Å. The shortest of these distances is actually smaller than the rhenium-rhenium distance found in metallic rhenium (2.75 Å). This and other short rhenium-rhenium distances indicate that chemical bonds exist between the rhenium atoms in the $ReSe_2$ lattice. These bonds are probably the primary cause of the distortion of the $ReSe_2$ structure relative to the $Cd(OH)_2$ structure.

The niobium selenide $Nb_3Se_4$ has a hexagonal structure [47] in which each niobium atom is surrounded by six selenium atoms at the corners of a deformed octahedron (Fig. 4). The whole structure might be regarded as built up of such octahedra joined by common edges.

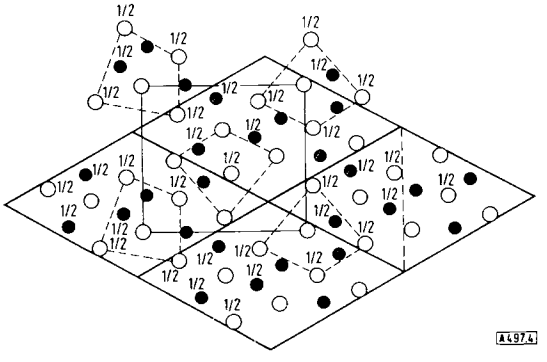

Fig. 4. [001] projection of the $Nb_3Se_4$ structure [74].
● Nb; ○ Se.

In analogy with the situation in the $ReSe_2$ structure, the niobium atoms are not located exactly in the centers of the octahedra, but are shifted from the center in such a manner that alternately longer and shorter niobium-niobium distances occur. The short metal-metal distances which are observed indicate that bonding exists between the niobium atoms.

Just as it is possible in the case of the $Ti_5Te_4$ structure to show certain similarities in the atomic arrangement of the NiAs and the $Ti_5Te_4$ structure by comparing corresponding groups of atoms, this can also be done for the $Nb_5Se_4$ and $Nb_3Se_4$ structures [47]. Such a comparison is possible on the basis of Fig. 4 and the $Ti_5Te_4$

[35] *S. Furuseth* and *A. Kjekshus*, Acta chem. scand. *18*, 1180 (1964).

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structure shown in Fig. 1 if one replaces the titanium and tellurium atoms in Fig. 1 by niobium and selenium atoms, respectively. The rectangle outlined in Fig. 4 is then seen to correspond to the square in Fig. 1. The most notable difference is that the selenium atoms present in the quadrilaterals shown with broken lines in Fig. 4 are replaced by niobium atoms in Fig. 1. To convert the $Nb_5Se_4$ structure into the $Nb_3Se_4$ structure, it is necessary to replace these niobium atoms by selenium atoms, and, further, to remove some other atoms from the $Nb_5Se_4$ structure in combination with a fairly extensive rearrangement of the atoms.

As in the sulfide systems, several tri-compounds also exist in the selenide systems; only niobium and rhenium do not form any triselenide. Instead, these metals form compounds even richer in selenium, $NbSe_4$ [48] and $Re_2Se_7$ [49], respectively. Niobium tetraselenide occurs in two or three modifications with structures as yet unknown. Two of the modifications have tetragonal symmetry. Dirhenium heptaselenide is apparently analogous to dirhenium heptasulfide although its existence still cannot be regarded as certain.

The triselenides of molybdenum and tungsten are amorphous to X-rays [39,44]. Zirconium triselenide [30] and hafnium triselenide [13] are evidently isostructural, just like the sulfides, and have the monoclinic structure found by *Krönert* and *Plieth* [23] for $ZrSe_3$. The structure is a typical layer structure (Fig. 5), in which the metal

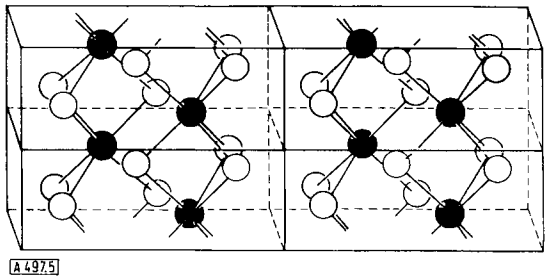


Fig. 5. The $ZrSe_3$ structure [23].
● Zr; ○ Se.

atoms are surrounded by four single selenium atoms and two $Se_2$ groups, resulting in a total of eight selenium atoms. The selenium-selenium distance in the $Se_2$ groups (2.34 Å) is twice the atomic radius of elemental selenium. Phases with structures of the $ZrSe_3$-type can therefore be regarded as partial poly-compounds $AX(X_2)$ with tetravalent metal atoms, divalent chalcogen atoms, and divalent, dimeric $X_2$ chalcogen groups.

In addition to the compounds already mentioned ($ZrS_3$, $ZrSe_3$, $HfS_3$, and $HfSe_3$) it is assumed that $TiS_3$ [50], ZrTe [51], $US_3$ [52–53], $USe_3$ [53,54], $UTe_3$ [53], and $ThTe_3$ [55] have structures of the $ZrSe_3$-type. On the other hand, it appears doubtful whether $NbS_3$ belongs to this structure type [24].

Tantalum triselenide also has a structure of monoclinic symmetry [25], but it is not of the $ZrSe_3$-type. In this respect, tantalum triselenide shows a similarity to tantalum trisulfide, which also has a different structure from that of $ZrSe_3$.

The structure of tantalum triselenide is characterized by a unit cell containing two crystallographically different tantalum atoms (I) and (II) and six crystallographically different selenium atoms, Se(I) to Se(IV) [56]. It follows from Fig. 6 that each tantalum atom is surrounded by

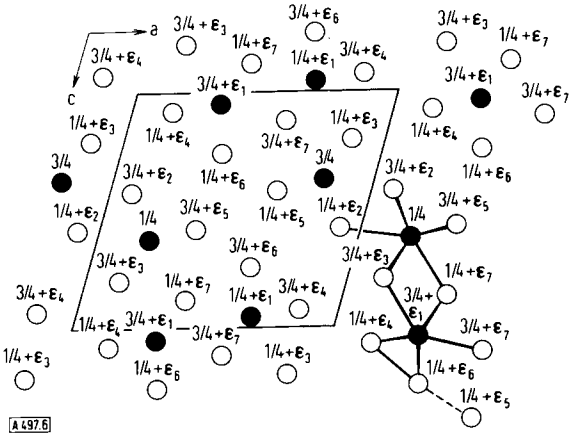


Fig. 6. [010] projection of the $TaSe_3$ structure [56].
● Ta; ○ Se.

eight selenium atoms. Six of the selenium atoms are at the corners of a trigonal prism, and two lie outside the rectangular faces of the prism. The two shortest selenium-selenium distances of 2.53 and 2.66 Å are somewhat greater than the selenium-selenium distances of 2.34 to 2.45 Å found in other compounds of similar type. However, they might still indicate the existence of selenium-selenium bonds in $TaSe_3$. Comparison with the $ZrSe_3$ structure shows that the coordiation of the metal atoms in the two structures is the same, but in the $ZrSe_3$ structure all the zirconium atoms are crystallographically equivalent.

Only preparative information is available about the molybdenum selenides $Mo_2Se_3$ and $Mo_2Se_5$ [57]. The hafnium selenides HfSe and $Hf_2Se_3$ have been prepared [13], but their crystal structures remain unknown.

### 3. Tellurides

Table 3 gives a survey of the phase and structural relationships in the telluride systems. The phase relationships are on the whole simpler than in the sulfide and

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selenide systems. The only phases with extended regions of homogeneity are the two zirconium telluride phases $ZrTe_{0.5-0.75}$ and $ZrTe_{0.8-2.0}$ [51]. The broad regions of homogeneity attributed to the niobium and tantalum tellurides by some investigators [43,58,59] have not been confirmed by others [25,31,47,60].

The zirconium-rich phase $ZrTe_{0.5-0.75}$ and zirconium tritelluride correspond in compositions and structural types to the zirconium-richest and zirconium-poorest in the sulfide and selenide systems of this metal.

any compound with a greater content of tellurium than the sesquitelluride [13]. In this respect, the hafnium/tellurium system differs markedly from the zirconium/tellurium system and also from the other hafnium/chalcogen systems.

A structure of the $Cd(OH)_2$/NiAs-type has been found for hafnium sesquitelluride [13]. Whether or not this phase has a region of homogeneity is not known. Neither is any information available on the structure of hafnium monotelluride.

Table 3. Tellurides of the 4d and 5d transition elements.

| Elements | Subtellurides $A_{1+x}Te$ | Monotellurides $A_{1-x}Te$ | Sesquitellurides $A_{1+x}Te_2$-phases | Ditellurides $ATe_2$ | Tritellurides $ATe_3$ | Tetratellurides $ATe_4$ |
|---|---|---|---|---|---|---|
| Zr | $ZrTe_{0.5-0.75}$ WC-type | | $ZrTe_{0.8-2.0}$ NiAs/$Cd(OH)_2$-type | | $ZrTe_3$ $ZrSe_3$-type | |
| Nb | $NbTe_{0.80}$ $Ti_5Te_4$-type | | $NbTe_{1.33}$ $Nb_3Se_4$-type | $NbTe_{2.00}$ Type? | | $NbTe_{4.00}$ $NbTe_4$-type |
| Mo | | | $MoTe_{1.5}$ Type? | $MoTe_2$ $MoS_2$-type | | |
| Hf | | HfTe Type? | $HfTe_{1.5}$ $Cd(OH)_2$/NiAs-type | | | |
| Ta | | | | $TaTe_{2.00}$ Type? | | $TaTe_{4.00}$ $NbTe_4$-type |
| W | | | | $WTe_2$ orthorhomb. | | |
| Re | | | | $ReTe_2$ orthorhomb. | | |

The homogeneity region of the $ZrTe_{0.8-2.0}$ phase is so wide that it includes the composition of the ditelluride, the sesquitelluride, the monotelluride, and compositions of still lower tellurides as well [51]. Consequently, the $Cd(OH)_2$-like structure of zirconium ditelluride changes gradually into a structure of the NiAs-type by addition of zirconium atoms. The zirconium/tellurium system differs in this respect from the other two zirconium/chalcogen systems, in which a structure of the $Cd(OH)_2$/NiAs-type is present only in a comparatively narrow concentration range of $ZrX_{1.7-2.0}$. At the compositions $ZrS_{0.9-1.5}$ and $ZrSe_{1.0-1.4}$ phases with a cubic superstructure of the NaCl-type exist [12,30].

*Hahn* and *Ness* [51] do not exclude the existence of a superstructure of the NiAs-type between ZrTe and $ZrTe_{1.3}$. Further investigations are therefore needed in order to clarify the phase and structural relationships in the whole range from ZrTe to $ZrTe_2$. In other systems where similar broad regions of homogeneity with continuous transitions from structures of the $Cd(OH)_2$-type into the NiAs-type were first assumed, it has later been found that the extended phase regions actually include several phases with related, but not identical structures.

It is also remarkable that zirconium is the only metal discussed in Table 3 which forms a tritelluride. Among the other metals the compounds richest in tellurium are the ditellurides of molybdenum, tungsten, and rhenium, and the tetratellurides of niobium and tantalum. Hafnium occupies a special position since it does not form

The tellurium-poor niobium phases $NbTe_{0.80}$ [31] and $NbTe_{1.33}$ [47] correspond to the analogous niobium selenides with regard to composition and structure type. In other respects the phase and structural relationships of the niobium and tantalum tellurides differ considerably from those of the sulfides and selenides of these metals. One notes in particular the absence of the broad regions of homogeneity and the polytypic structures common to the disulfides, diselenides, and the $A_{1+x}X_2$-phases. In contrast to the disulfides and diselenides and to what is given in the literature [43,61], the probably isostructural niobium and tantalum ditellurides are not hexagonal but have a not yet elucidated structure of lower symmetry [62,63].

The tetratellurides of niobium and tantalum are isotypic and have structures of tetragonal symmetry [25,60,64]. *Novoselova, Grigoryan, Simanov*, and *Ukrainskii* [58,59] attributed the same symmetry to the phases $NbTe_{2.33-4.0}$ and $TaTe_3$, which they considered as the phases richest in tellurium. The unit cell of the tetratellurides of niobium and tantalum is derived from a structure for which the subcell is shown in Fig. 7. The a-axis of the real cell is twice that of the subcell, the c-axis is three times as long. Each metal atom is surrounded by eight tellurium atoms in form of a slightly distorted square antiprism. Each tellurium atom is coordinated to two metal atoms and eleven tellurium atoms. Five of the tellurium atoms form a planar, irregular pentagon, and six form a trigonal prism. The shortest tellurium-

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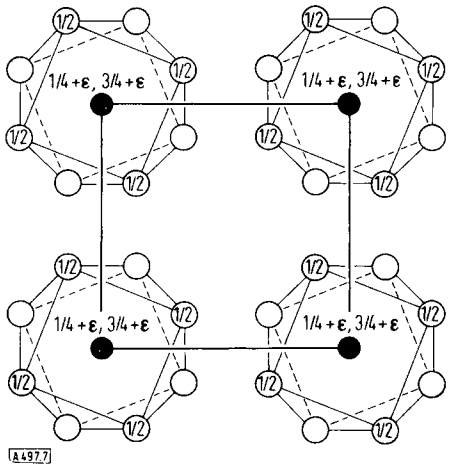


Fig. 7. [001] projection of the $NbTe_4$ structure [60].
● Nb; ○ Te

tellurium distance (2.867 Å for $NbTe_4$ and 2.790 Å for $TaTe_4$) allows the conclusion that tellurium-tellurium bonds exist in both tetratellurides. Although a certain similarity is present, the structure of the tetragonal modification of niobium tetraselenide [48] differs from the structures of the tetratellurides of niobium and tantalum.

## III. Arsenides and Antimonides of the 4d and 5d Transition Elements of Groups V to VII

Until recently the arsenides and antimonides of the 4d and 5d transition elements have received relatively little attention. However, this situation has now changed completely. Independently and almost simultaneously several research groups have carried out a number of investigations on the phase and structural relationships of the arsenides and antimonides of niobium, tantalum, molybdenum, and tungsten. The investigations have led to essentially consistent results.

A survey of the phases and structure types that can be regarded as established is given in Table 4. In addition to the systems mentioned, the tungsten/antimony system and the bismuth systems of niobium, tantalum, molybdenum, and tungsten have also been investigated [38]. No intermediate phases were detected in any of these systems. The existence of the phases MoAs, $MoAs_{1.04} \approx Mo_4As_5$, $W_2As$ and $W_4As_5$, described by *Boller* and *Nowotny* [36] has not been confirmed, neither by *Taylor*, *Calvert*, and *Hunt* [78], nor by *Jensen*, *Kjekshus*, and *Skansen* [38]. The $W_4As_5$ phase evidently is identical,

Table 4. Arsenides and antimonides of the 4d and 5d transition elements of groups V to VII of the periodic system.

| Elements | Arsenides | | | | Antimonides | | | |
|---|---|---|---|---|---|---|---|---|
| Nb | NbAs<br>NbAs-type<br>[35, 71, 72, 73a, 73b] | | $NbAs_2$<br>$NbAs_2$-type<br>[35, 72, 73a, 73c] | | $Nb_3Sb$<br>β-W-type<br>[35, 73a–76] | $Nb_5Sb_4$<br>$Ti_5Te_4$-type<br>[35, 36, 73a] | $NbSb_2$<br>$NbAs_2$-type<br>[35, 73a, 73c] | |
| Ta | TaAs<br>NbAs-type<br>[37, 71, 72] | | $TaAs_2$<br>$NbAs_2$-type<br>[37, 72] | | $Ta_3Sb$<br>β-W-type<br>[37, 76] | $Ta_5Sb_4$<br>$Ti_5Te_4$-type<br>[36, 37] | $TaSb_2$<br>$NbAs_2$-type<br>[37, 77] | |
| Mo | $Mo_5As_4$<br>$Ti_5Te_4$-type<br>[36, 38, 78] | $Mo_2As_3$<br>$Mo_2As_3$-type<br>[38, 78, 79] | $MoAs_2$<br>$NbAs_2$-type<br>[36, 38, 77, 78, 80] | | | | | $Mo_3Sb_7$<br>$Ir_3Ge_7$-type<br>[38] |
| W | | $W_2As_3$<br>$Mo_2As_3$-type<br>[38, 78, 79] | $WAs_2$<br>$NbAs_2$-type<br>[36, 38, 77, 78] | | | | | |
| Re | | | | $Re_3As_7$<br>$Ir_3Ge_7$-type<br>[67] | | | | |

Unlike the other tungsten dichalcogenides and the molybdenum dichalcogenides, tungsten ditelluride, which is the only intermediate phase in the tungsten/tellurium system, does not have a structure of the $MoS_2$-type but an as yet not elucidated orthorhombic structure [43, 65, 66]. Like tungsten, rhenium forms a ditelluride $ReTe_2$ with an orthorhombic structure that also has not yet been determined [67].

Molybdenum ditelluride and molybdenum sesquitelluride were first described by *Morette* [65] whose results were confirmed by *Perotinen* and *Newnham* [68]. Molybdenum ditelluride has a structure of the $MoS_2$-type [68–70]; the structure of molybdenum sesquitelluride remains to be determined.

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however, with the $W_2As_3$ phase of the last-mentioned authors. The same probably applies to the $Mo_4As_5$ phase, which should accordingly be regarded as $Mo_2As_3$.

Table 4 shows that niobium and tantalum form arsenides and antimodnies of identical compositions. The compounds have no detectable regions of homogeneity and can be regarded as stoichiometric[38]. All compounds of corresponding composition have structures of the same type.

A structure of the β-W-type, present for $Nb_3Sb$ and $Ta_3Sb$, has previously been found for about 40 to 50 different compounds. The structures are characterized, *inter alia*, by remarkably small metal-metal distances. This also applies to $Nb_3Sb$ and $Ta_3Sb$. Thus the shortest niobium-niobium distance is 2.632 Å in $Nb_3Sb$[35], while in metallic niobium it is 2.858 Å[81,82]. In $Ta_3Sb$ and metallic tantalum, the shortest tantalum-tantalum distances are 2.632 Å[37] and 2.863 Å[83], respectively.

The tetragonal structure of niobium monoarsenide has been determined independently by *Boller* and *Parthe*[71] and by *Furuseth* and *Kjekshus*[73a, b]. Each atom is surrounded at equal distances by six nearest neighbors of the other kind (Fig. 8). The structure may be considered as built up of almost regular, trigonal niobium prisms with an arsenic atom in the center. The prisms are rotated and displaced with respect to each other. A structure of the same type is found also for tantalum monoarsenide and for the monophosphides of niobium and tantalum[71,84].

All di-compounds of Table 4 have the structure type first found for $NbAs_2$[73a,73c]. The same type is suggested for $VP_2$, $VAs_2$, $NbP_2$, $TaP_2$, and α-$WP_2$[77]. A [010]-projection of the $NbAs_2$ structure is shown in Fig. 9. Each niobium atom is surrounded by six arsenic atoms at the corners of a trigonal prism and by two

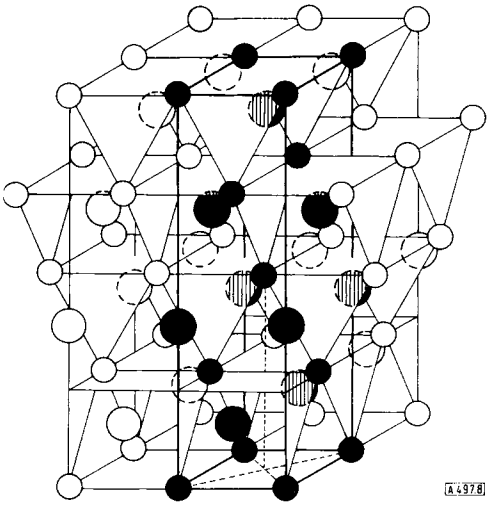


Fig. 8. The NbAs structure [71]. Small circles, Nb; large circles, As.

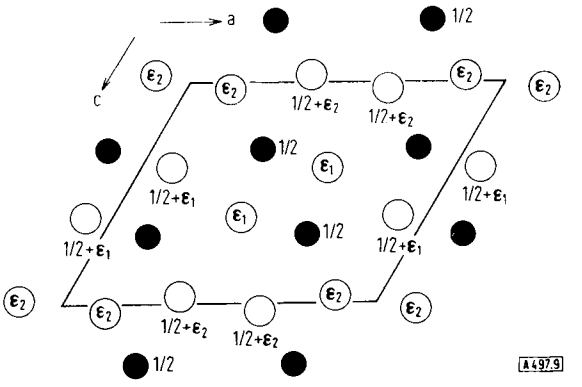


Fig. 9. [010] projection of the $NbAs_2$ structure [73c]. ● Nb; ○ As.

additional arsenic atoms and one niobium atom outside the rectangular faces of the prism. Two crystallographically different arsenic atoms, As (I) and As (II), are present. The arsenic atoms (I) have five niobium atoms as their nearest neighbors, forming a distorted square pyramid with one additional arsenic atom (I) outside the base of the pyramid. The arsenic atoms (II) are coordinated to three arsenic atoms (II) and three niobium atoms. The arrangement of the arsenic atoms (II) produces alternating longer and shorter arsenic (II)-arsenic (II) distances. In $NbAs_2$ the shorter distances are 2.446 Å, while in $NbSb_2$ the shorter antimony (II)-antimony (II) distances are 2.72 Å[73c]. The corresponding distances in $TaAs_2$ and $TaSb_2$ are 2.42 and 2.65 Å, respectively[37]. Compared to the shortest bond distances in metallic arsenic (2.507 Å) and antimony (2.904 Å)[85] indications are that half of the arsenic and antimony atoms in the diarsenides and diantimonides of niobium and tantalum are bound in pairs, corresponding to the formulae

$$\overset{+5\ -4\ -3}{Nb_2(As_2)As_2},\quad \overset{+5\ -4\ -3}{Nb_2(Sb_2)Sb_2},\quad \overset{+5\ -4\ -3}{Ta_2(As_2)As_2}\quad \text{and}\quad \overset{+5\ -4\ -3}{Ta_2(Sb_2)Sb_2}.$$

In agreement therewith, it has been shown that the compounds are diamagnetic. The mono-compounds NbAs and TaAs also are diamagnetic. On the other hand, the antimonide phases $Nb_5Sb_4$, $Ta_5Sb_4$, $Nb_3Sb$, and $Ta_3Sb$ with higher metal contents exhibit slight, almost temperature-independent paramagnetism, corresponding to a more metallic bond character[35,37].

Besides the diarsenides $MoAs_2$ and $WAs_2$ of the $NbAs_2$ type, molybdenum and tungsten form sesquiarsenides $Mo_2As_3$ and $W_2As_3$ of monoclinic symmetry[38,78,79]. Molybdenum also forms an arsenide $Mo_5As_4$, of the $Ti_5Te_4$-type, and an antimonide $Mo_3Sb_7$. This antimonide, and the rhenium arsenide of corresponding composition $Re_3As_7$, belong to a structure type first found for $Ir_3Ge_7$ by *Nial*[86].

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# The Kinetics of Crystal Growth

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*The fundamentals of the theory of crystal growth comprise the two concepts of growth via two-dimensional nuclei and growth with the aid of dislocations. Measurements of the relationship between rate of growth and supersaturation are particularly suitable for testing theoretical predictions. Experimental results are compared with predictions for crystal growth from the vapor phase, from solution, and from the melt. Depending on the experimental conditions, examples of both types of growth are met irrespective of the nature of the mother phase.*

## I. Introduction

Formation of a new crystalline phase from a supersaturated mother phase (supersaturated vapor, supersaturated solution, supercooled melt) requires the initial formation of a nucleus. This necessitates a fluctuation of the Gibbs free energy, the "work of nucleation." With regard to size and shape, the nucleus is in equilibrium with the surroundings. Spontaneous growth of the crystal becomes feasible only after it has grown to beyond the size of the nucleus. Additional growth thresholds can, however, determine the rate of growth.

Two stages can therefore be distinguished in the kinetics of crystal formation: nucleation, and growth of the nucleus. If many small crystals are formed during a crystallization process (rapid solidification of melts, formation of fine-grained precipitates), both steps are important in the kinetic treatment. In the formation of a few, larger crystals, the growth of the nuclei is the principal process. It is this process which forms the subject of this article.

A detailed picture of the growth mechanism has been developed since about 1925. Before then, work was concentrated largely on the interpretation of growth forms, for which purely geometric considerations (kinematic theory of crystal growth[1]), symmetry and structural properties of crystals (lattice plane density[2], principal bonding direction[3]), and thermodynamics (Gibbs condition[4], Wulff's theorem[5]) were utilized.

The basis for a molecular kinetic treatment was given by *Kossel*[6] and *Stranski*[7], who considered the deposition of single molecules in the formation of a crystal, and by *Volmer*[8], who derived an equation for the rate of growth. Basing his postulates on concepts due to *Gibbs*[9], *Volmer* assumed that nucleation was also necessary for the addition of each new lattice plane. The frequency of formation of these two-dimensional nuclei (cf. Fig. 1) determines the rate of growth. Subsequently, it was shown that two-dimensional nuclei are necessary only for the growth of certain types of crystal face[7]; but it is precisely these which determine the crystal growth form. The introduction of the average work of separation[10] led to a link between thermodynamic and statistical methods of treatment.

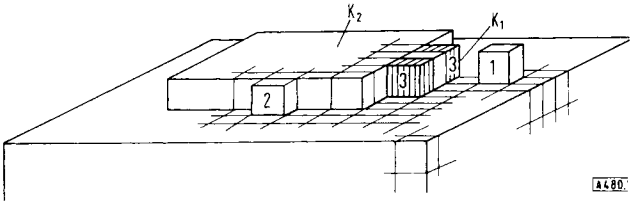


Fig. 1. Crystal face with two-dimensional nucleus ($K_2$), one-dimensional nucleus ($K_1$), an adsorption site on the face (1) and at the ledge (2), and kinks (3). Reproduced (with permission) from *B. Honigmann*: Gleichgewichts- und Wachstumsformen von Kristallen. Steinkopff, Darmstadt 1958 [22].

Sequences of growth rate for various types of face calculated from nucleation frequencies were in substantial agreement with experimental results. However, marked deviations were often encountered in the absolute values. These suggested that the simplifications adopted, such as the ideal lattice and spherically symmetrical bonding forces, as well as the neglect of adsorption, surface diffusion, and thermal roughening, were unjustified in many cases.

Initially, the influence of the structure of real crystals was considered in terms of the reduction in the work of nucleation at the concave edges of a mosaic structure[11]. *Burton, Cabrera,* and *Frank*[12,13] developed a new theory for the

[1] *A. Johnsen*: Wachstum und Auflösung der Kristalle. W. Engelmann, Leipzig 1910.

[2] *A. Bravais*: Etudes Cristallographiques. Gauthier-Villars, Paris 1866.

[3] *P. Niggli*: Geometrische Kristallographie des Diskontinuums. Borntraeger, Leipzig 1919.

[4] *P. Curie*, Bull. Soc. minéralog. France *8*, 145 (1885).

[5] *G. Wulff*, Z. Kristallogr. *30*, 309 (1898); *34*, 449 (1901).

[6] *W. Kossel*, Nachr. Ges. Wiss. Göttingen, math.-physik. Kl. *1927*, 135; Leipziger Vorträge *1928*, 1.

[7] *I. N. Stranski*, Z. physik. Chem. *136*, 259 (1928).

[8] *M. Volmer* and *A. Weber*, Z. physik. Chem. *119*, 277 (1926); *M. Volmer*: Kinetik der Phasenbildung. Steinkopff, Dresden and Leipzig 1939.

[9] *J. W. Gibbs*, Trans. Connecticut Acad. *3* (1875–1878); reprinted in: The Collected Works of J. W. Gibbs. Yale University Press, New Haven 1948.

[10] *I. N. Stranski* and *R. Kaischew*, Z. physik. Chem. *B 26*, 100, 114, 312 (1934).

[11] *I. N. Stranski* and *B. Honigmann*, Naturwissenschaften *35*, 156 (1948); Z. physik. Chem. *194*, 180 (1950).

[12] *F. C. Frank*, Discuss. Faraday Soc. *5*, 48 (1949); Philos. Mag. Suppl. *1*, 91 (1952); Z. Elektrochem., Ber. Bunsenges. physik. Chem. *56*, 429 (1952).

[13] *W. K. Burton, N. Cabrera*, and *F. C. Frank*, Nature (London) *163*, 398 (1949); Philos. Trans. Roy. Soc. London, Ser. *A 243*, 299 (1951).

growth of a real crystal on the basis of the screw dislocations introduced into the theory of plasticity by *Burgers*. Direct observation of dislocation lines and systems of growth steps, as well as determination of the theoretically required dependence of growth rate on the degree of supersaturation, enabled these postulates to be confirmed in many instances, but growth by dislocations by no means explains all the experimental results. Nucleation processes can become rate-determining, particularly during growth from highly supersaturated systems and from condensed or impure mother phases.

During the past few years allowance has been made for further factors such as adsorption and diffusion [14–20], and kinetically more complicated processes (growth from solution and melt, whisker and needle crystal growth, electrolytic growth, growth during recrystallization and chemical reactions) have been treated in detail. Only some of these types of growth can be dealt with here.

## II. Growth from the Vapor Phase

### 1. Equilibrium Form and Growth Form

The equilibrium form is the form of a crystal in thermodynamic equilibrium with its surroundings. Hence, the shape of a nucleus is always an equilibrium form. The faces of this equilibrium form and their size ratio are determined by the Gibbs condition that the surface free energy is a minimum for a constant number of structural units.

The growth form is determined by the rate of growth of the individual types of face. The slower the growth of a face, the faster is its extension in the growth form.

In an ideal crystal, faces are distinguished which require the formation of two-dimensional nuclei for the deposition of new lattice planes, and those which require merely one-dimensional nuclei or can grow without energy barriers. Only faces of the first type, which grow much more slowly than the others over a wide supersaturation range, participate in determining the growth form.

Because of lattice defects, *e.g.* screw dislocations, steps or ledges capable of growth are invariably present in the surface of real crystals. Formation of two-dimensional nuclei is therefore unnecessary even on faces of the first type. Their rate of growth is increased compared to corresponding faces of ideal crystals, but remains below the maximum corresponding to the frequency of impingement, since the units have to find their way to the growth sites by surface diffusion. Faces which in ideal crystals are able to grow without formation of two-dimensional nuclei are unaffected by defects in the crystals, since the distances between the kinks or the steps capable of growth have the same order of magnitude as the building unit spacing. Consequently, in real crystals also, only such faces contribute to the growth form which grow *via* two-dimensional nuclei in the case of ideal crystals.

It has been found that these faces controlled by two-dimensional nuclei correspond to those which arise from the equilibrium form [10]. This relationship still holds when the equilibrium conditions are altered by a high supersaturation or additional factors such as adsorption [10, 16]. For this reason, determination of the equilibrium form makes possible a theoretical elucidation of the faces making up the growing crystal.

### 2. Growth Rate Theory

Work of nucleation has to be expended on the faces of the equilibrium form of an ideal crystal for each new lattice plane (Fig. 1) [*]. To determine the growth rate of these faces, it is initially necessary to consider equilibrium conditions, since both the shape and the size of the two-dimensional nucleus must be known if the work of nucleation is to be evaluated. The shape is obtained from the Gibbs condition, with the Helmholtz free energy of the edge being a minimum. The size is obtained from the Gibbs-Thomson equation for the two-dimensional case [cf. Equation (5)], which relates nucleus size and supersaturation. Presupposing that the growth of two-dimensional nuclei is sufficiently rapid, the growth rate R is found to be [8, 14, 23–26]:

$$R = d \cdot I = d \cdot H \cdot e^{-\Delta G_n'/kT} \qquad (1)$$

where d is the step-height of the nucleus, I the nucleation frequency, H a frequency factor, and $\Delta G_n'$ the work of nucleation or, more accurately, the change in Gibbs free energy when a two-dimensional nucleus is formed; it is given by

$$\Delta G_n' = \frac{(\Sigma \rho_i r_i A_i)^2}{4kT \ln(p_h/p_\infty)} \qquad (2)$$

wherein $\rho$ is the specific Gibbs free ledge energy, r the spacing of structural units, A a geometric factor, i a subscript for the respective type of face, and $p_h/p_\infty$ the supersaturation ratio ($p_\infty$ is the vapor pressure of a sufficiently large crystal, and $p_h$ that of a micro-crystal of radius h). The *relative* supersaturation, $\Omega$, is defined by $\Omega = p_h/p_\infty - 1$.

Several derivations exist for Equation (1) (cf. [8, 14]) and give diverse expressions, particularly for the factor H, for which values between $10^{20}$ and $10^{28}$ are obtained [12, 14, 26].

[*] During growth of the nucleus, the addition of each new layer requires performance of the work necessary for a one-dimensional nucleus. At the temperatures generally used for crystal growth, this work factor does not represent a significant energy barrier.


[14] *J. P. Hirth* and *G. M. Pound*: Condensation and Evaporation. Pergamon Press, Oxford 1963.

[15] *A. A. Chernov*, Soviet Physics Usp. (Engl. Transl.) *4*, 116 (1961).

[16] *R. Lacmann*, Z. Kristallogr. *112*, 169 (1959).

[17] *I. N. Stranski*, *W. Gans*, and *H. Rau*, Ber. Bunsenges. physik. Chem. *67*, 965 (1963.

[18] *G. W. Sears*, J. chem. Physics *24*, 1045 (1955); *25*, 154 (1956).

[19] *I. N. Stranski*, Bull. Soc. franc. Minéralog. Cristallogr. *79*, 359 (1956).

[20] *O. Knacke* and *I. N. Stranski*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *60*, 816 (1956).

[21] *O. Knacke* and *I. N. Stranski*, Ergebn. exakt. Naturwiss. *26*, 383 (1952).

[22] *B. Honigmann*: Gleichgewichts- und Wachstumsformen von Kristallen. Steinkopff, Darmstadt 1958.

[23] *I. N. Stranski* and *R. Kaischew*, Z. physik. Chem. *B 26*, 317 (1934).

According to Equations (1) and (2), the rate of growth and the supersaturation are related exponentially (see Fig. 4). Equation (1) shows that R must become practically zero even at finite degrees of supersaturation. For the critical supersaturation, $\Omega_{cr}$, at which growth commences, values between 0.25 and 0.5 have been calculated for molecular crystals [13, 21, 27]. For metals, $\Omega_{cr}$ may be substantially greater [14].

The growth of real crystals is influenced above all by lattice defects which maintain existing growth steps or continuously form fresh ones. Screw dislocations are particularly significant. In contrast, point defects play only an indirect role in the growth kinetics, in that the formation or multiplication of dislocations can be affected by impurity or vacancy accumulations. A brief description of growth phenomena in the presence of screw dislocations will now be given. (A mathematically more rigorous treatment can be found in [13–15].)

Where a screw dislocation penetrates a crystal face, the crystal can grow without formation of two-dimensional nuclei. Further addition of units leads to the formation of a circular or polygonal spiral (see Fig. 2).

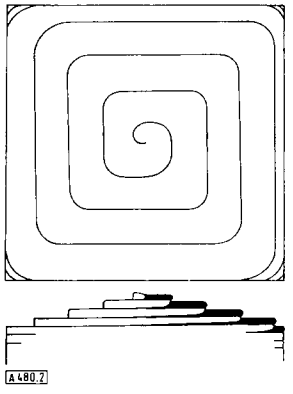


Fig. 2. Crystal face with a growth spiral (taken from [12]). Reproduced (with permission) from Transactions of the Faraday Society.

The growth rate of such a surface is determined by the step height of the growth front $d_0$, the distance between the steps s, and the lateral rate of advance of the steps, w.

$$R = d_0 w/s \qquad (3)$$

For the general case of a round spiral, the latter "rotates" at constant angular velocity about the point of penetration of the dislocation. When the rate of advance, w, is independent of the distance from the center, the Archimedean spiral fulfils the condition of a radius-independent angular velocity. The distance between the steps depends on the length of the edge of the two-dimensional nucleus corresponding to the relevant degree of supersaturation. If the initial radius of curvature of the spiral is taken to be the radius $r_n$ of a nucleus assumed to be circular (a greater step curvature cannot be stable), the distance between the steps is given by [*]:

$$s = 4\pi r_n \qquad (4)$$

$r_n$ is obtained from the Gibbs-Thomson equation for the two-dimensional case [8]:

$$kT \ln(p_h/p_\infty) = \rho f_0/r_n \qquad (5)$$

where $f_0$ is the area occupied by a structural unit.

The rate of advance w, which is determined essentially by the mean diffusion path $x_s$ of the surface molecules and the difference $\Delta\dot{N}$ between the number of molecules striking the surface per unit time at the temperature of the evaporating sample and at the temperature of the growing crystal, is given by

$$w_I = 2 x_s \alpha_K \alpha_H f_0 \Delta\dot{N} \qquad (6)$$

where $\alpha_K$ and $\alpha_H$ are two partial condensation coefficients [see Equation (12)]. Equations (3)–(6) and the approximations $\ln p_h/p_\infty \approx \Omega$ and $\Delta\dot{N} \approx \dot{N}\Omega$ together lead to the rate equation

$$R_I = d_0 x_s \dot{N} \alpha_K \alpha_H kT\Omega^2/2\pi\rho. \qquad (7)$$

Accordingly, $R_I$ is proportional to the square of the degree of supersaturation. Figure 3 illustrates this relation.

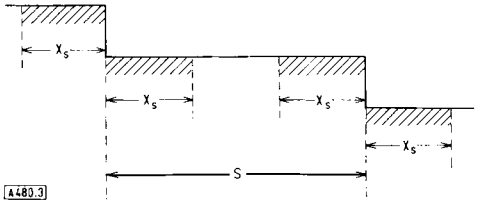


Fig. 3. Cross-section through a growing face. $x_s$: mean diffusion path; s: distance between steps.

The hatched regions on either side of the step represent the catchment area for molecules able to reach the step. Only this part of the total surface contributes to growth. Molecules which impinge on the blank part of the surface on the average re-evaporate before they reach a step. However, Equation (7) is valid only for low degrees of supersaturation, *i.e.* as long as the hatched regions in Fig. 3 do not intersect.

At higher degrees of supersaturation, s in Equation (4) becomes very small. The number of structural units reaching a step then no longer depends on $x_s$, since all impinging units do so. Equations (6) and (7) become

$$w_{II} = s f_0 \alpha_K \alpha_H \Delta\dot{N}/2 \qquad (8)$$

$$R_{II} = d_0 f_0 \dot{N} \alpha_K \alpha_H \Omega \qquad (9)$$

At higher degrees of supersaturation, R is proportional to $\Omega$.


[24] *R. Becker* and *W. Döring*, Ann. Physik *24*, 732 (1935).

[25] *R. Kaischew*, Acta physica Acad. Sci. hung. *8*, 75 (1958).

[26] *I. N. Stranski* and *L. Krastanow*, S.-B. Akad. Wiss. Wien, math.-naturwiss. Kl., Abt. IIb, *146*, 797 (1938).

[27] *M. Volmer* and *W. Schultze*, Z. physik. Chem. *A 156*, 1 (1931).


[*] For a mathematically more complicated spiral, $s = 19\, r_n$ [28].


[28] *N. Cabrera* and *M. M. Levine*, Philos. Mag. [8] *1*, 450 (1956).

Equations (7) and (9) represent the limiting cases for low and high degrees of supersaturation, respectively, of the equation given by *Burton, Cabrera,* and *Frank* [13]:

$$R_{I,II} = d_0 f_0 \dot{N} \alpha_K \alpha_H (\Omega^2/\Omega_*) \tanh (\Omega_*/\Omega) \text{ [*]} \quad (10)$$

$\Omega_*$ is the characteristic degree of supersaturation at which the quadratic relationship is transformed into the linear one:

$$\Omega_* = 2\pi\rho f_0/x_s kT \quad (11)$$

For a real crystal, R can be formally expressed by

$$R = \alpha R_{max} = \alpha_F \alpha_K \alpha_H R_{max} \quad (12)$$

where $\alpha$ is the overall condensation coefficient given by the ratio of the experimentally or theoretically determined rates of growth to the gas-kinetically maximum possible rate $R_{max} = f_0 d_0 \Delta\dot{N}$. The factor $\alpha$ can be resolved into partial condensation coefficients which allow for the following retardations during growth [**]: surface diffusion ($\alpha_F$), diffusion at the growth step ($\alpha_K$), and possible obstructions during incorporation in the kink ($\alpha_H$). The factor $\alpha_F$ is obtained from Equations (10) and (12) as $(\Omega/\Omega_*) \tanh (\Omega_*/\Omega)$. For $\Omega < \Omega_*$,

$$\alpha_F = \Omega/\Omega_* = 2 x_s/s \quad (13)$$

For $\Omega > \Omega_*$, $\alpha_F$ reaches the value 1. For simple metal and molecular lattices, $\alpha_K \approx 1$ [13,29]. For $\alpha_H$ we may write [13]:

$$\alpha_H = (1 + x_s \tau/r \tau_F)^{-1} \quad (14)$$

where $\tau_F$ is the residence time of a building unit on the face before it re-evaporates, r is the distance between the units in the step, and $\tau$ is the relaxation time, *i.e.* the time required to re-establish $\Omega = 0$ at the kink after incorporation of a unit. $\alpha_H$ becomes less than unity when the entropy of rotation of the adsorbed molecules is much greater than that of the molecules inside the solid.

The mean diffusion path $x_s$ which appears in Equations (6) to (14) can be related to the surface diffusion coefficient $D_F$ and to $\tau_F$ by means of the Einstein equation

$$x_s^2 = D_F \tau_F \quad (15)$$

with the following values for $D_F$ and $\tau_F$ [13,15]:

$$D_F = r^2 \nu e^{-(\varphi_{ads} - \varphi_{saddle})/kT} \quad (16)$$

$$\tau_F = (1/\nu') e^{\varphi_{ads}/kT} \quad (17)$$

$\nu$ and $\nu'$ are two frequency factors, of the order of $10^{-13}$ sec$^{-1}$, which as an approximation can be equated; $\varphi_{ads}$ and $\varphi_{saddle}$ denote the work of separation of a building unit from the adsorption site in the surface or from a saddle position between two adsorption positions. $x_s$ is then given by

$$x_s = r e^{\varphi_{saddle}/2kT} \quad (18)$$

Estimates for the close-packed faces of simple lattices lead to values of $10^2$ r to $10^3$ r [13,15] for the mean diffusion path.

## 3. Consideration of Further Factors Affecting Growth of Real Crystals

The equations for the rate of growth given in the previous section contain several simplifying assumptions. For comparison with results obtained under experimental conditions, these equations have to be modified. The principal considerations are:

(a) When the step spacing s is smaller than the mean diffusion path $x_s$ on the surface, the spiral may become unstable.

(b) Numerous dislocations are generally present.

(c) The surrounding gas phase usually contains foreign gases.

(d) High growth steps may form.

(a) According to *Hirth* and *Pound* [14,30,31], at $\Omega > \Omega_*$, *i.e.* when $s < x_s$ according to Equations (4), (5), and (11), the growth steps have a tendency to accelerate their advance. Since the outer spiral turns run ahead, s increases until the value 6 $x_s$ is reached asymptotically. $\alpha_F$ then becomes $1/3$ according to Equation (13). Within a limited region in the vicinity of the point of penetration of the dislocation, the smaller distance given by Equation (4) remains valid. The proportion of these regions increases with increasing dislocation density so that $\alpha_F$ varies between $1/3$ and 1 [14].

(b) The influence of the number of dislocations is governed by the ratio of the spacing $d_V$ between them and the radius of the nucleus $r_n$. Four possibilities arise already in the case of two screw dislocations [13,14]:

($\alpha$) Dislocations of opposite sign and $d_V > 2\pi r_n$. The two spiral systems unite to form circular terraces whose spacing corresponds to that between the individual spirals.

($\beta$) Dislocations of opposite sign but with $d_V < 2r_n$. Here the step joining the two centers is unable to grow because it is shorter than the nucleus. The effects of the two dislocations cancel.

($\gamma$) Dislocations of the same sign, $d_V > s/2 = 2\pi r_n$. Joining together of the parts of the two spirals leads to a spiral with a spacing between turns corresponding to that of the individual spiral.

($\delta$) Dislocations of the same sign but with $d_V < 2\pi r_n$. The two spirals do not intersect. Since s has only half its former magnitude, R is doubled.

In the general case of numerous dislocations, the growth rate is different from that found in the presence of a single screw dislocation when non-compensating screw dislocations of the same sign with a spacing smaller than $2\pi r_n$ are present on the surface. The arrangement with the largest number of such dislocations determines the rate of growth. If $\varepsilon$ is the number of these dislocations, R increases approximately by a factor $\varepsilon$. The increase is possible only as long as the distance between the growth steps is sufficiently large compared with $x_s$. Suitable dislocation groups therefore

[*] Here, the factor $\nu e^{-w/kT}$ used in [13] ($\nu$ = vibration frequency, w = molar heat of vaporization) is replaced by $f_0\dot{N}$.

[**] If not all impinging molecules enter the adsorbed layer, an additional partial condensation coefficient must be introduced.

[29] *H. Heyer*, Dissertation, Freie Universität Berlin, 1962.

[30] *J. P. Hirth* and *G. M. Pound*, J. physic. Chem. *64*, 619 (1960).

[31] *J. P. Hirth* and *G. M. Pound*, Acta metallica *5*, 649 (1957).

transform the quadratic law (7) into the linear one (9) for degrees of supersaturation smaller than $\Omega_*$ (cf. Equation 11). The formation of dislocation groups is related to the degree of supersaturation $\Omega$ in accord with the above criteria. As the degree of supersaturation grows, a splitting into individually effective dislocations ensues.

(c) Foreign substances contained in the mother phase can influence growth in various ways. Adsorption causes the specific free surface energy $\sigma$ and the specific free ledge energy $\rho$ to be reduced[*]. In the case of growth *via* two-dimensional nuclei, $\Delta G'_n$ and hence $\Omega_{cr}$ are lowered. At the same time, a frequency factor introduced in the statistical thermodynamic derivation of $\Delta G'_n$ decreases[14]. This causes the values of $\Delta G'_n$ and $\Omega_{cr}$ to increase, but in general the first-mentioned effect predominates.

During growth by a dislocation mechanism, a lowering of $\rho$ effects a decrease in the step spacing and a consequent acceleration of growth. Reduction in $x_s$, however, retards the growth. The most important factor is the decrease in concentration of structural units in the adsorbed layer[14], leading to a retardation of growth.

When relatively immobile foreign molecules or aggregates are present on the surface, these obstruct the advance of the steps when their spacing is smaller than $2r$[32]. The concentration of these particles depends on the growth rate and the number of foreign molecules $\dot{N}_F$ striking a unit area per unit time. Assuming uniform distribution, the limiting degree of supersaturation below which the steps no longer advance is given by

$$\Omega_{w=0} = \text{const}\,(\dot{N}_F)^{1/3} \qquad (19)$$

(d) If the height of a growth step is a multiple of that of a monomolecular step, w is given by

$$w_d = (d_0/d)\, w_{d_0}\,(1 + d/x_s) \qquad (20)$$

where $d_0$ and d denote the heights of the mono- and polymolecular steps, respectively, and $w_{d_0}$ is given by Equation (6). The second term in the brackets allows for the direct condensation on the front face of the step. Also s will change, and $\rho$ in Equation (5) must be replaced by

$$\rho_d = (d/d_0)\, a\, \rho_{d_0} \qquad (21)$$

where $\rho_d$ is the specific free ledge energy for a step of height d and $\rho_{d_0}$ that for a monomolecular step. For simple nonpolar lattices $a \approx 2$[29], but it can assume values of less than 1 for ionic lattices. When it is further considered that $f_0$, the area occupied by a building unit, must be divided by $d/d_0$ in the case of high steps, the value of s for high steps corresponding to Equation (4) is

$$s_d = a\, s_{d_0} \qquad (22)$$

According to *Chernov*[15, 33], the frontal area of high steps is not plane because of the preferential addition on the base and at the upper edge.

Various causes for formation of high steps have been put forward. According to *Frank*[34] and *Forty*[35], the height of the step is determined by the component of the Burgers vector[*] normal to the surface. Its magnitude can be determined by the substrate on which the crystal has formed or by "accidents" during growth[36].

If the line of dislocation progresses in the form of a spiral, the center of the latter "rotates" during growth. In this way, a macroscopic spiral is formed[37] (cf. also[38]).

If a time-dependent impurity adsorption is postulated[14, 39], the velocity of a step will depend on the distance from the preceding one. This causes an equidistant sequence of steps to become unstable. Where a step has assumed a position somewhat remoter from the preceding one, its velocity will be reduced further because adsorption has increased. It is therefore readily caught by the next step whose velocity increases as it approaches its predecessor.

Because of (a) to (d) the growth of a real crystal will generally be retarded. For $\Omega < \Omega_*$, the formal relationship

$$R_I' = (d_0\, \varepsilon/d\, a\, b) R_I \qquad (23)$$

may be written, where $\varepsilon$ allows for the increase in $R_I$ caused by groups of dislocations, while $d/d_0$, a, and b allow for the decrease in $R_I$ caused by high steps, the reduction in $\rho$, and the effect of adsorption on w.

Fig. 4 shows the relationship between the rate of growth and the degree of supersaturation in schematic form. It demonstrates that in the case of real crystals the degree of supersaturation can give rise to different growth mechanisms, whose ranges of validity are defined by $\Omega_*$ and $\Omega_{cr}$. For the different substances and the special growth conditions discussed above, $\Omega_*$ and $\Omega_{cr}$ can differ widely. During growth in less pure surroundings (*e.g.* with foreign gases in the mother

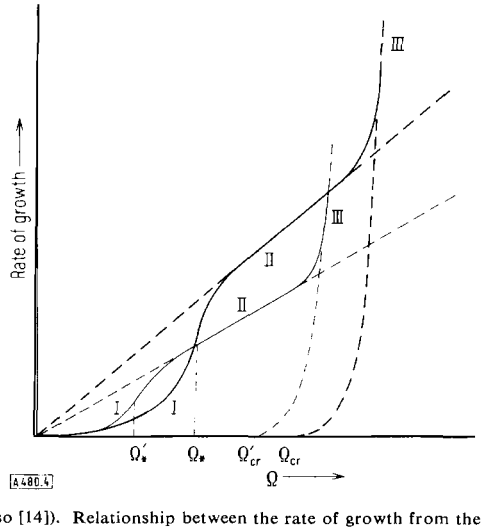


Fig. 4 (cf. also [14]). Relationship between the rate of growth from the vapor and the degree of supersaturation. The thick solid curve is the growth rate of real crystals according to Equations (7) (range I), (9) (range II), and (1) (range III).

Where no dislocations are present, growth can only commence at $\Omega = \Omega_{cr}$. The transition from the quadratic to the linear relationship is indicated by $\Omega_*$ [see Equation (11)]. The thinner curve gives a possible course of $R'_I = f(\Omega)$ [Equation (23)] with $\Omega'_*$ and $\Omega'_{cr}$ as transition points between the three ranges.

[*] When the effect is relatively large, the crystal form may change [16, 17, 19, 20].

[32] *N. Cabrera* and *D. A. Vermilyea* in: Growth and Perfection of Crystals (Rep. internat. Conf. on Crystal Growth). Wiley, New York 1958, p. 393.

[33] *A. A. Chernov* and *E. D. Dukova*, Soviet Physics Cristallogr. (Engl. Transl.) *5*, 627 (1960).

[34] *F. C. Frank*, Philos. Mag. [7] *42*, 1014 (1951).

[35] *A. J. Forty*, Philos. Mag. [7] *43*, 337 (1952).

[*] For the definition of the Burgers vector see, *e.g.*, *A. Seeger* in: Handbuch der Physik. Springer Verlag, Berlin-Göttingen-Heidelberg 1955, Vol. VII/1, p. 383.

[36] *W. T. Read jr.*: Dislocations in Crystals. McGraw-Hill, New York 1953.

[37] *S. Amelinckx*, *W. Bontinck*, and *W. Dekeyser*, Philos. Mag. [8] *2*, 1264 (1957).

[38] *A. R. Lang*, J. appl. Physics *28*, 497 (1957).

[39] *F. C. Frank* in [32], p. 411.

phase) the values are generally smaller. This behavior explains the different mechanisms observed for approximately the same degrees of supersaturation.

## 4. Experimental Studies

For growth from the vapor phase, the values of $\Omega_{cr}$ will hardly ever be less than 0.5. At the lower degrees of supersaturation employed for growing single crystals, therefore, growth takes place according to the quadratic Equation (7) or the linear relationship (9). The presence of dislocations is almost invariably required during growth from the vapor phase (only whisker growth provides exceptions). Evidence for a nucleation mechanism has been observed only in the case of dendritic growth and growth of whiskers at degrees of supersaturation above $\Omega_{cr}$.

*Volmer* and *Schultze*[27] have investigated the growth of iodine, naphthalene, and white phosphorus at 0 °C and supersaturations between 0.004 and 0.08[*]. For naphthalene and phosphorus, they found only a linear growth relationship, but for iodine the rate of growth decreased below $\Omega = 0.04$ faster than expected from the linear relationship, and at $\Omega = 0.004$ the growth rate was practically zero. The authors interpret this result as a confirmation of the nucleation theory, while *Burton*, *Cabrera*, and *Frank*[13] subsequently carried out an evaluation according to the quadratic relation.

*Bradley* and *Drury*[40] studied the growth of iodine and carbon tetrabromide crystals. For iodine, the measurements were carried out between 0 and 25 °C and at supersaturations between 0.002 and 0.07. The monoclinic modification of $CBr_4$, stable up to 47 °C, was studied at 40 °C for supersaturations between 0.0004 and 0.03, and the cubic structure at 50, 55, and 59 °C for Ω-values between 0.0001 and 0.04. A quadratic relationship between R and Ω was found for iodine and cubic $CBr_4$, while a linear change was observed for monoclinic $CBr_4$ down to the lowest supersaturation employed.

*Parker* and *Kushner*[41] studied the condensation of zinc at 390 °C and Ω-values between 0.009 and 0.09. These authors found an only approximately linear relationship with $\alpha \approx 0.1$. In contrast, *Rapp*, *Hirth*, and *Pound*[42] obtained $\alpha \approx 1$ at 70 °C and higher values of Ω.

For β-methylnaphthalene and *p*-toluidine, *Chernov* and *Dukova*[33] found a relationship between the growth rate and Ω which corresponds approximately to regions I and II in Fig. 4 (see Fig. 5).

The characteristic degree of supersaturation $\Omega_*$ [see Equation (11)] was greater for higher ($d = 60\ d_0$) than for lower steps ($d$ = several $d_0$). As Ω increased, the spirals disappeared and a circular step surrounding the point of origin of the dislocation remained. This behavior was interpreted by postulating a splitting of the original spiral with a high Burgers vector into separate dislocations.

*Kitchener* and *Strickland-Constable*[43] determined the growth and evaporation rates on the (111) faces of orthorhombic sulfur and the (110) and (111) faces of orthorhombic benzophenone, as well as on polycrystalline benzophenone,

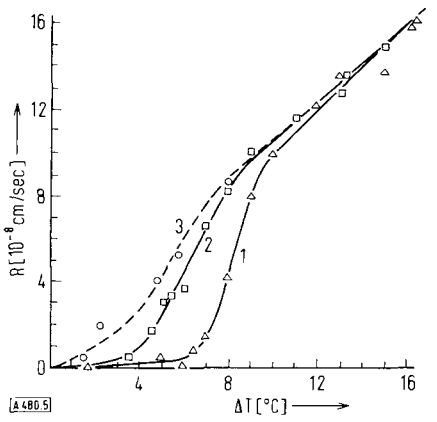


Fig. 5. Growth rate of β-methylnaphthalene in relation to the height of the step. 1: $d = 4d_0$; 2: $d = 40d_0$; 3: $d = 60d_0$ (from [33]).

as a function of Ω between 15 and 60 °C. During growth, Ω was varied between 0.07 and 0.20 and during evaporation between 0.05 and 0.15. The resulting curves (Fig. 6) are linear for the larger values of Ω. Here $\alpha < 0.1$. The bent portion was treated according to Equation (7).

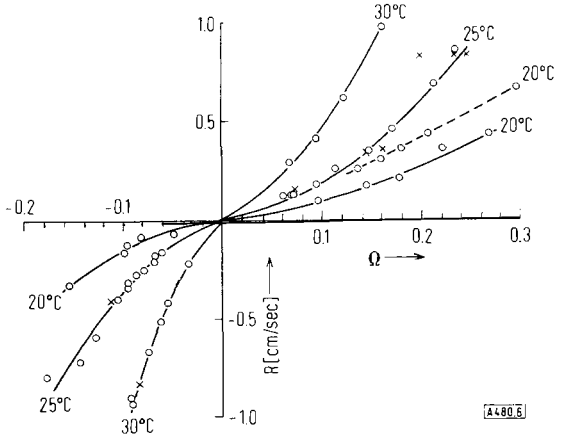


Fig. 6. Growth rate and evaporation rate of the (110) faces of benzophenone at 20, 25, and 30 °C (taken from [43]). - - - Measurements made immediately after those at 30 °C; × control values.

Investigations on ice crystals by *Shaw* and *Mason*[44] gave a quadratic relationship between Ω and R. In addition, R was strongly dependent on the size of the crystal. The derivative $d(2h)^2/dt$ (2h is the distance between opposite faces) was found to be constant for a given value of Ω.

Measurements of the growth rate of individual (110) faces of urotropine and (111) faces of arsenolite crystals[29,45] indicated an approximately quadratic relationship between Ω (0.004–0.4) and R for microscopically smooth faces, while a defective face in the same Ω range gave an approximately linear relationship (Fig. 7).

The increase in R related to the change-over to the linear relationship was explained by an increase in the dislocation density.

The dependence of the rate of advance of the growth steps w on the ratio $d/d_0$ (d = step height) was measured for naphthalene, biphenyl, and *p*-toluidine crystals at $\Omega = 0.01$ by *Lemmlein*, *Dukova*, and *Chernov*[46,47]. The resulting curves are reproduced in Fig. 8 and obey Equation (20).

[*] Here and in the following supersaturation denotes the relative supersaturation Ω.

[40] *R. S. Bradley* and *T. Drury*, Trans. Faraday Soc. *55*, 1848 (1959).

[41] *R. L. Parker* and *L. M. Kushner*, J. chem. Physics *35*, 1345 (1961).

[42] *R. A. Rapp*, *J. P. Hirth*, and *G. M. Pound*, Canad. J. Physics *38*, 709 (1960).

[43] *S. A. Kitchener* and *R. F. Strickland-Constable*, Proc. Roy. Soc. (London) *A 245*, 93 (1958).

[44] *D. Shaw* and *B. J. Mason*, Philos. Mag. [7] *46*, 249 (1955).

[45] *R. Honigmann* and *H. Heyer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 74 (1957).

[46] *G. G. Lemmlein* and *E. D. Dukova*, Soviet Physics Crystallogr. (Engl. Transl.) *1*, 112 (1956).

[47] *G. G. Lemmlein*, *E. D. Dukova*, and *A. A. Chernov*, *ibid. 2*, 426 (1957).

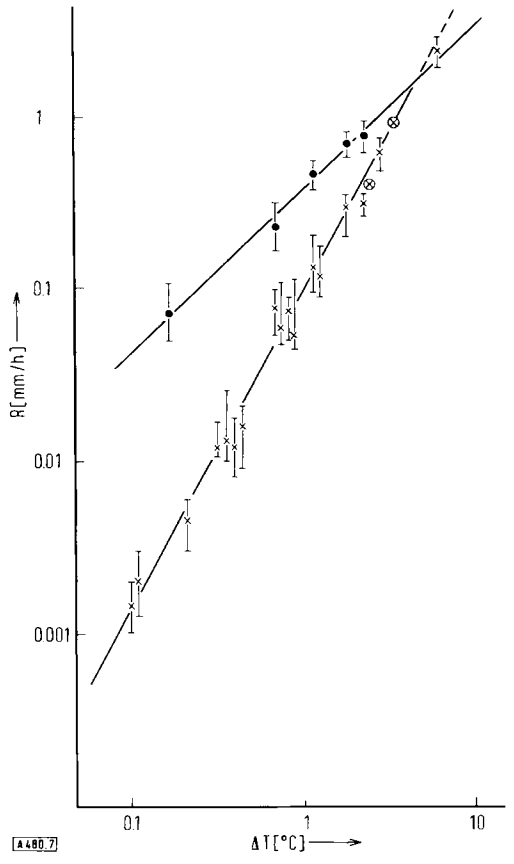


Fig. 7. Growth rate of the (110) faces of urotropine at 70 °C. ×: microscopically smooth faces; ●: defective faces; $\Omega \approx 0.08\Delta T$. ⊗: averaged values for smooth surfaces obtained by a different method.

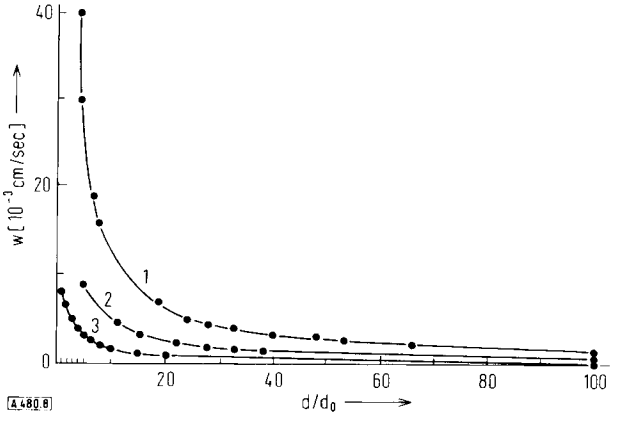


Fig. 8. Relationship between the rate of advance w of the growth steps and the ratio $d/d_0$ (d = step height).
1: *p*-toluidine; 2: biphenyl; 3: naphthalene (from [47]).

*Hallett*[48] investigated the growth of ice crystals at atmospheric pressure in relation to the temperature and the degree of supersaturation. The rate of advance of the steps on the basal face was found to be inversely proportional to the step height, in accordance with Equation (20).

Numerous other papers furnish information about the mechanism of crystal growth without giving growth rate figures. Let us mention only two experimental techniques which give details about the surface structure at atomic dimensions. The first concerns studies with the field electron and the field ion microscopes[49–51], the second deals with electron microscopic studies of gold decorated NaCl surfaces[52].

[48] *J. Hallett*, Philos. Mag. [8] *6*, 1073 (1961).

The presence of pure solvent is enough to reduce appreciably the value of the specific free ledge energy ρ. This leads to a decrease in the work of two-dimensional nucleation and a displacement of $\Omega_{cr}$ toward small values. In addition, diffusion in the solution can become the rate-determining factor. Since surface diffusion is also decreased, direct addition on the step or on the kink begins to compete with the route mother phase → surface → step → kink.

### 1. Growth Rate Theory

The nucleation theory yields an equation for the rate of growth differing from Equation (1) by a factor $e^{-\Psi_{L/k}}$, which makes allowance for the activation energy $\Psi_L$ for the transfer of a molecule from solution into the crystal.

For real crystals, a sequence of growth steps brought about by screw dislocations is again made the basis of the theory[15]. The rate of advance w is now given by:

$$w = \pi\, v_0\, \beta\, (c_\sigma - c_e) = \pi v_0 \beta c_e \Omega (1 + \frac{\beta r}{D} \ln \frac{s}{\pi r} \sinh \frac{\pi}{s} \delta)^{-1} \qquad (24)$$

where $v_0$ is the volume of the molecule, $c_\sigma$ the concentration of the solution, $c_e$ the saturation concentration, and β a factor which allows for the rate of exchange of building units between step and solution. D is the diffusion coefficient and δ the thickness of the diffusion layer. The factor β diminishes when the number of kinks in the step is reduced. Using Equation (3), the rate of growth becomes

$$R_I = dw/s = f_0 \beta k T c_e \Omega^2 \left[4\rho\,(1 + \frac{\beta r}{H} \ln \frac{\delta \Omega_*}{r\Omega} \sinh \frac{\Omega}{\Omega_*})\right]^{-1} \qquad (25)$$

In this equation, the expression in parentheses represents the relationship between the condensation coefficient and the supersaturation. In Equations (24) and (25) $\Omega = (c_\sigma - c_e)/c_e$, and $\Omega_*$ is given by

$$\Omega_* = 4\, f_0\, \rho / kT\delta \qquad (26)$$

For $\Omega \ll \Omega_*$, the growth steps are so far apart that the diffusion fields do not overlap. As in growth from the vapor phase, R is proportional to $\Omega^2$. As Ω increases, s becomes less than δ. Equation (25) is then transformed into

$$R_{II} = \frac{D\, v_0 c_e}{\delta} \Omega - \left(1 + \frac{\beta r}{D} \ln \frac{\Omega_* \delta}{2\Omega r}\right) \frac{D^2\, v_0\, c_e\, \Omega_*}{\beta\, r\, \delta} \qquad (27)$$

This almost linear function of Ω cuts the ordinate below the origin when extrapolated. An approximation for the range $0.01 < \Omega < 0.2$ is

$$R = (\beta\, r\, k\, T\, c_e / 4\sigma)\, K\, \Omega^L \qquad (28)$$

[49] *E. W. Müller*, Ergebn. exakt. Naturwiss. *27*, 290 (1953).

[50] *E. W. Müller*, Adv. Electronics Electron Physics *13*, 87 (1960).

[51] *R. Gomer*: Field Emission and Field Ionization. Harvard University Press, Cambridge 1961.

[52] *H. Bethge*, Physica Status solidi *2*, 775 (1962).

The values of the constants K and L are determined by those of the parameters in Eqs. (25) and (27). Fig. 9 shows the relationship between the growth rate and the degree of supersaturation.

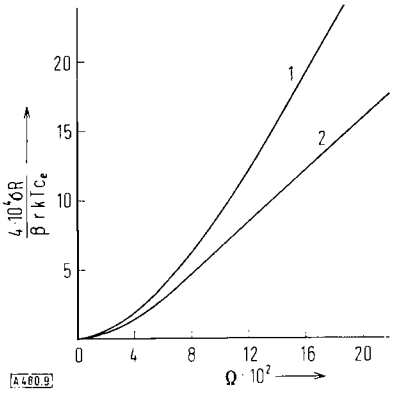


Fig. 9. Normalized growth rate from solution as a function of supersaturation (according to Equation (28); from [15]).
Curve 1: K = $4\times10^{-2}$, L = 1.65, $\delta$ = $3.5\times10^{-5}$ cm; curve 2: K = $1.7\times10^{-2}$, L = 1.42, $\delta$ = $7\times10^{-5}$ cm.

## 2. Experimental Investigations

*Booth* and *Buckley*[53] measured the growth rates of individual faces of ethylenediamine L-tartrate crystals and obtained the relationship shown in Fig. 10. The curves match the theoretical ones in Fig. 9. The presence of impurities reduces the growth rate and causes a displacement of $\Omega_*$ to smaller values.

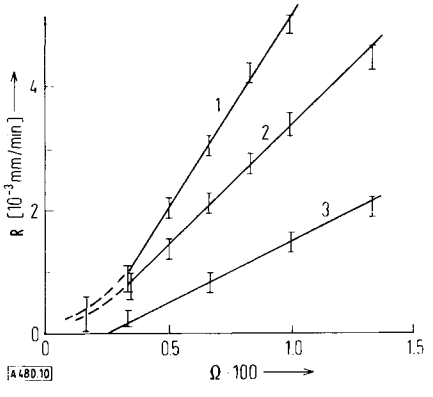


Fig. 10. Growth rate of ethylenediamine L-tartrate crystals from solution. 1: at 52 °C; 2: at 42 °C; 3: at 42 °C with 0.5 g/l added boric acid (from [53]).

*Bennema*[54] observed a linear relationship between R and $\Omega$ for the growth of potassium alum from aqueous solution, with $\Omega$ lying between 0.0001 and 0.01.

Studies of the layer-growth of β-methylnaphthalene crystals from alcoholic solution by *Kozlovskii* and *Lemmlein*[55] confirmed the relationship given by Equation (20).

In contrast, several observations can be interpreted by a nucleation mechanism. *Spangenberg* and *Nitschmann*[56] found that NaCl crystals obtained from aqueous solution begin to grow only above $\Omega_{cr}$ = 0.00045. A supersaturation region which is ineffective for growth is, however, found only when the crystal is bounded by (100) faces. Crystals with artificially created (011) and (111) faces start growing as soon as supersaturation is reached. This is important because it makes the interpretation of the cessation of growth as an adsorption effect very unlikely. *Neuhaus*[57] also found a critical degree of supersaturation of $\Omega_{cr}$ = 0.0028 for $CuCl_2 \cdot 2H_2O$. However, the observed linear rise of R with increasing supersaturation in the adjacent region of $\Omega$ values between 0.0028 and 0.007 is in conflict with a two-dimensional nucleation mechanism.

*Michaels* and *Colville*[58] studied the growth of adipic acid crystals at 25–45 °C from pure aqueous solutions and after the addition of anionic and cationic surface-active substances, and found an exponential relationship between R and $\Omega$ for values of $\Omega$ between 0.16 and 1.20 for the (110), (010), and (001) faces of the orthorhombic crystals. Anionic additives slow down growth markedly, cationic ones only slightly.

[53] *A. H. Booth* and *H. E. Buckley*, Nature (London) *169*, 367 (1952).

[54] *P. Bennema*, Thesis, Universität Groningen 1965.

[55] *M. I. Kozlovskii* and *G. G. Lemmlein*, Soviet Physics Crystallogr. (Engl. Transl.) *3*, 352 (1958).

[56] *K. Spangenberg* and *G. Nitschmann*, Z. Kristallogr. *A 102*, 285 (1940).

## IV. Growth from the Melt

Growth from the melt is subject to the same rules which govern growth from solution, but in addition, the effect of thermal conductivity is significant since there is much less difference between the coefficients of thermal conductivity of the crystals and the melt than between those of the crystal and the solution. New growth-form criteria are thereby created. Where the heat is taken up by the crystal, as in most pulling and solidification processes, rounded crystals are generally formed, since the growth front is now determined by the position of the isothermal surface at the melt temperature and not by kinetic processes[27]. Only where stronger supercooling or greater differences in thermal conductivity cause the removal of sufficient heat through the crystal to lead to the formation of a region of supercooled melt in front of the crystal, is the kinetic process again able to compete, with possible appearance of polyhedral shapes. Where the heat is taken up by the melt, only polyhedral shapes will be formed.

The experimental study of growth kinetics is made difficult above all by the fact that the temperature of the melt in the immediate vicinity of the phase boundary and therefore the effective degree of supercooling is not known accurately.

### 1. Growth Theory

The nucleation theory again supplies an expression analogous to Equation (1) with an additional term $e^{-\Psi_s/kT}$ where $\Psi_s$ is the activation energy for the transition of a molecule from the melt into the crystal[8,23,59–61]. Using

$$\Delta G'_n = A\, M\, \rho^2\, T_s/2\, d_0\, \gamma\, \Lambda_s\, \Delta T \qquad (29)$$

[57] *A. Neuhaus*, Angew. Chem. *71*, 678 (1959).

[58] *A. S. Michaels* and *A. R. Colville Jr.*, J. physic. Chem. *64*, 13 (1960).

[59] *M. Volmer* and *M. Marder*, Z. physik. Chem. *A 154*, 97 (1931).

[60] *W. I. Danilov* and *W. I. Malkin*, Zh. fiz. Khim. *28*, 1837 (1954).

[61] *D. Turnbull*, Solid State Physics *3*, 225 (1956).

where A is a geometric factor, M the molecular weight, $T_s$ the temperature of the melt, $\gamma$ the density, $\Lambda_s$ the molar heat of fusion and $\Delta T = T_s - T$ is the degree of supercooling, R is obtained as

$$R = d\, He^{-\Psi_s/kT}\, e^{-\Delta G'_n/kT} \qquad (30)$$

Although our knowledge of the melt-crystal interface is as yet very incomplete – both a step structure and a more or less uniform distribution of the kinks have been proposed for the growing face [15] – direct observations of the growth of spirals in phenyl salicylate [62] and in β-methylnaphthalene [63] as well as observations of growth steps after removal of the melt [64–66] appear to indicate that treatment by the theory of dislocations is justified. The following expression for R [15] is analogous to Equation (25):

$$R = f_0 \beta_T \lambda_s T_s \Omega^2 \left[ 4\rho \left(1 + \frac{\beta_T r \lambda_s}{\varkappa} \ln \frac{\delta\Omega}{r\Omega}\right) \sinh \frac{\Omega}{\Omega_*} \right]^{-1} \qquad (31)$$

where $\Omega$ is the relative degree of supercooling $(T_s - T)/T_s$, $\lambda_s$ is the molecular heat of fusion, and $\varkappa$ the thermal conductivity. $\beta_T$, like $\beta$ in Equation (25), denotes the rate of particle exchange between the melt and the step, and is given approximately by

$$\beta_T = D\, \lambda_s / v_0\, r\, k T_s^2 \qquad (32)$$

where D is the coefficient of diffusion through the melt.

The existence of either a linear or a quadratic relationship between R and the degree of supercooling depends not only on the ratio $\Omega/\Omega_*$ but also on $\varkappa$. A high thermal conductivity tends to make the factor $r\beta_T\lambda_s/\varkappa$ zero, and favors the quadratic relationship. As in the case of the solutions, R can be written as the following function of $\Omega$ for small values of $\Omega$:

$$R = (f_0 \beta_T \lambda_s T_s / 4\rho)\, K\, \Omega^L \qquad (33)$$

When plausible values of r, $v_0$, $\rho$, $\beta_T$, D, and $T_s$ are introduced, one obtains $K \approx 0.1$ and $L \approx 1.7$. L depends weakly and K strongly on the assumed values.

## 2. Experimental Investigations

Numerous investigations confirm the relationship (33). The equations obtained for R are shown in Table 1 in the form $R = K' (\Delta T)^L$.

Other work points to growth *via* two-dimensional nuclei. This is true also for some of the substances listed in Table 1, for which Equation (33) applies only during the initial stages, so that the references quoted can be taken only partially as confirmation of the dislocation growth mechanism.

The curve found by *Volmer* and *Marder* [59] for glycerol fits Equation (30) over the measured supersaturation range.

Table 1. Growth from the melt; experimental values of the parameters in the equation $R = K'(\Delta T)^L$ (cf. [15, 61]).

| Substance | K' [cm/sec °K] | L |
|---|---|---|
| Water [67] | $1.6\times10^{1}$ | 1.7 |
| Water [68] from −2 to −3.1 °C | $1.3\times10^{2}$ | 2.9 |
| from −3 to −6.5 °C | $7.55\times10^{2}$ | 2.32 |
| Glycerol [59] | $8\times10^{6}$ | 1.7 |
| Phenyl salicylate [69] ($\Delta T < 6$ °C) | $4\times10^{4}$ | 1.7 |
| Phenyl salicylate [69] ($\Delta T > 6$ °C) | $1.56\times10^{5}$ | 2.3 |
| Tin [70] | 0.7 | 1.8 |
| Phosphorus [71, 72] | 1.0 | 1.7 |

*Hillig* [67] found an exponential relationship between R and the degree of supercooling for the growth of microscopically smooth basal planes of ice:

$$R = 0.03\, e^{-0{,}35/\Delta T}\ \text{cm/sec} \qquad (34)$$

Defective faces exhibited a higher growth rate (*ca.* 300 times as great at $\Delta T = 0.03$ °C) proportional to $\Delta T^{1.3}$.

*Danilov* and *Malkin* [60] also found an exponential relationship for phenyl salicylate up to a supercooling of 2.6 °C. The latent region extending up to 1.6 °C supercooling is particularly noteworthy (cf. Fig. 11).

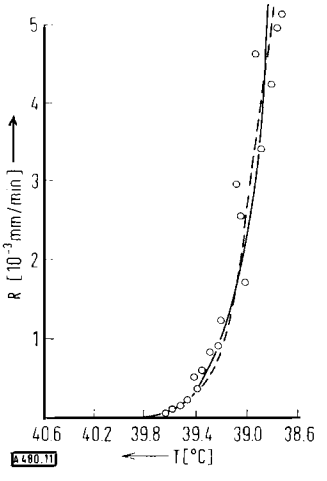


Fig. 11. Growth rate of phenyl salicylate from the melt (taken from [60]). – – – –: calculated curve.

## V. Growth of Platelets, Whiskers, and Proper Whiskers

A special form of growth is the formation of either platelets or acicular crystals which are generated during preferential growth in either two or only one direction. The acicular crystals are divided into whiskers and proper whiskers (or squeezed whiskers), according to whether their growth takes place at the tip or the base, though the term "whisker" is mostly applied to both forms. Literature surveys are given, *e.g.*, in [73–75].


[62] *W. I. Malkin*, Thesis, Moscow 1952.

[63] *M. I. Kozlovskii*, Thesis, Moscow 1958.

[64] *L. Graf*, Z. Metallkunde *42*, 336 (1951).

[65] *C. Elbaum* and *B. Chalmers*, Canad. J. Physics *33*, 196 (1955).

[66] *W. A. Tiller*, J. Metals *9*, 847 (1957).

[67] *W. B. Hillig* and *D. Turnbull*, J. chem. Physics *24*, 914 (1956).

[68] *T. B. Chalmers* in [73], p. 291.

[69] *H. Pollatschek*, Z. physik. Chem. *142*, 289 (1929).

[70] *A. Rosenberg* and *W. C. Winegrad*, Acta metallica *2*, 342 (1954).

[71] *D. Gernez*, C. R. hebd. Séances Acad. Sci. *95*, 1278 (1882).

[72] *R. E. Powell*, *T. S. Gilman*, and *J. H. Hildebrand*, J. Amer. chem. Soc. *73*, 2525 (1951).

[73] *R. H. Doremus*, *B. W. Roberts*, and *D. Turnbull*: Growth and Perfection of Crystals (Rep. internat. Conf. on Crystal Growth). Wiley, New York 1958.

[74] *H. K. Hardy*, Research *8*, 57 (1955); Progr. Metal Physics *6*, 45 (1956).

[75] *S. S. Brenner*, Science (Washington) *128*, 569 (1958).

## 1. Whisker Growth

The growth process during the formation of whiskers is characterized by an initially high velocity in the longitudinal direction with simultaneous cessation of growth of the side faces. At a critical length the rapid growth suddenly stops. End and side faces now grow at normal rates, or the growth ceases entirely. The axis of the whiskers always follows crystallographic directions of low indices. Occasionally, changes in orientation occur so that kinked whiskers are formed [76,77]; spiral forms are less common [77].

Adsorption processes are evidently important factors in the growth of platelets and whiskers; whisker growth from the vapor phase is observed only when foreign gases are present. For instance, zinc whiskers are formed from the vapor [78] at partial pressures of He or $H_2$ between 10 and 600 mm. As the partial pressure increases, the whiskers become longer and thinner. In contrast, very high foreign gas pressures, especially of non-inert gases, lead to clusters and shorter whiskers or to dendritic forms. The conditions for whisker formation lie therefore halfway between those for isometric crystals and for dendrites.

*Sears* [79] postulated a preferential orientation of the screw dislocations in the crystal to explain the growth mechanism. Whiskers are supposed to contain one or more dislocations parallel to the long axis, while platelets have a two-dimensional network of dislocations. Accordingly, the end faces grow *via* a dislocation mechanism while the dislocation-free side faces require the formation of two-dimensional nuclei.

The structural units striking the side faces reach the tip by diffusion along the surface and are there incorporated into the lattice. This explains why whiskers are able to grow substantially more quickly than is indicated by the gas-kinetic impingement rate.

A theoretical treatment of the diffusion rate for the growth of whiskers from the vapor phase is contained in references [80–83]. According to these, the rate of growth of a whisker is given by

$$R = \Delta\dot{N}\, x_s\, (2\, m_0/r_N\gamma)\, \tanh\,(l/x_s), \qquad (35)$$

where $l$ and $r_N$ are the length and radius of the whisker, $m_0$ is the mass of a building unit, and $\gamma$ the density. For $l < x_s$, R is given by

$$R = \Delta\dot{N}\, l\, (2\, m_0/r_N\gamma), \qquad (36)$$

while for $l > x_s$

$$R = \Delta\dot{N}\, x_s\, (2\, m_0/r_N\gamma). \qquad (37)$$

Shorter whiskers therefore obey an exponential and longer whiskers a linear growth law. $x_s$ was found to be 65 $\mu$ (at 53 °C) for potassium and 50–122 $\mu$ for mercury (at −51 to −68 °C.).

Whisker and platelet growth from the vapor phase has been studied above all for mercury [79,82,84,85,90] and for potassium [80–82,86–88,91]. A linear dependence of the growth rate on supersaturation was found by *Dittmar* and *Neumann* [80] for potassium, and by *Sears* [79] for mercury. The exponential relationship was observed by *Gomer* [90] and by *Parker* and *Hardy* [91] during studies on mercury and potassium with the field electron microscope. *Parker*, *Anderson*, and *Hardy* [82] found both relationships with both these substances. Fig. 12 shows the longitudinal growth rate of potassium whiskers [89].

These experiments confirm the concept according to which the rapid whisker growth ceases when $\Omega > \Omega_{cr}$, because under this condition the side faces can grow *via* two-dimensional nuclei.

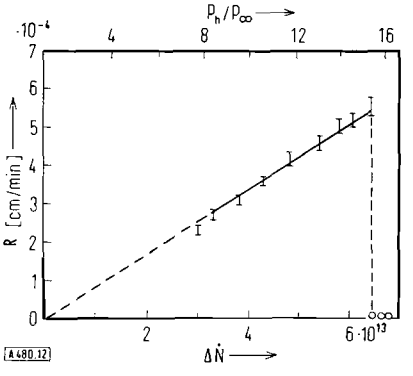


Fig. 12. Longitudinal growth rate of potassium needles at 55.8 °C $\Delta\dot{N}$ is the difference between the number of impingements obtained from the kinetic theory of gases at the temperature of the vapor and the temperature of the crystal. $p_h/p_\infty$ is the supersaturation ratio. The rate of growth R decreases sharply when the critical supersaturation for the side faces is rached (from [89]).

Objections to the above growth mechanism are provided by the dislocation content of the whiskers [92], since whiskers with and without axial dislocations have been found.

Whiskers are also formed during growth from solution, from the melt, and from solid phases [73].

## 2. Growth of Proper Whiskers

Spontaneous growth of proper whiskers occurs during the annealing of thin metal layers deposited on metal or glass substrates.


[76] *G. S. Baker*, Acta metallica *5*, 353 (1957).

[77] *S. S. Brenner*, Acta metallica *4*, 62 (1956).

[78] *R. V. Coleman* and *G. W. Sears*, Acta metallica *5*, 131 (1957).

[79] *G. W. Sears*, Acta metallica *3*, 361, 367 (1955).

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[81] *S. J. Hruska* and *J. P. Hirth*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 479 (1961).

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Examples are layers (*ca.* 1 μ thick) of Sn, Sb, Bi, Zn, Cd, and of Sn–Al and Pb–Cu alloys on copper, tombac, steel, and glass substrates [93–99]. The surrounding vapor phase has no effect on the progress of growth. The whiskers produced generally have a diameter equal to the layer thickness, and grow to a length of several millimeters. They consist of material of the respective layer or in the case of alloys generally of one of the components. Growth ensues by building up at the base of the whisker, so that the often irregularly shaped head remains unaltered. The longitudinal axis lies in a low-index direction.

It is postulated that the growth of proper whiskers represents a special form of recrystallization [73, 100]. The normal recrystallization which initially occurs during tempering after deposition of the layer is inhibited by stationary grain boundaries when the grain size reaches the order of magnitude of the layer thickness [101]. Growth of whiskers with a diameter equal to this grain size then takes place out of the layer. The driving force consists of stresses generated in the layer by the strongly anisotropic thermal expansion of the crystals [96]. Temperature changes of a few degrees are sufficient to bring this about. The material transport presumably takes place by grain boundary diffusion. When all stresses have been eliminated, longitudinal growth and formation of fresh whiskers cease almost at once and at the same time. At higher temperatures (above about 200 °C) the activation energy for the movement of the inhibited grain boundaries is available, making possible normal recrystallization.

Growth of proper whiskers can be produced also by mechanical deformation. One example is the formation of tin whiskers on tinned steel [99]. Application of pressure enabled the rate of growth to be increased by a factor of $10^4$ [102]. It is assumed that dislocation rings move out from the substrate during growth [103–107].


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At more rapid growth rates, crystal forms often arise which, because of their appearance, are designated as dendrites. The dendritic branches represent preferred growth directions which correspond to lower-index crystallographic directions of the respective lattice. Dendritic growth occurs when $\Omega \gg \Omega_{cr}$ and when the development of the nuclei is retarded by diffusion or by heat conduction processes.

Information about the growth process is provided by observations of the alteration of the dendritic axes with increasing degree of supersaturation during crystallization of NaCl from pure and impure solutions [108]. As the degree of supersaturation increases, the dendritic direction changes in the sequence (111) → (110) → (100). An explanation for this change was found in the difference between the work of nucleation at the corner, edge, and face of ionic crystals [26, 108, 109]. Both the pre-exponential factor H and the work of two-dimensional nucleation $\Delta G'_n$ in Equation (1) have maximum values in the center of the face, fall off at the edges, and are a minimum in the corners. All nucleation work factors decrease as the degree of supersaturation is increased, so that the frequency factor H becomes the decisive quantity in determining the nucleation frequency. The same change in dendritic direction with rising degree of supersaturation occurs when the work of nulceation is reduced by adsorption. Addition of increasing concentrations of formamide, urea, and aminoacetic acid led to a shift of the dendritic growth from (111) to (100) [110, 111].

Experiments from the melt and with other NaCl-type crystals gave the same result. Analogous studies with CsCl, CsI, and TlCl showed [108] a shift of the dendritic axis in the order (100) → (111) → (110).


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# Kinetic Relationships between Reactions in the Gas Phase and in Solution

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*Dedicated to Professor W. Klemm on the occasion of his 70th birthday*

*Some recent examples of reactions proceeding both in the gas phase and in solution have been investigated to determine their kinetics and mechanisms. The ratio of the corresponding rate constants, $k_G$ and $k_L$, of the elementary processes studied has been found to be about unity for unimolecular reactions and between 1 and 10 for bimolecular reactions. The mechanisms, overall rates, rate constants, and activation energies have been determined for the homogeneous gas reaction $NOCl + Cl_2O = NO_2Cl + Cl_2$ and the reaction $NOCl + N_2O_5 = NO_2Cl + 2\ NO_2$, carried out in $C_2F_3Cl_3$.*

## I. Introduction

Of the thousands of reactions that have been studied in solution, hardly ten have also been investigated in the gas phase. This is very surprising since it is of general theoretical interest to compare the kinetics of a reaction occurring in solution with those of a gas-phase reaction. Moreover, from a molecular point of view it is easier to describe the reaction in the gas than in a condensed phase, since in the latter the reacting entities are constantly in contact with four, six, or more surrounding particles.

The reason why so few solution reactions have also been studied in the gas phase is that a great number of reactions taking place in different solvents with various degrees of ease proceed *via* ionic mechanisms featuring polar or charged species. Polar solvents promote ionic reactions – the more polar the solvent the faster is the reaction. Ionic processes do not occur in the gas phase, except on a surface or at very high temperatures. Thus alkyl halides and esters are not hydrolysed in the gas phase to any measurable extent, and when we attempt to force the reaction by increasing the temperature, competing reactions become predominant.

It follows, therefore, that a reaction can be carried out in both the gas phase and in solution only if the interaction between the reacting molecule and the solvent molecules is so small that the non-ionic mechanism of the gas-phase reaction can equally well proceed in solution. In principle, this should be possible by the use of a non-polar, inert solvent.

For our kinetic investigations we selected reactions which had been studied in the gas phase and tried to carry them out in solution, in order to test the validity of the mechanisms determined for the gas-phase reactions. The reactions in question, *i.e.* those of $ClO_2$ and $Cl_2O$ with NOCl, $NO_2/N_2O_4$, and $N_2O_5$, are generally characterized by complicated kinetics. Our basic approach was as follows: provided that the elementary steps of the process do not change when the reaction, first carried out as a truly homogeneous gase-phase reaction, is performed in solution, the kinetic features found in the first case should also be valid (at least qualitatively) in the second case, particularly since the sequence of steps is assumed to be non-cyclic. When in fact the same overall stoichiometry and rate equation are found in both phases, we can infer that the elementary steps and their sequence also are the same, and the proposed mechanism of the gas reaction is then confirmed. When, however, the overall reaction and/or the rate equation are different for the reaction in solution, there are two possibilities: either the mechanism of the gas-phase reaction has been replaced by an ionic process in solution, or what we assumed to be a homogeneous gas reaction really has some heterogeneous character owing to wall effects. When the gas reaction is not homogeneous, we cannot expect to find the same kinetics in solution, since the latter process is not affected by the walls of the vessel.

## II. Survey of the Inorganic Reactions Investigated

The gas-phase reactions that have so far also been investigated in solution are listed in Table 1. Reactions (I) to (V) proceed in the non-polar, inert solvent 1,1,2-trichloro-1,2,2-trifluoroethane (denoted here by $C_2F_3Cl_3$) in the same way as they do in the gas phase:

Table 1. Reactions carried out in different phases.

| Overall reaction [a] | Phase [b] |
|---|---|
| (I) $ClO_2 + 3\,NO_2 = NO_3Cl + N_2O_5$ | Gas [1, 2] |
| | Solution [3, 8] |
| | Melt [4] |
| (II) $Cl_2O + 2\,NO_2 = NO_3Cl + NO_2Cl$ | Gas [5] |
| | Solution [6] |
| (IIa) $2\,Cl_2O + 2\,NO_2 = 2\,NO_3Cl + Cl_2$ | Melt [5] |
| (III) $ClO_2 + 2\,NOCl = NO_2Cl + NO_2 + Cl_2$ | Gas [7] |
| | Solution [8] |
| (IV) $4\,ClO_2 + 2\,N_2O_5 = 4\,NO_3Cl + 3\,O_2$ | Gas [1, 2] |
| | (Solution, melt) [9] |
| (V) $2\,Cl_2O + 2\,N_2O_5 = 2\,NO_3Cl + 2\,NO_2Cl + O_2$ | Gas [1] |
| | Solution [6] |
| (Va) $Cl_2O + N_2O_5 = 2\,NO_3Cl$ | Melt [5] |
| (VI) $Cl_2O + NOCl = Cl_2 + NO_2Cl$ | Gas [11] |
| | Solution [3] |
| (VIa) $Cl_2O + NOCl = 3/2Cl_2 + NO_2$ | Melt (−78 °C) [11] |
| (VII) $N_2O_5 + NOCl = 2\,NO_2 + NO_2Cl$ | Gas [12] |
| | Solution [13] |

[a] The formula $NO_2$ is used here to denote the mixture $NO_2/N_2O_4$ in the rapidly established equilibrium $2\ NO_2 \rightleftharpoons N_2O_4$. However, in some cases, particularly in condensates, practically only $N_2O_4$ is present.
[b] Solvent: $C_2F_3Cl_3$.

[1] *Th. Jacobsen*, Dissertation, Universität Kiel, 1955.

the stoichiometry and the rate equation are the same. Under otherwise the same conditions, reactions (I) to (III) are about three times as fast in solution at room temperature as in the gas phase. For the reactions (IV) and (V) even the rates are the same for the two phases. This is not surprising, since these reactions are governed by the dissociation of dinitrogen pentoxide [6, 10].

That each of reactions (I) to (V) is characterized by the same overall equation in the two phases has been proved, *inter alia*, by extinction measurements on the solutions after the reaction has reached completion (for references, see Table 1). The kinetics of these reactions will be briefly described in Section III. The fact that the kinetics remain the same in solution confirms the mechanisms proposed for the gas reactions.

The following bimolecular processes occur in reactions (I) to (IV):

$$NO_2 + ClO_2 \rightarrow NO_3 + OCl \quad (1)$$

$$NO_2 + Cl_2O \rightarrow NO_2Cl + OCl \quad (2)$$

$$NO_2 + NOCl \rightarrow NO_2Cl + NO \quad (3)$$

The rate constants and the activation energies of these steps can be found by studying the overall reactions in the gas and the liquid phase (cf. Table 2).

In the formation of nitryl chloride and chlorine from nitrosyl chloride and chlorine monoxide in the gas phase [reaction (VI), Table 1], it has recently been possible to eliminate the wall effect almost entirely and to interpret the kinetics of the reaction. Unlike reactions (I)–(V), this reaction seems to be a single elementary step whose rate is given by

$$3.98 \times 10^9 \exp(-9100/RT)[Cl_2O][NOCl]\ \text{l mole}^{-1}\ \text{sec}^{-1}. \quad (4)$$

The reaction in $C_2F_3Cl_3$ is still to be investigated.

It has not yet been possible to carry out the formation of nitryl chloride and nitrogen dioxide from nitrosyl chloride and dinitrogen pentoxide [reaction (VII)] as a homogeneous gas reaction. The overall reaction has been carried out in $C_2F_3Cl_3$; its rate is well reproducible. The rate equation and the mechanism are discussed in Section III, 4.

Table 1 also contains some qualitative data on the reactions in the solvent-free, liquid condensate of the reacting gases. Under these conditions, the course followed in the gas phase can sometimes be repeated in qualitatively the same form, whereas in other cases different end-products are obtained, as in reactions (IIa), (Va), and (VIa), in which chlorine monoxide is invariably one of the reactants. No kinetic measurements were carried out on these reactions.

## III. Description of the Reactions Investigated

### 1. Reactions (I) and (IV) and the Bimolecular Process (1)

The overall reactions

$$ClO_2 + 3\ NO_2 = NO_3Cl + N_2O_5 \quad (I)$$

$$4\ ClO_2 + 2\ N_2O_5 = 4\ NO_3Cl + 3\ O_2 \quad (IV)$$

always occur side by side, since a mixture of $ClO_2$ and $NO_2$ gives rise to $N_2O_5$ which participates in reaction (IV), and the $NO_2$ formed as an intermediate in the reaction of $ClO_2$ with $N_2O_5$ cannot be fully consumed in the reaction (I). Although reactions (I) and (IV) proceed simultaneously in the same reaction mixture, two or three separate steps can still be clearly observed, at least in the gas phase (cf. Fig. 1) [14].

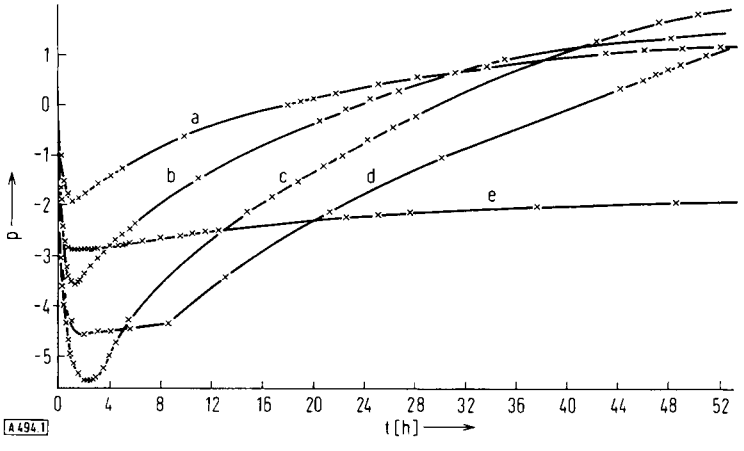


Fig. 1. Change in the pressure with time of the gaseous system $ClO_2/NO_2/N_2O_4$ at 25 °C.

| Curve | Initial pressure [mm Hg] $ClO_2$ | $NO_2 + N_2O_4$ | Formula units $NO_2/ClO_2$ |
|---|---|---|---|
| a | 43.7 | 202.0 | 6.85 |
| b | 60.0 | 200.3 | 4.95 |
| c | 79.1 | 198.0 | 3.70 |
| d | 79.7 | 116.3 | 2.02 |
| e | 79.7 | 64.6 | 1.05 |

Ordinate: Pressure (graduations of a spiral manometer, 1 unit = 11.76 mm Hg; initial scale reading set to zero).

The pressure drop in the first 1 to 2 hours (first stage) is caused almost exclusively by reaction (I). In mixtures a, b, and c, containing an excess of $NO_2$, the rise in pressure beyond the minimum is due to the dissociation of $N_2O_5$. In mixtures d and e, containing an excess of $ClO_2$, this pressure increase is only gradual. It is in the course of this second stage that the $N_2O_5$ formed in (I) reacts with excess $ClO_2$ to give chlorine nitrate [15] and oxygen according to

[2] *H. Martin* and *Th. Jacobsen*, Angew. Chem. *67*, 524 (1955).

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[5] *H. Martin*, *W. Meise*, and *E. Engelmann*, Z. physik. Chem. N.F. *24*, 285 (1960).

[6] *W. Meise*, Dissertation, Universität Kiel, 1957; *H. Martin* and *W. Meise*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *63*, 162 (1959).

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[8] *H. Martin*, *G. Fuchs*, and *L. Wartini*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *67*, 984 (1963).

[9] No distinction has so far been noticed between the reaction of $ClO_2$ with $N_2O_5$ in solution or melt and that in the gas phase.

[10] See, *e.g.*, *K. J. Laidler*: Chemical Kinetics. McGraw-Hill, New York 1950, p. 113.

[11] *K.-G. Prusseit*, Dissertation, Universität Kiel, 1965.

[12] *R. E. Weston Jr.*, Dissertation, Stanford University, 1950.

[13] *L. Wartini*, unpublished work.

[14] *A. Storjohann*, Dissertation, Universität Kiel, 1953.

[15] Cf. also *H. Martin*, Angew. Chem. *70*, 97 (1958).

reaction (IV). When the excess of $ClO_2$ is small (curve d) and is consumed in reaction (IV) ($N_2O_5$ being still present), the second stage gives rise abruptly to a third stage also constituted by the dissociation of $N_2O_5$.

Fig. 2 shows a kink in the pressure curves for a mixture of $N_2O_5$ with a stoichiometric deficiency of $ClO_2$, plotted against the overall time of the reaction (IV) (the initial mixture was composed of pure components)[1]. It can be seen from Fig. 2

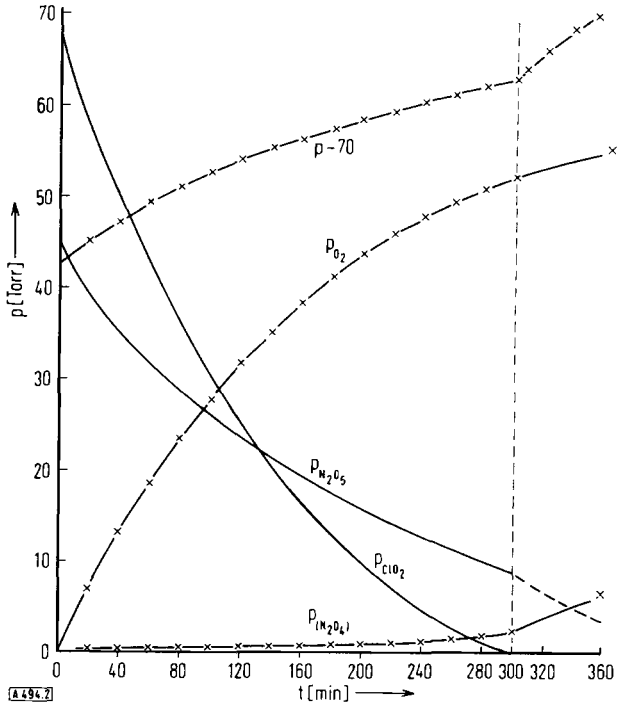


Fig. 2. Change in the total pressure p (given as p−70 mm Hg) of the system $ClO_2/N_2O_5$ and in the partial pressures of $ClO_2$, $N_2O_5$, $O_2$, and $N_2O_4$ at 40.5 °C; $p(N_2O_4) = pN_2O_4 + 1/2\ pNO_2$; initial pressures 67.4 mm Hg ($ClO_2$) and 45.2 mm Hg ($N_2O_5$).

that a small amount of $NO_2/N_2O_4$ is formed besides $NO_3Cl$ and $O_2$ during reaction (IV)[16]. The curve of the partial pressure of $O_2$ shows no kink at the moment of disappearance of the $ClO_2$, and the rate of formation of $O_2$ is not affected by the concentration of $ClO_2$, but obeys the equation

$$d[O_2]/dt = (1/2)\, k_{N_2O_5}\, [N_2O_5] \qquad (5)$$

where $k_{N_2O_5}$ is the rate constant for the dissociation of $N_2O_5$. The absence of a kink in the $p_{O_2}$ curve proves that reaction (IV) is governed by the dissociation of $N_2O_5$, more precisely, by step (7) in the following set of reactions[1,2].

$$N_2O_5 \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} NO_3 + NO_2 \qquad (6, -6)$$

$$NO_3 + NO_2 \xrightarrow{k_7} NO_2 + NO + O_2 \qquad (7)$$

$$NO + NO_3 \xrightarrow{k_8} 2\ NO_2 \qquad (8)$$

$$NO + ClO_2 \xrightarrow{k_9} NO_2 + OCl \qquad (9)$$

$$NO_2 + ClO_2 \xrightarrow{k_1} NO_3 + OCl \qquad (1)$$

$$NO_2 + OCl \xrightarrow{k_{10}} NO_3Cl \qquad (10)$$

This reaction sequence gives a quantitative account of the processes taking place in mixtures of $ClO_2$, $NO_2$, $N_2O_4$, and $N_2O_5$. The fast bimolecular step (8) has been included because it plays a part in the dissociation of pure $N_2O_5$. In mixtures containing $ClO_2$, step (8) is suppressed by the bimolecular step (9). The above reaction scheme leads to the following rate equation:

$$-d[ClO_2]/dt = (k_6k_7/k_{-6})\,[N_2O_5] + k_I\,[NO_2]\,[ClO_2] = k_{IV}\,[N_2O_5] + k_I\,[NO_2]\,[ClO_2] \qquad (11)$$

where constants $k_{IV}$ and $k_I$ can be determined experimentally and their values in the gas phase and in solution ($C_2F_3Cl_3$) are as follows:

$(k_I)_G = 2.25\times 10^7 \exp(-11000/RT)$ l mole$^{-1}$ sec$^{-1}$ [8],
$(k_{IV})_G = 1.8\times 10^{13} \exp(-24600/RT)$ sec$^{-1}$ [6],
$(k_I)_L = 4\times 10^8 \exp(-12000/RT)$ l mole$^{-1}$ sec$^{-1}$ [8],
$(k_{IV})_L = 2.0\times 10^{13} \exp(-24500/RT)$ sec$^{-1}$ [6].

The rate equation (11) encompasses the limiting overall reactions (I) and (IV), *i.e.* the reaction rates for mixtures containing no $N_2O_5$ or no $NO_2$.

The rate constant for the dissociation of $N_2O_5$, $k_{N_2O_5}$, obtained as $2\,k_6k_7/k_{-6}$ from steps (6) to (8), is twice as high as $k_{IV}$, for which Equation (11) gives $k_6k_7/k_{-6}$. This relationship has been confirmed experimentally by *Jacobsen*[1] for the gas reaction[17].

## 2. Reactions (II) and (V) and the Bimolecular Process (2)

The formation of chlorine nitrate and nitryl chloride in accordance with

$$Cl_2O + 2\ NO_2 = NO_3Cl + NO_2Cl \qquad (II)$$

is governed in both phases by the rate equation

$$-d[Cl_2O]/dt = k_{II}\,[Cl_2O][NO_2] \qquad (12)$$

where

$(k_{II})_G = 4.35\times 10^7 \exp(-11600/RT)$ l mole$^{-1}$sec$^{-1}$ [5]

and

$(k_{II})_L = 3.5\times 10^7 \exp(-10400/RT)$ l mole$^{-1}$sec$^{-1}$ [6].

Reaction (II) may be considered to consist in the following steps:

$$NO_2 + Cl_2O \xrightarrow{k_2} NO_2Cl + OCl \qquad (2)$$

$$NO_2 + OCl \xrightarrow{\text{fast}} NO_3Cl \qquad (13)$$

where the rate-determining step is (2). Thus $k_2$ can be determined by measuring the constants $k_{II}$.

Fig. 3 shows that the gas-phase reaction is subject to the wall effect: the decomposition of the end-product is strongly accelerated even by a quartz wall, which exerts a much lower catalytic action than a glass wall. The fact that the same reaction can be carried out in the liquid phase proves, however, the validity of the interpretation of the gas reaction[6].

[16] Therefore, strictly speaking, the overall reaction is $4\ ClO_2 + (2 + 2x)N_2O_5 = 4\ NO_3Cl + (3 + x)O_2 + 2x\ N_2O_4$ (IV') However, the value of x deviates noticeably from zero only in mixtures containing a deficiency of $ClO_2$ [1].

[17] Since $k_{N_2O_5} = 15.8\times 10^{-3}$ min$^{-1}$ (40.5 °C), the value of $k_{IV}$ should be $k_{IV} = 7.9\times 10^{-3}$ min$^{-1}$. The measurements on the systems $ClO_2/NO_2/N_2O_4$ and $ClO_2/N_2O_5$ gave $k_I = 1.62\times 10^{-3}$ mm Hg$^{-1}$ min$^{-1}$ (40.5 °C) and $k_{IV} = 8.2\times 10^{-3}$ min$^{-1}$ (40.5 °C) [1].

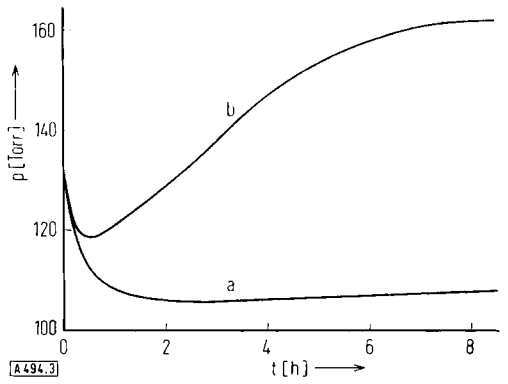


Fig. 3. Change in pressure of the gaseous system $Cl_2O/NO_2/N_2O_4$ in a 1000 ml quartz flask at 40 °C. Curve a: no packing; curve b; packed with quartz Raschig rings. Initial pressures 50 mm Hg ($Cl_2O$), 68.5 mm Hg ($NO_2$), and 14 mm Hg ($N_2O_4$).

The formation of chlorine nitrate and nitryl chloride from $Cl_2O$ and $N_2O_5$ (instead of $NO_2$) according to

$$2\,Cl_2O + 2\,N_2O_5 = 2\,NO_3Cl + 2\,NO_2Cl + O_2 \qquad (V)$$

is characterized in both phases by the rate equation:

$$-\,d[Cl_2O]/dt = k_{N_2O_5}\,[N_2O_5] \qquad (14)$$

The rate constant has virtually the same value in both cases:

$(k_{N_2O_5})_G = 3.6\times10^{13}\exp(-24600/RT)\ sec^{-1}$
and
$(k_{N_2O_5})_L = 4.0\times10^{13}\exp(-24500/RT)\ sec^{-1}$ (in $C_2F_3Cl_3$) [6].

In contrast to the system $ClO_2/N_2O_5$, no measurable amount of $NO_2$ is formed during the reaction in the system $Cl_2O/N_2O_5$. Consequently, the reaction is described satisfactorily by Equation (14). It is still uncertain whether the $NO_2$ formed eventually in the dissociation of $N_2O_5$ reacts further with $Cl_2O$ according to (II), or whether $Cl_2O$ is intercepted earlier in the dissociation of $N_2O_5$, possibly in the fast reaction $NO + Cl_2O \rightarrow NOCl + OCl$.

### 3. Reaction (III) and the Bimolecular Process (3)

The reaction of chlorine dioxide with nitrosyl chloride according to:

$$ClO_2 + 2\,NOCl = NO_2Cl + NO_2 + Cl_2 \qquad (III)$$

in both phases obeys the rate equation

$$-\,d[ClO_2]/dt = k_{III}\,[NOCl]\,[NO_2] + k_I\,[ClO_2]\,[NO_2] \qquad (15)$$

with
$(k_{III})_G = 1.9\times10^7\ \exp(-10000/RT)\ l\ mole^{-1}sec^{-1}$ [7]
and
$(k_{III})_L = 2.3\times10^8\exp(-10700/RT)\ l\ mole^{-1}sec^{-1}$
in $C_2F_3Cl_3$ [8]. The values for $k_I$ are given in Section III, 1.

The rate of reaction (III), which is autocatalysed by $NO_2$, is explained by the two concurrent reaction sequences (3), (16), and (17), and (1), (18), and (17), if the constants $k_3$ and $k_1$ of the rate-determining steps (3) and (1) are identified with the empirical constants $k_{III}$ and $k_I$.

$$NO_2 + NOCl \xrightarrow{k_3} NO + NO_2Cl \qquad (3)$$
$$NO + ClO_2 \rightarrow NO_2 + OCl\ (fast) \qquad (16)$$
$$OCl + NOCl \rightarrow NO_2 + Cl_2\ (fast) \qquad (17)$$
$$NO_2 + ClO_2 \xrightarrow{k_1} NO_3 + OCl \qquad (1)$$
$$NO_3 + NOCl \rightarrow NO_2 + NO_2Cl\ (fast) \qquad (18)$$
$$OCl + NOCl \rightarrow NO_2 + Cl_2\ (fast) \qquad (17)$$

The rather unusual course of this reaction is shown in Fig. 4.

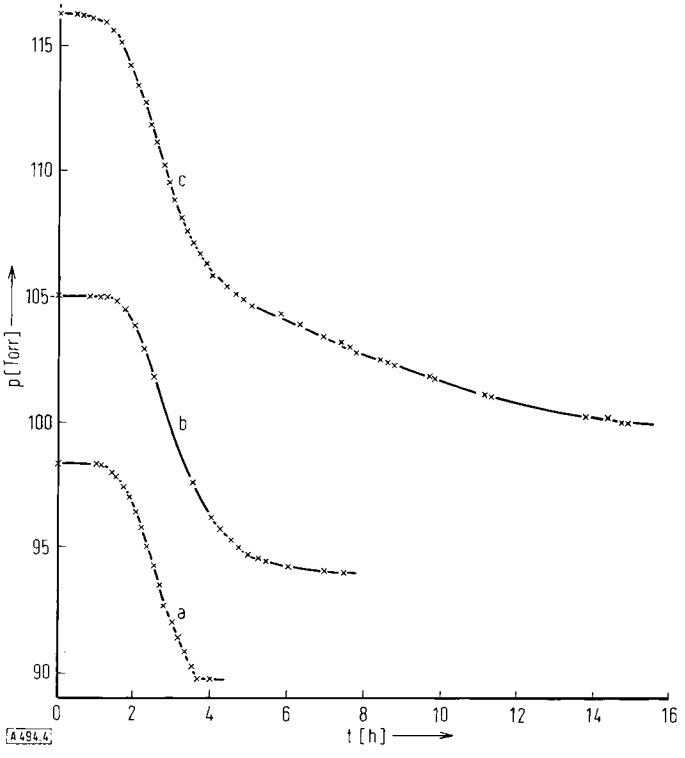


Fig. 4. Change in pressure of the gaseous system $ClO_2/NOCl$ at 0 °C.

| Curve | Initial pressure [mm Hg] $ClO_2$ | NOCl | Initial $p_{NOCl}/p_{ClO_2}$ |
|---|---|---|---|
| a | 28.1 | 70.2 | 2.5 |
| b | 35.0 | 70.0 | 2.0 |
| c | 46.6 | 69.7 | 1.5 |

The salient features of the reaction are the hesitant initiation (autocatalysis), the sharp decline of the reaction of a starting mixture deficient in $ClO_2$ (case a), normal decay in the stoichiometric starting mixture (case b), and the delayed decay with excess of $ClO_2$, owing to a transition to the slower reaction (I) between $NO_2$ and excess of $ClO_2$ (case c). All these features recur in solution [8].

Although the overall reaction can also be explained by a chain mechanism, the steps to be included are much less feasible than those mentioned above [7]. The fact that the reaction can be repeated in solution proves the validity of the above open reaction sequences.

### 4. Reaction (VII) in Solution

The reaction of dinitrogen pentoxide with nitrosyl chloride according to

$$N_2O_5 + NOCl = N_2O_4 + NO_2Cl \qquad (VII)$$

leads to nitrogen dioxide and nitryl chloride. When the reaction is carried out in $C_2F_3Cl_3$ [13] at −10 to −35 °C, the former product is present almost entirely in the form of $N_2O_4$. The initial reaction rate is given by

$$-(d[NOCl]/dt)_0 = k_0 [N_2O_5]_0^2 [NOCl]_0 \quad (19)$$

with $k_0 \approx 0.7$ l² mole$^{-2}$ min$^{-1}$ (at −10 °C). The reaction is thus of third order. After time t, however, the rate is expressed by

$$-d[NOCl]/dt = k_{20} [N_2O_5] [NOCl] \quad (20)$$

*i.e.* the reaction becomes second-order.

The two rate equations can be explained by assuming that, similarly to $N_2O_5$, the resulting $N_2O_4$ acts as a catalyst, possibly in accordance with the following scheme:

$$N_2O_5 + NOCl \underset{k_{-21}}{\overset{k_{21}}{\rightleftharpoons}} N_2O_5 \cdot NOCl \quad (21, -21)$$

$$N_2O_5 \cdot NOCl + N_2O_5 \xrightarrow{k_{22}} NO_2Cl + N_2O_4 + N_2O_5 \quad (22)$$

$$N_2O_5 \cdot NOCl + N_2O_4 \xrightarrow{k_{23}} NO_2Cl + N_2O_4 + N_2O_4 \quad (23)$$

This leads to the rate equation:

$$\frac{d[NOCl]}{dt} = \frac{k_{21}k_{22}[N_2O_5]^2[NOCl] + k_{21}k_{23}[N_2O_5][N_2O_4][NOCl]}{k_{22}[N_2O_5] + k_{23}[N_2O_4] + k_{-21}} \quad (24)$$

This in turn leads to Equation (25) if we put $[N_2O_5] + [N_2O_4] = [N_2O_5]_0$ and make the plausible assumptions $k_{22} \approx k_{23} = k'$ and $k'[N_2O_5]_0 \ll k_{-21}$.

$$-d[NOCl]/dt = (k_{21}k'/k_{-21})[N_2O_5]_0[N_2O_5][NOCl] \quad (25)$$

If we put $k_{21}k'/k_{-21} = k_0$ and $k_{21}k'[N_2O_5]_0/k_{-21} = k_{20}$, this rate equation is seen to be identical with Equations (19) and (20) constructed on an experimental basis.

The reaction has also been investigated in the gas phase, and *Weston* [12] has postulated a wall reaction with the rate equation $-d[N_2O_5]/dt = k[N_2O_5][NOCl]$. He found, however, that the results are difficult to reproduce. A mechanism for a homogeneous gas reaction could not be proposed.

A small, negative temperature coefficient has been obtained for the second-order rate constants in both phases [12, 13]. This can be explained by the rate equation (25), if we assume that the equilibrium (21, −21) is displaced to the left as the temperature increases, and that processes (22) and (23) have low activation energies.

Since the reaction has a negative activation energy both in the gas phase and in solution, we may assume that the mechanisms are similar in both phases and that we would also find rate equations of the type of (19) and (20) for the gas reaction if the wall effect were eliminated.

## IV. Theoretical Interpretation of $k_L/k_G$

Both the classical collision theory and the transition-state theory have been applied to studying the effect on the rate of a gas-phase reaction of filling the space between the reacting particles with an inert medium (assumed not to interact strongly with the reactants or the activated complex and to leave the activation energy unchanged). Owing to the lack of an exact theory of liquids, it is not surprising that the results are discordant and represent only approximations.

### 1. Bimolecular Processes

On the basis of the theories of *Debye* and *Menke* concerning the spatial structure of liquid mercury, *Rabinowitch* [18] derived values for bimolecular collision factors in solution, which are only a few times as great as those for the corresponding gas reactions. Thus, according to the collision theory, a reaction carried out in solution (under otherwise the same conditions) should be somewhat faster than the same reaction in the gas phase. Using the theory of the transition state, *Evans, Polanyi, Bell, et al.* [19] came to a similar conclusion. On the basis of an empirical linear relationship between heat and entropy of solution, they found that $A_L/A_G = \exp(650/RT)$, where $A_L$ and $A_G$ are the frequency factors in the liquid and the gaseous phase, respectively. It follows, therefore, that the relationship

$$k_L/k_G = A_L/A_G \approx 2 \text{ to } 3 \quad (26)$$

(at room temperature) should hold, provided that the activation energy is the same in the two phases.

However, the transition state theory leads to higher values when we use the free volumes $V_{f,i} = RT_i \exp(-\Delta S_i^V/R)$, where $\Delta S_i^V$ is the entropy of vaporization at the boiling point $T_i^\circ$, and the vapor pressures $p_i^\circ$ of the reactants A, B, . . . and the activated complex $X^\ddagger$ [20]. In this case we obtain for the ratio between the reaction rate in solution and that in the gas phase

$$k_L/k_G = (p_A^\circ \cdot p_B^\circ \cdot \cdots / p_{X^\ddagger}^\circ)(RT/V_o)^{\Delta n}(\gamma_A \cdot \gamma_B \cdots / \gamma_{X^\ddagger})$$

$$= e^{\Sigma \Delta H_i^V/RT} \cdot \left(\frac{T_A}{V_{f,A}} \cdot \frac{T_B}{V_{f,B}} \cdots \Big/ \frac{T_{X^\ddagger}}{V_{f,X^\ddagger}}\right) \cdot \left(\frac{T}{V_o}\right)^{\Delta n} \cdot \left(\gamma_A \cdot \gamma_B \cdots / \gamma_{X^\ddagger}\right) \quad (27)$$

or with the approximations $V_{f,A} \approx V_{f,B} \approx \cdots \approx V_f$ and $T_A \approx T_B \approx \cdots \approx T_{X^\ddagger} \approx T$

$$k_L/k_G = e^{\Sigma \Delta H_i^V/RT}(V_f/V_o)^{\Delta n}(\gamma_A \cdot \gamma_B \cdots / \gamma_{X^\ddagger})$$

in which $V_0$ is the volume of 1 mole of solvent plus solute, $\Delta n$ is the difference in the number of moles, the $\gamma_A$, $\gamma_B$, $\cdots$ $\gamma_{X^\ddagger}$ are the activity coefficients, and the $\Delta H_i^V$ are the enthalpies of vaporization.

When the bimolecular processes,

$$A + B \rightleftarrows X^\ddagger \rightarrow \text{products} \quad (28)$$

in which $\Delta n = -1$ for the formation of the activated complex $X^\ddagger$, are carried out in an ideal solution, in which the activity coefficients are unity, Equation (27) can be written in the form:

$$k_L/k_G = \exp\left[\left(\Delta H_{X^\ddagger}^V - \Delta H_A^V - \Delta H_B^V\right)/RT\right](V_f/V_o) \quad (29)$$

[18] *E. Rabinowitch*, Trans. Faraday Soc. *33*, 1225 (1937).

[19] See, *e.g.*, [10], p. 120.

[20] See, *e.g.*, *A. A. Frost* and *R. G. Pearson*: Kinetics and Mechanism. Wiley, New York-London 1961. See there for further literature.

If, in addition, the activation enthalpies are the same in the two phases, *i.e.* $(\Delta H^{\neq})_L = (\Delta H^{\neq})_G$, it follows from the general relationship

$$(\Delta H^{\neq})_L - (\Delta H^{\neq})_G \quad \Sigma \Delta H_i^V \tag{30}$$

that the stoichiometric sum $\Sigma \Delta H_i^V = \Delta H_X^V{}^{\neq} - \Delta H_A^V - \Delta H_B^V - \cdots$ of the enthalpies of vaporization disappears from the exponential terms of Equations (27) and (29), leading with the approximation $V_f \approx 0.5$ ml/mole to:

$$k_L/k_G = V_o/V_f \approx 100 \tag{31}$$

Table 2 shows the experimental values of $k_L/k_G$ for bimolecular processes investigated quantitatively so far in the gas phase and in solution. The value of this ratio is seen to vary between 0.9 and 10. The disagreement with the prediction of Eq. (31) may be due partly to the non-ideal nature of the liquid mixtures and partly to the fact that the reactants have different free volumes. Further, the exponential term in Equation (29) may be less than unity, *i.e.* the stoichiometric sum of the enthalpies of vaporization is negative. This possibility is supported by the experimental values of the activation energies. With the exception of the two reactions in which the value of $k_L/k_G$ is comparatively high (cyclopentadiene + acrolein and $NO_2 + Cl_2O$), the activation energies are larger in solution than in the gas phase (within the limits of error, which are considerable). Moreover, it is not the experimental activation energies, but the $\Delta H^{\neq}$ values that are to be equated in the determination of the stoichiometric sum of the enthalpies of vaporization ($\Sigma \Delta H_i^V$) according to Equation (30). In the case of bimolecular processes in solution and in the gas phase, the following relations hold for these $\Delta H^{\neq}$ values:

$$(\Delta H^{\neq})_L = E_L - RT \tag{32}$$

$$(\Delta H^{\neq})_G = E_G - 2\,RT \tag{33}$$

The values of $\Delta H^{\neq}$ obtained in this way are also listed in Table 2. When these values are used to calculate $\Sigma \Delta H_i^V$ with the aid of Equation (30) and when the resulting values are inserted in (29), the exponential function in the latter equation is in fact seen to be less than unity, being about 0.3 for the dimerization of cyclopentadiene, about 0.07 for reaction (1), and about 0.11 for reaction (3). For these three reactions, the ratios predicted by Equation (29) (in conjunction with $V_o/V_f = 100$) are $k_L/k_G \approx 30$, 7, and 11 respectively, these values being closer to the experimental results than those predicted by Equation (31).

Table 2. Bimolecular processes capable of proceeding in different phases.

| Bimolecular process | Phase | E [kcal] | $\Delta H^{\neq}$ [kcal] | k (20 °C) [l mole$^{-1}$ sec$^{-1}$] | $k_L/k_G$ (20 °C) |
|---|---|---|---|---|---|
| $pH_2 + O_2 \rightarrow oH_2 + O_2$ [21] | $H_2O$ | — | | 0.175 | 1.1 |
| | Gas | ≈ 0 | | 0.153 | |
| 2 Cyclopentadiene → dicyclopentadiene [22] | $CS_2$ | 16.9 | 16.3 | $4.0\times10^{-7}$ | 0.9 |
| | $C_6H_6$ | 16.4 | 15.8 | $7.6\times10^{-7}$ | 1.7 |
| | $CCl_4$ | 17.1 | 16.5 | $8.9\times10^{-7}$ | 2.0 |
| | Paraffin | 17.4 | 16.8 | $13.2\times10^{-7}$ | 3.0 |
| | Melt | 16.2 | 15.6 | $5.1\times10^{-7}$ | 1.1 |
| | Gas | 16.7 | 15.5 | $4.5\times10^{-7}$ | |
| Cyclopentadiene + Acrolein → 5-Norbornene-2-carbaldehyde [23] | $C_6H_6$ | 13.7 | 13.1 | $7.8\times10^{-5}$ | 10 |
| | Gas | 15.2 | 14.0 | $0.76\times10^{-5}$ | |
| $NO_2 + ClO_2 \rightarrow NO_3 + OCl$ (1) | $C_2F_3Cl_3$ | 12.0 | 11.4 | 0.42 | 2.8 |
| | Gas | 11.0 | 9.8 | 0.15 | |
| $NO_2 + Cl_2O \rightarrow NO_2Cl + OCl$ (2) | $C_2F_3Cl_3$ | 10.4 | 9.8 | 0.57 | 6.0 |
| | Gas | 11.6 | 10.4 | 0.095 | |
| $NO_2 + NOCl \rightarrow NO_2Cl + NO$ (3) | $C_2F_3Cl_3$ | 10.7 | 10.1 | 2.3 | 3.7 |
| | Gas | 10.0 | 8.8 | 0.62 | |

In the bimolecular processes (1) to (3), in which A is invariably $NO_2$ while B is, respectively, $ClO_2$, $Cl_2O$, and NOCl, the ratio of the rate constants $k_L/k_G$ can also be estimated from the solubilities of the reactants in the solvent. In the gas and the liquid phases, Equations (34) and (35) should hold for the activation equilibrium (28):

$$K_G^{\neq} = [X^{\neq}]/([A]\cdot[B]) \tag{34}$$

$$K_L^{\neq} = ([X^{\neq}]\cdot l_X{}^{\neq})/([A]\, l_A \cdot [B]\, l_B) = K_G^{\neq}\cdot l_X{}^{\neq}/(l_A \cdot l_B) \tag{35}$$

where $l_X{}^{\neq}$, $l_A$, and $l_B$ are the Ostwald solubility coefficients. Since k is proportional to $K^{\neq}$ (T = const.), the relationship

$$k_L/k_G = K_L^{\neq}/K_G^{\neq} = l_X{}^{\neq}/(l_A\cdot l_B) \tag{36}$$

should also hold. We should therefore be able to calculate $k_L/k_G$ from the solubilities. The solubilities of the activated complexes $X^{\neq} = NO_2\cdot B^{\neq}$ are admittedly unknown, but we may try to estimate them by correlating them with the solubility of $N_2O_4$, whose structure is likely to be similar to that of the activated complex. We then assume that the solubility is increased by a certain factor when one $NO_2$ group in $N_2O_4$ is replaced by component B (more soluble in $C_2F_3Cl_3$) and that this factor is half of that connecting the solubilities of pure $NO_2$ and of pure B. We thus put

$$l_{NO_2B}{}^{\neq} \approx l_{N_2O_4}\cdot l_B/2\, l_{NO_2} \tag{37}$$

Substitution in Equation (36) leads to the estimate:

$$k_L/k_G = l_{NO_2B}{}^{\neq}/(l_{NO_2}\cdot l_B) = l_{N_2O_4}/2\, l_{NO_2}^2 \tag{38}$$

Using the values $l_{N_2O_4} = 180$ and $l_{NO_2} = 3.6$ to 5, we obtain $k_L/k_G = 3.6$ to 6.9 for reactions (1) to (3). These values are seen to be in good agreement with the experimental results listed in Table 2.

### 2. Unimolecular Processes and the Dissociation of $N_2O_5$

For unimolecular processes, the theoretical rate in the gas phase is found to be about the same as that in solution, *i.e.*

$$k_L/k_G \approx 1 \tag{39}$$

[21] *L. Farkas* and *H. Sachsse*, Z. physik. Chem. *23*, 1, 19 (1933).

[22] *A. Wassermann*, Mh. Chem. *83*, 543 (1952). The values of k listed in Table 2 were calculated from the values for A and E given there.

[23] *A. Wassermann*, Trans. Faraday Soc. *34*, 128 (1938).

provided that the activation energy E is the same in the two phases. For such processes, Equation (27) can be simplified to

$$k_L/k_G = \left(p_A^\circ/p_{X^\ddagger}^\circ\right)\cdot\left(\gamma_A/\gamma_{X^\ddagger}\right) = e^{\Sigma\Delta H_i^V/RT}\gamma_A/\gamma_{X^\ddagger} \qquad (40)$$

When the activation energies are the same, which in this case means $(\Delta H^\ddagger)_G = (\Delta H^\ddagger)_L$, the exponent $\Sigma\Delta H_i^V = \Delta H_X^{V\ddagger} - \Delta H_A^V$ also disappears by virtue of Equation (30) and $k_L/k_G$ is given simply by the ratio of the activity coefficients of the reactant A and of the activated complex $X^\ddagger$ in the solution. Moreover, when the polarity of $X^\ddagger$ is not very different from that of A, the two activity coefficients will be approximately the same.

With the exception of the racemization of diaminodimethylbiphenyl, the experimental values are in reasonably good agreement with Equation (39) (see Table 3). When $E_G$ is greater than $E_L$, $k_L/k_G$ is seen to be greater than unity. Conversely, when $E_G < E_L$ (the dissociation of acetyl peroxide), $k_L/k_G < 1$. This behavior is expected on the basis of Equations (40) and (30), provided that $\gamma_A = \gamma_{X^\ddagger}$. In the first of the above two cases the exponent in (40) is positive and in the second it is negative. Admittedly, not even a semiquantitative confirmation can be offered for Equation (40), with the possible exception of the dissociation of dicyclopentadiene.

The dissociation of $N_2O_5$ has been investigated extensively, in the gas phase and in solution[10] in several solvents, *e.g.* $C_2F_3Cl_3$[6], $CCl_4$, $CHCl_3$, $H_2ClC-CH_2Cl$, $H_3C-CHCl_2$, $HCl_2C-CCl_3$, $H_3C-NO_2$, $Br_2$, $N_2O_4$, and $HNO_3$. Except in the last-mentioned solvent, in which a higher E and a correspondingly smaller k have been found, the activation energies and the rate constants of this reaction do not vary significantly with the medium, and excellent agreement is found with Equation (39).

It should be pointed out that the dissociation of $N_2O_5$ is not unimolecular, but is a complicated process involving the steps (6), (−6), (7), and (8) (cf. Section III, 1). Its first-order rate constant is given by $k_{N_2O_5} = 2k_6k_7/k_{-6}$, *i.e.* it is composed of three rate constants of which only $k_6$ refers to a unimolecular reaction. Thus, if we find that $(k_{N_2O_5})_L/(k_{N_2O_5})_G = 1$, this merely proves that the expected ratio $(k_6)_L/(k_6)_G = 1$ holds if, furthermore, the relationship $(k_{-6})_L/(k_{-6})_G = (k_7)_L/(k_7)_G$ is valid for the two bimolecular steps (−6) and (7). Since these steps are very similar, the above relationship between $k_{-6}$ and $k_7$ is very likely to be valid. This is further supported by the observation that the experimental values of $k_L/k_G$ listed in Table 2 differ only slightly from each other for other bimolecular reactions of $NO_2$ [reactions (1) to (3)].

Table 3. Unimolecular processes capable of proceeding in different phases.

| Unimolecular process | Phase | E [kcal] | k [sec$^{-1}$] | Temp. [°C] | $k_L/k_G$ |
|---|---|---|---|---|---|
| (+)-α-Pinene → (±)-limonene [24] | Melt | — | $5.0\times10^{-7}$ | 184 | 1.4 |
| | Petrolatum | ≈40 | $2.15\times10^{-6}$ | 198 | 1.5 |
| | Gas | 43.7 | $3.7\times10^{-7}$ | 184 | |
| | | | $1.43\times10^{-6}$ | 198 | |
| Racemization of 2,2'-diamino-6,6'-dimethylbiphenyl [25] | Diphenyl ether | 45.1 | $7.4\times10^{-5}$ | 380 | 3.5 |
| | Gas | 45.1 | $2.1\times10^{-5}$ | 380 | |
| Dicyclopentadiene → 2 cyclopentadiene [23] | Melt | 34.5 | $6.3\times10^{-7}$ | 120 | 1.4 |
| | Paraffin | 34.2 | $8.9\times10^{-7}$ | 120 | 2.0 |
| | Gas | 35 | $4.5\times10^{-7}$ | 120 | |
| Di-t-butyl peroxide → 2 t-butoxyl [26] | Cumene | 37.5 | $5.2\times10^{-5}$ | 135 | 1.4 |
| | t-Butylbenzene | 38.0 | $5.0\times10^{-5}$ | 135 | 1.4 |
| | Tri-n-butylamine | 37.0 | $4.2\times10^{-5}$ | 135 | 1.2 |
| | Gas | 39.1 | $3.6\times10^{-5}$ | 135 | |
| Acetyl peroxide → 2 acetoxyl [27] | Isooctane | 32.2 | $1.49\times10^{-4}$ | 85.2 | 0.7 |
| | Cyclohexane | 31.4 | $1.27\times10^{-4}$ | 85.2 | 0.6 |
| | Benzene | 32.3 | $1.62\times10^{-4}$ | 85.2 | 0.7 |
| | Toluene | 32.0 | $1.59\times10^{-4}$ | 85.2 | 0.7 |
| | Acetic acid | 30.2 | $1.30\times10^{-4}$ | 85.2 | 0.6 |
| | Propionic acid | — | $1.66\times10^{-4}$ | 85.2 | 0.7 |
| | $CCl_4$ [28] | 33.4 | $1.2\times10^{-4}$ | 85.2 | 0.5 |
| | Gas | 29.5 | $2.24\times10^{-4}$ | 85.2 | |

The experimental data listed in Tables 2 and 3 are insufficient to test the quantitative validity of the theoretical postulates concerning the change occurring in the rate constants of elementary processes when a gas-phase reaction is changed into a reaction in solution. There is, however, no doubt that the transition-state theory leads to a useful correlation between the rate of reactions in the gas phase and in solution.

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[25] *G. B. Kistiakowsky* and *W. R. Smith*, J. Amer. chem. Soc. *58*, 1043 (1936).

[26] *J. H. Raley*, *F. F. Rust*, and *W. E. Vaughan*, J. Amer. chem. Soc. *70*, 88, 1336 (1948).

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# Color Centers in Alkali Borate Glasses Containing Cobalt, Nickel, or Copper

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*Dedicated to Prof. W. Klemm on the occasion of his 70th birthday*

*The absorption spectra and the magnetic moments of $Co^{2+}$, $Ni^{2+}$, and $Cu^{2+}$ in alkali borate glasses of various compositions and in halide-containing glasses have been explained from the point of view of the ligand field theory. Spectra and magnetic moments are highly dependent on the composition of the base glass; this must be ascribed to the change in the coordination of the transition-metal ions. There are far-reaching analogies with corresponding complexes in solution or in the crystalline state.*

## 1. Introduction

Earlier investigations on borate glasses containing $Co^{2+}$, $Ni^{2+}$, or $Cu^{2+}$ as coloring transition-metal ions were designed to give further information on the color centers in these glasses [1,2]. It is just these transition-metal ions which appeared suitable, since glasses can be prepared with only one oxidation state of the metal, and therefore no complications due to a second oxidation state can arise. Moreover, many complexes of these ions have been investigated in detail. Their magnetic behavior, and particularly their spectra, have been interpreted from the viewpoint of ligand field theory, and this facilitated the interpretation of the spectra and of the magnetic susceptibilities of the colored glasses.

It has long been known that a transition-metal ion can exhibit different colors in different glasses, even when its valence remains unchanged [3]. Since the color changes in the glasses considered here cannot be ascribed to a change in the oxidation state, they must be due to the change in the environment of the transition-metal ion. The magnetic moment of the transition-metal ion changes largely parallel with the color; this phenomenon can be explained by the different orbital contributions when the coloring ion is in states of octahedral or tetrahedral coordination. It will be shown below that the laws which follow from the ligand field theory for transition-metal complexes in solution or in the crystalline state apply also to the color centers present in glasses.

## 2. Alkali Borate Glasses

The base glasses used were alkali borate glasses with different kinds and amounts of alkali-metal oxides. These glasses were selected since their structure is comparatively well known.

According to the network theory proposed by *Zachariasen* [4], $B_2O_3$ glass is built up of a two- or three-dimensional network of plane $BO_3$ groups. Each oxygen atom ("bridging oxygen") is common to two structural groups. This can be written as $\rangle B-O-B\langle$ (the B–O–B angle being less than 180 °). When a metal oxide, *e.g.* $Na_2O$, is fused with $B_2O_3$, the oxygen of the added oxide is completely incorporated into the network, with the formation of tetrahedral $BO_4$ groups, an equivalent amount of $Na^+$ ions being present in the interstices of the three-dimensional network. This process takes place up to about 16.7 mole-% of $Na_2O$, which corresponds to $Na_2O \cdot 5B_2O_3$. When the glass contains this amount of an alkali-metal oxide, every tenth $BO_3$ group in the network becomes converted into a $BO_4$ group.

At higher contents of alkali-metal oxide no further $BO_4$ tetrahedra are formed, but the network is disrupted and at the same time non-bridging oxygen appears:

$$Na_2O + \rangle B\text{-}O\text{-}B\langle \longrightarrow 2\ Na^{\oplus} + 2\ {}^{\ominus}O\text{-}B\langle$$

This difference in the behavior of the $B_2O_3/Na_2O$ system at small and large contents of alkali-metal oxide has been investigated frequently. This "boric acid anomaly" occurs not only in binary alkali-metal borate glasses, but also in the borosilicate glasses.

The network theory, applied *e.g.* to silicate glasses, has accounted correctly for many observed properties of various glasses. It is supported, *inter alia*, by X-ray investigations [5]. However, in $B_2O_3$ glass and the alkali-borate glasses, the coordination relationships are obviously very much more complicated than the network theory would indicate. A comparison of the network in vitreous $B_2O_3$ with that in crystalline $B_2O_3$ is clearly indicated.

The infrared spectrum of $B_2O_3$, which crystallizes in the hexagonal system, agrees closely with that of $B_2O_3$ glass [6], but not with that of a modification of $B_2O_3$

[1] *K. Breit* and *R. Juza*, Glastechn. Ber. *27*, 117 (1954).

[2] *R. Juza* and *K.-H. Schultz*, Z. anorg. allg. Chem. *316*, 89 (1962).

[3] *W. A. Weyl*: Coloured Glasses. The Society of Glass Technology, Sheffield 1959.

[4] *W. H. Zachariasen*, J. Amer. chem. Soc. *54*, 3841 (1932).

[5] *B. E. Warren*, *H. Krutter*, and *O. Morningstar*, J. Amer. ceram. Soc. *19*, 202 (1936).

[6] *F. Dachille* and *R. Roy*, J. Amer. ceram. Soc. *42*, 78 (1959).

formed under high pressure. Without doubt the coordination relationships in $B_2O_3$ glass and in the hexagonally crystalline $B_2O_3$ are very similar. The structure of the latter has been determined by *Berger*[7], although only from powder photographs. The mean coordination number of the boron is between three and four. The hexagonal $B_2O_3$ is constructed of two types of highly deformed $BO_4$ tetrahedra. In type b, the $BO_4$ group contains a shallow trigonal $BO_3$ pyramid (O–O distance 2.39 Å; B–O 1.45 Å; height of the pyramid 0.4 Å); in type a, the shallow $BO_3$ pyramid is still more irregular than in type b.

Detailed X-ray investigations[8] on $B_2O_3$ glass show a far more regular arrangement of the atoms than is proposed by the classical model of *Zachariasen* and of *Warren*. Shallow $BO_3$ pyramids are again present; they take the place of the plane $BO_3$ groups of *Zachariasen* and *Warren's* model. Nevertheless, the $B_2O_3$ glass does not contain the three-dimensional lattice structure of hexagonal $B_2O_3$, even in small regions, required by the crystallite hypothesis of the vitreous state. The $BO_3$ groups are in layers having a substantially regular arrangement and these, in turn, form thin bundles of layers. Such bundles are arranged in unordered fashion and are linked statistically to one another through individual $BO_3$ chains or irregular layers.

Unfortunately, there are no corresponding X-ray investigations of alkali-metal borate glasses. From NMR measurements on potassium borate glasses[9] it has been concluded that the proportion of $BO_4$ groups increases up to about 17 mole-% of $K_2O$ in the sense of *Warren*'s assumptions[5]. While, however, according to *Warren*[5] the proportion of $BO_4$ groups tends to decrease again with increasing amounts of alkali-metal oxide added, according to *Svanson*[9] this proportion tends to increase. However, there is probably no necessity for a fundamental change in the basic assumptions on the incorporation of alkali-metal oxide that have been described above.

## 3. $Co^{2+}$, $Ni^{2+}$, and $Cu^{2+}$ Ions in the Ligand Field

### a) The One-Electron Orbital Scheme of $Co^{2+}$

Free bivalent ions of cobalt, nickel, or copper possess five degenerate 3d one-electron orbitals. According to Pauli's principle, these are occupied by electrons as shown in the center of Fig. 1 for an isolated $Co^{2+}$ ion. In complexes, these ions frequently form centers of regular coordination polyhedra, in which they are surrounded by identical ligands at the same distance. For this reason, additional forces in the form of a ligand field with the symmetry of the corresponding coordination polyhedra act on the five 3d orbitals so that their original degeneracy is cancelled. If the field has octahedral or tetrahedral symmetry, one triply degenerate group ($d_{xy}$, $d_{xz}$, $d_{yz}$) and one doubly degenerate group ($d_{x^2-y^2}$, $d_{z^2}$) of orbitals arise[10,11].

The splitting for the octahedral case is shown on the right of Fig. 1; the triply degenerate state is denoted by the symmetry symbol $t_{2g}$, and the doubly degenerate by the symbol $e_g$. In this

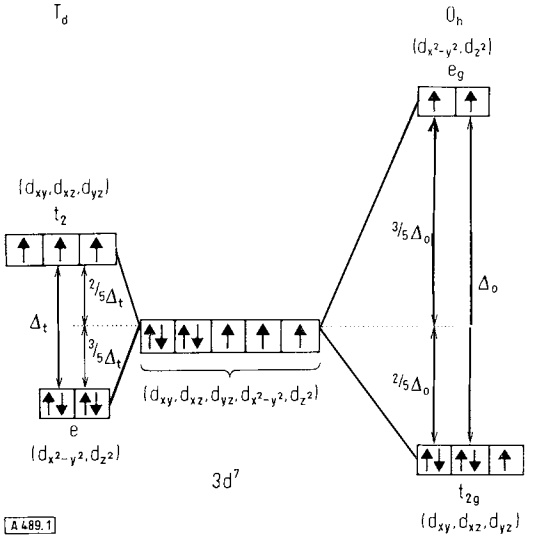


Fig. 1. One-electron orbital scheme of $Co^{2+}$ in octahedral (right) and tetrahedral (left) ligand fields. $\Delta_o$, $\Delta_t$ = energy differences (ligand field strengths) between the $t_{2g}$ and $e_g$ and between the $t_2$ and e levels (not to scale).

case, the electron configuration of the $Co^{2+}$ is $t_{2g}^5 e_g^2$ (that of $Ni^{2+}$ is $t_{2g}^6 e_g^2$, and that of $Cu^{2+}$ $t_{2g}^6 e_g^3$). The $e_g$ orbitals $d_{x^2-y^2}$ and $d_{z^2}$ are destabilized, since they point to the ligands located in the direction of the x-, y-, and z-axes. This does not apply to the $t_{2g}$ orbitals; they are stabilized in the field. The difference between energies of the $t_{2g}$ and the $e_g$ levels, which gives the field strength in the case of cubic symmetry of the ligand field, is denoted by $\Delta_o = 10\ Dq$[12].

In the tetrahedral field (Fig. 1, left), the doubly degenerate state is given the symmetry symbol e and the triply degenerate state the symbol $t_2$. Here the electron configuration of $Co^{2+}$ is $e^4 t_2^3$ (that of $Ni^+$ is $e^4 t_2^4$, and that of $Cu^{2+}$ $e^4 t_2^5$). In the tetrahedral field the $t_2$ orbitals are destabilized; they come closer in space to the tetrahedrally arranged ligands than the stabilized e orbitals. For the energy difference between e and $t_2$ levels we have, assuming the same distances and same ligands, $\Delta_t = 4/9\Delta_o$. The tetragonal deformation of an originally octahedral field will be discussed in connection with the copper containing glasses (Section 6).

With constant coordination of the central ion, the ligand field strength $\Delta = 10\ Dq$ depends on the type of ligands. Ligands with weak fields lead to a small value of Dq, and ligands with strong fields to a large one. The following sequence applies to the field strengths of the ligands of interest in this paper: $I^- < Br^- < Cl^- < F^- < H_2O$[13] (see also Section 8).

All complexes discussed here are high-spin complexes: in accordance with the rule of maximum multiplicity, one electron first enters each orbital with the formation of the greatest possible total spin angular momentum. "Low-spin complexes", which can in principle arise with $Co^{2+}$, are not formed by the ligands under discussion here (oxygen and chloride, bromide, and iodide) since their ligand fields are too small.

[7] *S. V. Berger*, Acta crystallogr. *7*, 611 (1953).

[8] *H. Richter, G. Breitling*, and *F. Herre*, Z. Naturforsch. *9a*, 390 (1954).

[9] *S. E. Svanson, E. Forslind*, and *J. Krogh-Moe*, J. physic. Chem. *66*, 174 (1962).

[10] *J. H. Van Vleck*, J. chem. Physics *3*, 807 (1935).

[11] *L. E. Orgel*: An Introduction to Transition Metal Chemistry-Ligand Field Theory. Methuen, London 1960.

[12] *W. G. Penney* and *R. Schlapp*, Physic. Rev. *41*, 194 (1932); *42*, 666 (1932).

[13] *R. Tsuchida*, Bull. chem. Soc. Japan *13*, 388 (1938).

b) Energy-Level Diagram of $Co^{2+}$

With its seven electrons in the 3d shell, the $Co^{2+}$ ion in the ground state has a spin angular momentum of S = 3/2 and an orbital angular momentum of L = 3; consequently, the ground state is given as $^4F$ (cf. Fig. 2). At a fairly large distance (14500 $cm^{-1}$ for the gaseous ion) there is another

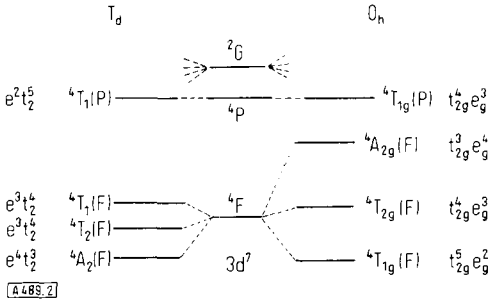


Fig. 2. Energy-level diagram of $Co^{2+}$. Left, splitting in the tetrahedral ligand field; right, that in the octahedral ligand field.

quartet level, $^4P$, then the levels $^2G$, $^2H$, $^2P$ ... follow in quick succession. All transitions relate to electron transitions within the 3d level.

When $Co^{2+}$ is incorporated in the center of tetrahedral or octahedral coordination polyhedra, the levels are changed under the influence of the ligand field; some of the levels are split and some displaced. The electron configurations given in the one-electron orbital scheme (Fig. 1) correspond to the ground states in the octahedral field ($^4T_{1g}$) and in the tetrahedral field ($^4A_2$).

The transition from the $^4F$ level, which applies to the free ion, to the subsequent level of the same multiplicity in the octahedral or the tetrahedral ligand field is shown schematically in Fig. 3 (after *Orgel*[11]) as a function of the field. Starting from a ligand field strength 0 for the free ion, $^4F$ is split into three subsequent levels of the same multiplicity, the electron configurations of which are given at the edge of the figure. The symbols also give the degeneracy: triple for T, double for E, and single for A and B levels[14].

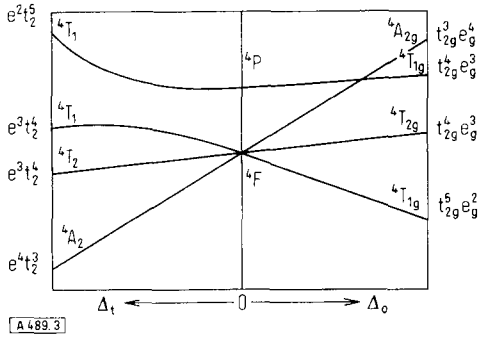


Fig. 3. Orgel diagram of the quartet levels for $Co^{2+}$ according to [11]. Abscissa: ligand field strength.

## 4. Alkali Borate Glasses Containing Cobalt

### a) Optical Investigations

The base glasses were made by fusing $B_2O_3$ and alkali-metal carbonate at 850 to 960 °C in a platinum crucible. CoO was melted into these glasses under protective gas; the oxidation number of +2 of cobalt in the glass was checked analytically.

[14] *R. S. Mulliken*, Physic. Rev. *43*, 279 (1933).

The classes used for the optical investigations contained an average of 0.2% by weight of Co. The glasses were ground to plane-parallel plates whose absorption between 50000 and 4000 $cm^{-1}$ was measured with a Zeiss PMQ II spectrophotometer[15] [*].

As already known, the content of alkali-metal oxide affects the color of the glasses. Glasses with a low content of $Na_2O$ are bright red-purple, those rich in $Na_2O$ intensely blue[16]. The bands of the purple glass with a low alkali content can be ascribed to $Co^{2+}$ in an octahedral environment, and that of the alkali-rich blue glass to $Co^{2+}$ in a tetrahedral environment.

The spectrum of the alkali-poor red-purple cobalt sodium borate glass (base glass $Na_2O{\cdot}7B_2O_3$) is shown in Fig. 4. The absorption bands with the assigned transitions are given in Table 1. The Orgel diagram of $Co^{2+}$ (Fig. 3) also gives the electron configurations of the

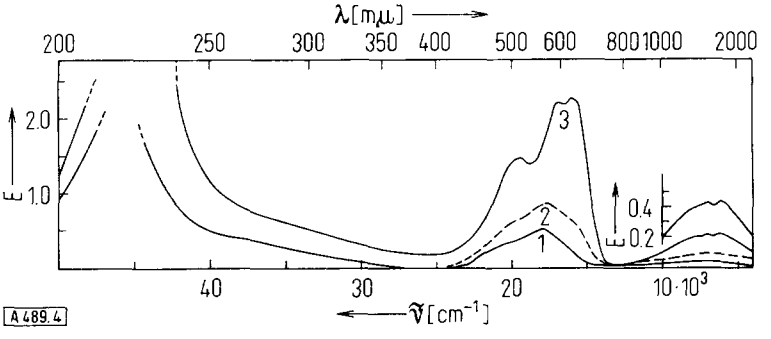


Fig. 4. Spectra of cobalt sodium borate glasses with the base glass compositions $Na_2O{\cdot}7B_2O_3$ (red-purple, curve 1), $Na_2O{\cdot}4.6B_2O_3$ (blue-purple, curve 2), and $Na_2O{\cdot}3\ B_2O_3$ (blue, curve 3). Ordinate: extinction.

Table 1. Band assignment in the spectrum of an alkali-poor, purple cobalt, sodium borate glass (base glass $Na_2O{\cdot}7\ B_2O_3$) and comparative spectra. (sh) = shoulder.

| Co-glass $\tilde{\nu}$ ($cm^{-1}$) | $[Co(H_2O)_6]^{2+}$ $\tilde{\nu}$ ($cm^{-1}$) [17] | CoO/MgO $\tilde{\nu}$ ($cm^{-1}$) [18] | Assignment |
|---|---|---|---|
| 7500 | 8000 | 8470 | $^4T_{1g} \rightarrow {}^4T_{2g}(F)$ |
| 18000 | 16000 | 18000 | $^4T_{1g} \rightarrow {}^4A_{2g}(F)$ |
| 21000 (sh) | 20200 | 19800 | $^4T_{1g} \rightarrow {}^4T_{1g}(P)$ |
| *ca.* 46000 | — | — | Charge-transfer |

ground state and the excited states. The spectra of $[Co(H_2O)_6]^{2+}$ [17] and of $Co^{2+}$ in MgO [18] are also given for comparison. According to this, the $Co^{2+}$ in the glass is present in an octahedral environment. A similar gradation of the wave numbers as for the three $Co^{2+}$ complexes shown in the table is found for the corresponding $Ni^{2+}$ compounds; it depends on the strength of the ligand field (cf. Section 8). The charge-transfer bands appearing in the diagrams are also described in Section 8.

[*] The extinctions given in this paper refer to a layer thickness of 1 mm and to 1 g of the transition metal per 100 g of glass; the absorption of the base glass has been taken into account.

[15] Experiments at wave numbers below 4000 $cm^{-1}$ are still in progress, since here a new preparative and measuring technique is required.

[16] For a spectroscopic analysis primarily of colored silicate glasses, see *C. R. Bamford*, Physics Chem. Glasses *3*, 189 (1962).

[17] *C. J. Ballhausen* and *C. K. Jørgensen*, Acta chem. scand. *9*, 394 (1955).

[18] *W. Low*, Physic. Rev. *109*, 256 (1958).

The spectrum of the alkali-rich blue cobalt-containing sodium borate glass (base glass $Na_2O{\cdot}3B_2O_3$) exhibits a weak band system in the near infrared, a stronger one in the visible, and a very strong absorption band in the ultraviolet. The band assignments are given in Table 2. Comparison with the absorption spectrum of extremely alkaline $Co^{2+}$ solutions (50% NaOH solution) [19] and

Table 2. Band assignment in the spectrum of an alkali-rich, blue cobalt sodium borate glass (base glass $Na_2O{\cdot}3\ B_2O_3$) and in a comparative spectrum. (sh) = shoulder.

| Co-glass $\tilde{\nu}$ ($cm^{-1}$) | Alkaline $Co^{2+}$ soln. $\tilde{\nu}$ ($cm^{-1}$) [19] | Assignment |
|---|---|---|
| 4060 [a] | 4230 [b] | $^4A_2 \rightarrow {}^4T_2(F)$ |
| 6200 | 6300 | |
| 7000 | 7200 | $^4A_2 \rightarrow {}^4T_1(F)$ |
| 8000 (sh) | 8100 | |
| 15900 | 16050 | $^4A_2 \rightarrow {}^4T_1(P)$ |
| 16900 | 17250 | |
| 19500 | 18850 | $^4A_2 \rightarrow {}^2G$ subs. level |
| *ca.* 45000 | — | Charge-transfer |

[a] Calculated by the method given in [22].
[b] Calculated [19].

with the spectrum of tetrahedrally coordinated $Co^{2+}$ ions in $Zn_{0.99}Co_{0.01}O$ and $Co_{0.1}Mg_{0.9}Al_2O_4$ [20] shows that the $Co^{2+}$ in the alkali-rich glass is present in tetrahedral coordination.

In principle, three quartet-quartet transitions are to be expected (cf. Fig. 2):

$^4A_2 \rightarrow {}^4T_2(F)$, $^4A_2 \rightarrow {}^4T_1(F)$, $^4A_2 \rightarrow {}^4T_1(P)$.

All three $^4T$ states should be split by spin-orbit coupling, so that a multiplet structure of the corresponding absorption bands is to be expected [21]. The lowest transition $^4A_2 \rightarrow {}^4T_2$ (which occurs at about 4200 $cm^{-1}$ in $Zn_{0.99}Co_{0.01}O$) could not be observed, since it lies near the limit of the range of the instrument employed (Zeiss PMQ II). In the visible region, there is a system of three bands with two strong and one medium component. It is not likely that these bands are based only on the transition to the $^4T_1(P)$ level, since there is a $^2G$ state just above the $^4P$ state of the free $Co^{2+}$ ion. Two of its subsequent levels, namely $^2E(G)$ and $^2T_1(G)$, cross the level $^4T_1(P)$ even at small ligand field [19]. Consequently, the energetically highest band (19500 $cm^{-1}$) may be assigned to a $^4A_2 \rightarrow {}^2G$ subsequent level transition and the other two bands to the $^4A_2 \rightarrow {}^4T_1(P)$ transition.

### b) Magnetic Investigations

According to the ligand field theory, the magnetic behavior of transition-metal ions is also connected with their spatial environment [23,24]. Consequently, it was necessary to determine whether changes occur in the magnetic moments of the transition-metal ions in the glasses, for example, with a varying content of alkali, and whether these changes can be explained in agreement with the optical findings. The glasses used for magnetic measurements contained an average of ten times as much transition metal as those for the optical measurements, *i.e.* 2% by weight, so that the moment of the transition ion could be determined with sufficient accuracy [*].

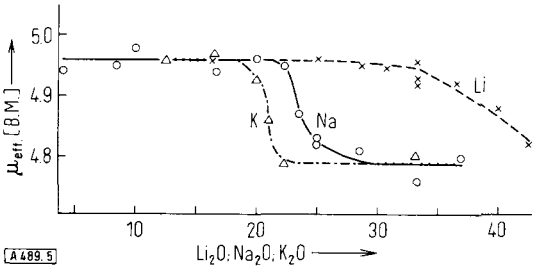


Fig. 5. Magnetic moment of $Co^{2+}$ in lithium, sodium, and potassium borate glasses as a function of the content of the alkali-metal oxide. Left, purple glasses, octahedral arrangement; Right, blue glasses, tetrahedral arrangement. Abscissa: Alkali-metal oxide content, mole-%.

As can be seen in Fig. 5, the effective magnetic moment ($\mu_{eff}$) of the $Co^{2+}$ ion decreases at low contents of the alkali-metal oxide in potassium glasses and at high contents of the alkali-metal oxide in sodium and in lithium glasses [1]. The decrease in the moment takes place at about the same content of the alkali-metal oxide as the color change of the glass, and thus is related to the change in the coordination number.

The high moment in the alkali-poor glass is explained below by a comparatively large component of the orbital angular momentum, *i.e.* by comparatively weak spin-orbit coupling; the opposite applies to the alkali-rich glass.

When only the spin moment is active for the $Co^{2+}$ ion with the electron configuration $3d^7$, we obtain

$$\mu_{eff} = \sqrt{4S(S+1)} = 3.87 \text{ B. M.}$$

When, in addition, there is full orbital contribution, we have

$$\mu_{eff} = \sqrt{4S(S+1) + L(L+1)} = 5.20 \text{ B. M.}$$

The experimental values for high-spin $Co^{2+}$ complexes lie between these limits. The magnetic behavior to be expected in an octahedral or a tetrahedral environment can be deduced qualitatively from the energy-level diagram of the $Co^{2+}$ ion (Fig. 2). Here only these two cases will be mentioned, since the octahedral or tetrahedral arrangement of the oxygen environment of the ions in the alkali-poor and alkali-rich glasses, respectively, follows from the optical measurements.

Since the magnetic behavior is determined predominantly by the ground state of the ion, only the levels succeeding $^4F$ will be considered. The electron configu-

[*] To determine the magnetic moments, the susceptibilities were measured between 90 and 373 °K with the "Magnet Binder E 20 E 1" with current stabilization. The susceptibilities of the base glasses were taken into account.


[19] *F. A. Cotton, D. M. L. Goodgame,* and *M. Goodgame,* J. Amer. chem. Soc. *83,* 4690 (1961).

[20] *D. Reinen,* Z. anorg. allg. Chem. *327,* 238 (1964).

[21] *R. Stahl-Brada* and *W. Low,* Physic. Rev. *113,* 775 (1959).

[22] *F. A. Cotton* and *M. Goodgame,* J. Amer. chem. Soc. *83,* 1777 (1961).

[23] *B. N. Figgis* and *J. Lewis* in *J. Lewis* and *R. G. Wilkins*: Modern Coordination Chemistry. Interscience, New York 1960, p. 400.

[24] *B. N. Figgis* and *J. Lewis,* Progr. inorg. Chem. *6,* 37 (1964).

ration in the 3d shell in the octahedral field is described by $t_{2g}^5 e_g^2$, *i.e.* by a triply degenerate T level, while in the tetrahedral field it is described by $e^4 t_2^3$, and therefore by a nondegenerate A state. *Penney* and *Schlapp* [12] showed that a contribution from the orbital moment can appear only when the ground state is a T state. If these considerations are applied to the $Co^{2+}$ ion in the sodium borate glass, we obtain a higher effective moment for the octahedrally surrounded ion in the alkali-poor glass than for the tetrahedrally surrounded ion in the alkali-rich glass. As Fig. 5 shows, this is in fact the case: in the alkali-poor glasses the coloring ion has an effective moment of about 4.95 and in the alkali-rich glasses of about 4.80 B. M.

However, even with tetrahedrally surrounded $Co^{2+}$ a higher moment is found than would be expected from the spin-only equation. The reason for this is the participation of the higher, triply degenerate T levels, which are energetically not far from the A level and which permit an orbital contribution to be expected. In the one-electron orbital scheme (Fig. 1), therefore, the electron configuration of the $Co^{2+}$ ion should not be described by $e^4 t_2^3$ alone but partly by $e^3 t_2^4$ as well.

## 5. Alkali Borate Glasses Containing Nickel [2]

In the ground state, the $Ni^{2+}$ ion possesses a spin angular momentum S = 1 and an orbital angular momentum L = 3; consequently, the ground state is $^3F$. The levels above are $^1D$ and $^3P$, as shown schematically in Fig. 6. The splittings under the influence of an octahedral field (right) [25–27] and a tetrahedral field (left) [27, 28] are also shown.

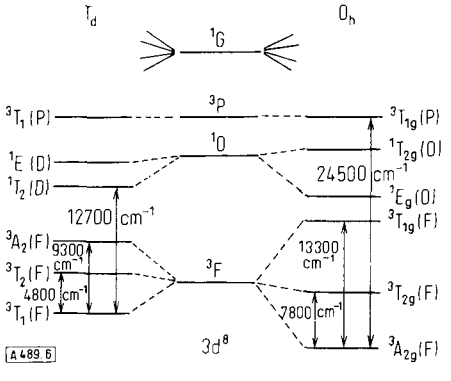


Fig. 6. Energy-level diagram of $Ni^{2+}$. Left, splitting in the tetrahedral ligand field; right, splitting in the octahedral ligand field.

### a) Optical Investigations

The spectrum of the yellow-green alkali-poor nickel potassium borate glasses (base glass $K_2O{\cdot}10B_2O_3$) shows three absorption bands (cf. Fig. 7) whose maxima are assigned to transitions in the energy-level diagram of $Ni^{2+}$ for an octahedral environment (Fig. 6). The spectra of $[Ni(H_2O)_6]^{2+}$ [25, 26] and of $Ni^{2+}$ in MgO [29] can be used for comparison.

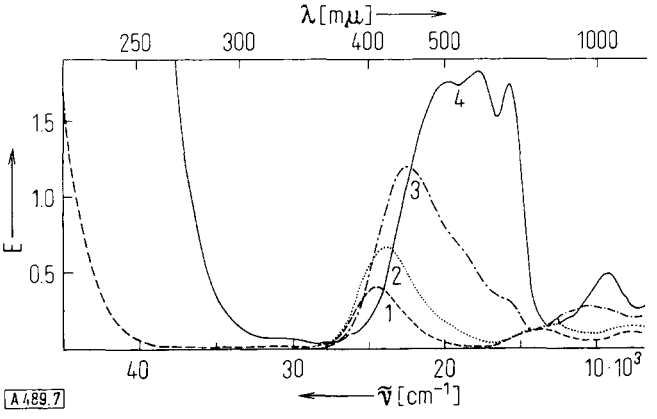


Fig. 7. Spectra of nickel potassium borate glasses with the base glass compositions $K_2O{\cdot}10\ B_2O_3$ (yellow-green, curve 1), $K_2O{\cdot}4\ B_2O_3$ (amber yellow, curve 2), $K_2O{\cdot}3\ B_2O_3$ (amber brown, curve 3), and $K_2O{\cdot}2\ B_2O_3$ (deep purple, curve 4).

The ligand field splitting $\Delta = 10$ Dq can be estimated from the band at 7800 $cm^{-1}$, since this is based on the transition $^3A_{2g} \rightarrow {}^3T_{2g}$ (F), which corresponds to 10 Dq. Consequently, the ligand field in the nickel potassium borate glass (7800 $cm^{-1}$) would be weaker than in the $[Ni(H_2O)_6]^{2+}$ complex (8300–8500 $cm^{-1}$) or in the $NiO_6$ octahedra ($Ni^{2+}$ incorporated in MgO) (8600 $cm^{-1}$).

Whether, in addition to the band at 13300 $cm^{-1}$, a band exists between 13000 $cm^{-1}$ and 15000 $cm^{-1}$ with the participation of a $^3A_{2g} \rightarrow {}^1E_g$ (D) multiplicity-forbidden transition, cannot be decided from our measurements on nickel-containing potassium borate glasses; in the corresponding sodium borate glasses (cf. Fig. 8) it is found at 14600 $cm^{-1}$.

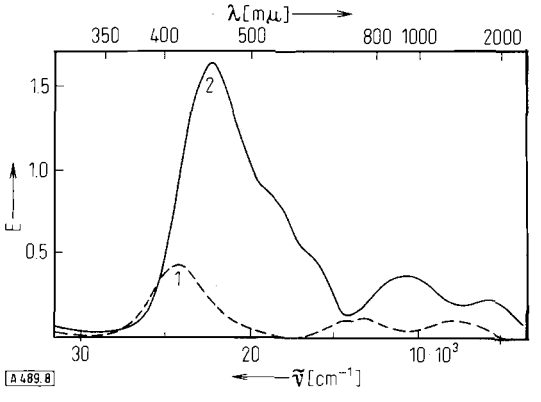


Fig. 8. Spectra of nickel sodium borate glasses with the base glass compositions $Na_2O{\cdot}10\ B_2O_3$ (yellow-green, curve 1) and $Na_2O{\cdot}2\ B_2O_3$ (amber brown, curve 2).

The spectrum of the deep purple alkali-rich nickel-containing potassium borate glass (base glass $K_2O{\cdot}2B_2O_3$) differs strongly from that of the glass with octahedrally coordinated $Ni^{2+}$ (cf. Fig. 7). The spectrum can be assigned to the transitions in the energy-level

[25] *C. K. Jørgensen*, Acta chem. scand. *9*, 1362 (1955).
[26] *C. Furlani*, Z. physik. Chem. N. F. *10*, 291 (1957).
[27] *A. D. Liehr* and *C. J. Ballhausen*, Ann. Physics *2*, 134 (1959).
[28] *H. Hartmann* and *H. Fischer-Wasels*, Z. physik. Chem. N. F. *4*, 297 (1955).
[29] *W. Low*, Physic. Rev. *109*, 247 (1958).

diagram of $Ni^{2+}$ in a tetrahedral environment (cf. Fig. 6) and agrees approximately with the spectrum of tetrahedrally coordinated $Ni^{2+}$ in $Ni_{1.9}Zn_{0.1}SiO_4$ [30].

A particularly important indication of the presence of a $NiO_4$ coordination tetrahedron is the occurrence of the band at 4800 $cm^{-1}$, which we have assigned to the $^3T_1 \rightarrow {}^3T_2(F)$ transition. For $Ni^{2+}$ coordinated octahedrally by oxygen in the glass, the ligand field band of lowest energy occurs at 7800 $cm^{-1}$.

As in the alkali-poor glass, here again the ligand field splitting can be estimated from the $^3T_1 \rightarrow {}^3T_2(F)$ (4800 $cm^{-1}$) transition. The multiplicity-forbidden triplet-singlet transition (12700 $cm^{-1}$) is observed with many tetrahedral metal complexes. However, because it is forbidden, the band is only weak. The three bands (15700, 17800, and 19700 $cm^{-1}$) in the region of the transition $^3T_1 \rightarrow {}^3T_1(P)$ have so far not been interpreted unambiguously [31, 32].

The spectrum of a yellow green alkali-poor nickel sodium borate glass (base glass: $Na_2O \cdot 10\ B_2O_3$) agrees completely with that of the corresponding potassium glass (cf. Fig. 8). On the other hand, the spectrum of the amber-brown alkali-rich nickel sodium borate glass (base glass $Na_2O \cdot 2\ B_2O_3$) is very different from that of the purple potassium glass of the corresponding composition. The alkali-rich sodium glass shows a mixed color like a potassium glass of medium alkalinity (base glass approximately $K_2O \cdot 3\ B_2O_3$); octahedrally and tetrahedrally coordinated $Ni^{2+}$ ions are present.

### b) Magnetic Investigations

Fig. 9 shows the change of the magnetic moments of the $Ni^{2+}$ ion in sodium and potassium borate glasses as a function of the content of the alkali-metal oxide. For the $Ni^{2+}$ ion, with the electron configuration $3d^8$, one would expect an effective moment of 2.83 B. M. for the spin-only case, or $\mu_{eff}$ = 4.47 B. M. with complete orbital contribution. It can be seen from the energy-level diagram (Fig. 6) that here, in contrast to the cobalt glasses, a lower moment is to be expected for the octahedral coordination (A ground state) than for the tetrahedral coordination (T ground state). In the series of the nickel potassium borate glasses, values of 3.30 B. M. have been found for $Ni^{2+}$ in the $NiO_6$ octohedra and 3.65 for $Ni^{2+}$ in the $NiO_4$ tetrahedra.

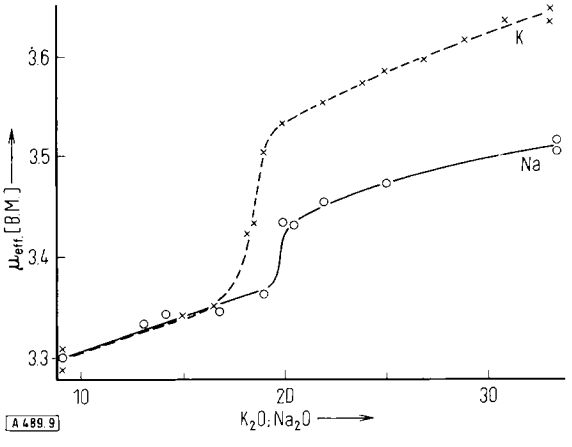


Fig. 9. Magnetic moment of $Ni^{2+}$ in the sodium and potassium borate glasses as a function of the content of the alkali oxide. Left, yellow-green glasses, octahedral arrangement; right, purple glass (with K), tetrahedral arrangement, and amber-brown glass (with Na), tetrahedral and octahedral arrangements. Abscissa: content of alkali oxide in mole-%.

In the nickel sodium borate glasses, the values for the alkali-poor glass are 3.30 B. M. ($NiO_6$ octahedra) and that for the alkali-rich glass 3.50 B. M.: the last figure is, however, a statistical average over $NiO_6$ and $NiO_4$ polyhedra simultaneously present, as expected on the basis of the spectra.

In the case of nickel glasses, the magnetic moment is more suitable than in the case of cobalt glasses as an indicator of the tetrahedral or octahedral coordination of the color center in the glass. This may be due to the fact that – as can be seen from the energy-level diagrams of $Ni^{2+}$ (Fig. 6) and $Co^{2+}$ (Table 2) – the distance between the A level and the first T level in octahedrally coordinated nickel, at 7800 $cm^{-1}$, is almost twice as great as in the tetrahedrally coordinated cobalt at 4060 $cm^{-1}$. Consequently, with the octahedrally coordinated $Ni^{2+}$ ion attainment of the triply degenerate T level, which leads to orbital contribution, requires a greater energy than for the tetrahedrally coordinated $Co^{2+}$ ion. Hence, the difference between the effective "spin-only moment" found and the moment to be expected from the spin-only formula for octahedrally coordinated $Ni^{2+}$ (*ca.* 0.5 B. M.) is also substantially smaller than with tetrahedrally coordinated $Co^{2+}$ (*ca.* 0.9 B. M.).

## 6. Alkali Borate Glasses Containing Copper

With S = $^1/_2$ and L = 2, the $Cu^{2+}$ ion has the ground state $^2D$; there are no other levels for the $3d^9$ configuration. When the $Cu^{2+}$ ion is incorporated in the center of octahedral or tetrahedral coordination polyhedra, two subsequent levels arise in each case by the splitting of the ground state in the ligand field (cf. Fig. 10). On the right of Fig. 10 is shown the splitting in the case of tetragonal-bipyramidal symmetry of the ligand field [33].

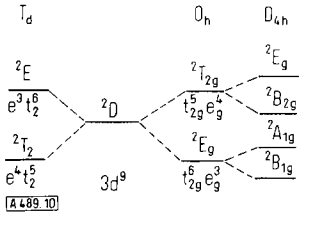


Fig. 10. Energy-level diagram of $Cu^{2+}$. Left of $^2D$ term, the splitting in the tetrahedral ligand field; right, that in the octahedral and in the tetragonal-bipyramidal ligand field.


[30] *O. Schmitz-DuMont, H. Gössling*, and *H. Brokopf*, Z. anorg. allg. Chem. *300*, 159 (1959).

[31] *C. Furlani* and *G. Mopurgo*, Z. physik. Chem. N. F. *28*, 93 (1961).

[32] *G. P. Smith, C. H. Liu*, and *T. R. Griffiths*, J. Amer. chem. Soc. *86*, 4796 (1964).

[33] *C. J. Ballhausen*: Introduction to Ligand Field Theory. McGraw-Hill, New York 1962.

This case is important with the $Cu^{2+}$ ion because no undistorted octahedral $Cu^{2+}$ complex is known [34].

### a) Optical Investigations

The spectrum of the blue-green alkali-poor copper sodium borate glass (base glass $Na_2O{\cdot}12\ B_2O_3$) is shown in Fig. 11. It has a weak broad absorption band in the visible region, and a strong band in the ultraviolet. Comparison with the spectrum of the $[Cu(H_2O)_6]^{2+}$ ion [35] shows that the $Cu^{2+}$ must be present in the glass in approximately octahedral coordination. Only one ligand field band appears, as expected for octahedral coordination according to the energy-level diagram. Since there is no other transition in the neighborhood the band should be a Gaussian curve [36]. Closer inspection shows, however, that the observed band consists of two superposed bands (cf. Table 3). The assignment was therefore carried out on the basis of the tetragonally distorted ligand field which should occur with $Cu^{2+}(lig)_6$ coordination polyhedra on the basis of the strong Jahn-Teller effect occurring in the case of a $3d^9$ electron configuration [34].

The dark blue alkali-rich glass containing copper (base glass $Na_2O{\cdot}2\ B_2O_3$) shows, like the alkali-poor glass, a broad absorption band in the visible region and one band in the ultraviolet. However, the spectra of the two glasses differ from one another in two points, which possibly indicate a partial tetrahedral coordination: the band in the visible has a higher intensity and the charge-transfer band rises more steeply and at lower energy; this shift has also been observed in the transition of cobalt (cf. Fig. 2) and of nickel (cf. Fig. 7) from a coordination number of 6 to one of 4.

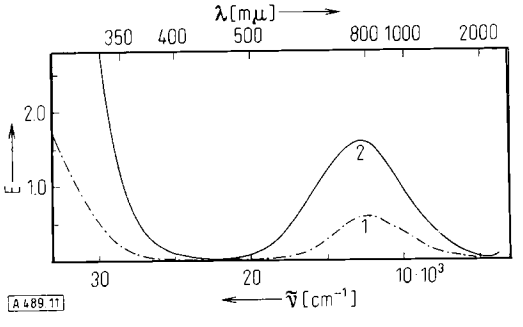


Fig. 11. Spectra of copper sodium borate glasses with the base glass compositions $Na_2O{\cdot}12\ B_2O_3$ (blue-green, curve 1), and $Na_2O{\cdot}2\ B_2O_3$ (dark blue, curve 2).

Table 3. Band assignment in the spectrum of the alkali-poor, blue-green copper sodium borate glass (base glass $Na_2O{\cdot}12\ B_2O_3$) and in a comparative spectrum.

| Cu-glass $\tilde{\nu}$ ($cm^{-1}$) | $[Cu(H_2O)_6]^{2+}$ $\tilde{\nu}$ ($cm^{-1}$) [35] | Assignment |
|---|---|---|
| 9300 | 9300 | $^2B_{1g} \rightarrow {}^2B_{2g}$ |
| 12300 | 12700 | $^2B_{1g} \rightarrow {}^2Eg$ |
| *ca.* 35000 | — | Charge-transfer |

[34] *J. D. Dunitz* and *L. E. Orgel*, Advances inorg. Chem. Radiochem. *2*, 15 (1960).

[35] *J. Bjerrum, C. J. Ballhausen*, and *C. K. Jørgensen*, Acta chem. scand. *8*, 1275 (1954).

[36] *C. K. Jørgensen*, Acta chem. scand. *8*, 1495 (1954).

### b) Magnetic Investigations

The results of the magnetic investigation may help to elucidate the coordination relationships. Up to a base glass composition of $Na_2O{\cdot}7\ B_2O_3$ the alkali-poor copper glasses (cf. Fig. 12) show an effective moment of 1.95 B. M. for the $Cu^{2+}$ ion. The moment rises to 2.10 B.M. in the glass richest in alkali ($Na_2O{\cdot}2\ B_2O_3$) [37].

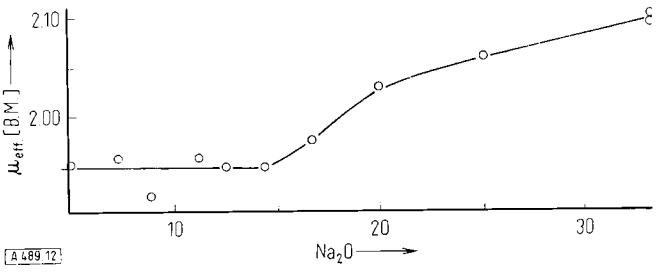


Fig. 12. Magnetic moment of $Cu^{2+}$ in sodium borate glasses as a function of the content of sodium oxide. Left, blue-green glass, tetragonal-bipyramidal structure; right, blue glass; for structure see text. Abscissa: Content of sodium oxide in mole-%.

According to theoretical investigations [38, 39] on the magnetic moment of $Cu^{2+}$ complexes in ligand fields of various symmetries, the $Cu^{2+}$ ion in octahedral or tetragonal-bipyramidal fields should have a moment of 1.73 to 1.9 B. M., *i.e.* near the spin-only value of 1.73. In a tetrahedral environment, a substantially higher value of 2.2 B. M. should appear. This stronger orbital contribution in the tetrahedral field is based on the triply degenerate ground state $^2T_2$ (cf. Fig. 10), while with the only doubly degenerate $^2Eg$ ground state or the non-degenerate $^2B_{1g}$ ground state in fields of symmetry $O_h'$ or $D_{4h}$ the orbital contribution should scarcely be involved. The values found (1.95 and 2.10 B. M., respectively) may indicate that the transition-metal ion is present in octahedral coordination in the alkali-poor glass, and already to some extent in tetrahedral coordination in the alkali-rich glass.

It cannot, however, be decided with certainty from the spectra and magnetic moments whether only distorted octahedral or, in addition, tetrahedral structural groups are present in the alkali-rich glass; there may be a superposition of both, as is observed in nickel-containing sodium borate glasses (cf. Fig. 8). A decision as to whether glasses with $Cu^{2+}$ ions surrounded only tetrahedrally by oxygen can be prepared will probably be provided by measurements on analogous copper potassium or, better, copper cesium borate glasses.

## 7. Transition-Metal Complexes and Glass Structure

The extent of correspondence of $MX_6$ or $MX_4$ structural groups in glass and in crystalline compounds is striking. The immediate environment of the transition-metal ion in glass has, according to the optical results, the same

[37] The magnetic investigations on copper-containing glasses were carried out by Dr. *H. Printzen*.

[38] *K. Ito* and *T. Ito*, Austral. J. Chem. *11*, 406 (1958).

[39] *N. Figgis*, Nature (London) *182*, 1568 (1958).

high symmetry as in the corresponding dissolved or solid compounds. In glass – the comparison can be carried furthest in the halogen complexes to be described in Section 8 – no additional band splitting, which would show a reduction in symmetry, can be observed either. The tetragonal symmetry of the $CuO_6$ polyhedron in glass is also found in crystalline materials, *e.g.* in copper ferrite [40]. The spatial arrangement of the oxygen atoms is determined by the direction and occupancy of the d-orbitals responsible for the bond. The spatial arrangement of the ligands, which evidently remains after solidification, is made possible by the high mobility of the ions in the glass melt.

Boric oxide glass itself dissolves heavy metal oxides to only a small extent. This is probably due to the very firm bond between oxygen and boron. Each oxygen atom is shared by two shallow $BO_3$ pyramids. The polarizing action of the transition metal ions on the oxygen is of great importance for the formation of complexes. However, it is low in the case of a $B_2O_3$ bridging oxygen, since this atom is under the highly contrapolarizing action of the two borons to which it is bound.

The addition of an alkali-metal oxide increases the solubility of transition-metal oxides in the glass. The spectrum remains constant over a comparatively wide range: thus, the spectrum of nickel in glass of composition $K_2O{\cdot}5B_2O_3$ coincides with that in the glass $K_2O{\cdot}10\ B_2O_3$, shown in Fig. 7. In this range of compositions, as shown in Section 2, the $BO_3$ groups are converted increasingly into $BO_4$ groups. The oxygen in the tetrahedral $BO_4$ groups is also bridging oxygen: it is also contrapolarized by two boron atoms, but less strongly than the bridging oxygen in the $BO_3$ groups. In crystalline polyborates, the B–O distance in the plane structural groups is 1.38 Å, and in the tetrahedral groups 1.48 Å [41]. The increase in the distance requires a smaller contrapolarizing action of the boron. It must be assumed that the associated increase in the polarizability of the oxygen due to the transition-metal ions is responsible for the increase in the solubility of the metal oxides and for the formation of $MO_6$ complexes. The metal-oxygen bond should here be regarded as strongly polar.

Borate glasses with more than 17 mole-% of sodium oxide contain "non-bridging" oxygen, which is associated with an excess of negative charge but which is substantially less contrapolarized by boron. Consequently, the requirements of the formation of the $MX_4$ complexes, in which the proportion of covalent bonding is greater, are satisfied. A short discussion of the ligand fields of bridging and non-bridging oxygen is given at the end of Section 8.

The ideas on the coordination of color centers in glasses are supported by the magnetic behavior, but the conclusions drawn from the latter are less stringent. However, this is not due to the vitreous state of the samples investigated; with crystalline complexes, too, the magnetic behavior is frequently complicated to such an extent by different orbital contributions that convincing conclusions can be drawn only with difficulty. On the other hand, a particularly simple magnetochemical situation exists in the glasses investigated, at least with the contents of transition-metal ions considered here. Very low values of the constant $\Theta$ in the Curie-Weiss law are always found; they are generally between $-5$ and $-20\,^{\circ}K$. Thus practically no interactions occur between the 3d electrons of neighboring metal ions; it is prevented by the great distance in the boron-oxygen network.

The change in color of the glasses and the change in the magnetic moment depend not only on the content of alkali but also on the natures of the transition metal and of the alkali-metal oxide used.

Of the ions $Co^{2+}$, $Ni^{2+}$, and $Cu^{2+}$, when incorporated into sodium borate glasses, the transition to tetrahedral coordination takes place completely with $Co^{2+}$. In the case of $Ni^{2+}$, both types of coordination are present, and with $Cu^{2+}$ only a very low fraction is converted to tetrahedral coordination. This is due to the decrease of crystal field stabilization in a tetrahedral environment in the sequence $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$ [34].

An influence of the type of alkali-metal oxide ($Li_2O$, $Na_2O$, and $K_2O$) on the position and width of the transition region is also found, as can be seen best from the change in the magnetic moments of cobalt (cf. Fig. 5). With $Li_2O$, the tetrahedral coordination is evidently no longer achieved completely in the cobalt glass, whereas this is the case with $Na_2O$ and $K_2O$. Similarly, the tetrahadral coordination is achieved in the nickel-containing $K_2O$ glasses, but not with $Na_2O$. This difference in the behavior of the alkali-metal oxides is in our opinion connected with the importance of nonbridging oxygen atoms for the formation of the tetrahedral complexes. The concentration of the non-bridging oxygens is, however, difficult to measure. The concentration of oxygen ions has been determined in glass melts by EMF measurements; it is higher in potassium borate melts than in sodium and lithium borate melts of the same alkali content [42]. This result undoubtedly also gives a point of reference for the situation in the glasses; it explains the occurrence of tetrahedral coordination polyhedra in glasses of the heavy alkali metals. Regarded from the point of view of polarization of the oxygen, the polarizing action of the small alkali-metal ion in lithium borate glasses competes with that of the transition metal, while in the glasses with larger alkali-metal ions, having a smaller polarizing action, this competition takes place to a smaller extent.

## 8. Halide-Containing Cobalt and Nickel Glasses

The color of a glass can be changed by the addition of alkali-metal halides in the melt [1,2,43]. We wished to determine under what circumstances such changes in

[40] *E. Prince* and *R. G. Treutling*, Acta crystallogr. *9*, 1025 (1956).

[41] *J. Krogh-Moe*, Acta crystallogr. *13*, 889 (1960); Ark. Kemi *14*, 439 (1959).

[42] *W. Stegmaier* and *A. Dietzel*, Glastechn. Ber. *18*, 297 (1940).

[43] *W. C. Taylor*, Glass Ind. *7*, 90 (1925).

the color and possibly also in the magnetic moment of the transition metal ion occurred in cobalt- and nickel-containing glasses, whether the changes could be related to the ideas on color centers, and whether the ligand field theory can be applied.

We shall discuss first those cases in which the incorporation of alkali-metal halides has no influence on the color of the glasses. Table 4 gives a survey; on the average, 10 moles of halide were added per mole of the transition

Table 4. Survey of the color, magnetic moment, and coordination of the transition-metal ion in halide-containing alkali borate glasses with cobalt and nickel.

| Glass | Additive | Color | $\mu_{eff}$ (B. M.) | Coordination |
|---|---|---|---|---|
| Alkali-poor cobalt glass ($Na_2O{\cdot}7\ B_2O_3$) | — | Red-purple | 4.95 | $O_6$ |
| | F | Red-purple | 4.94 | $O_6$ |
| | Cl | Blue | 4.89 | $Cl_4$ |
| | Br | Blue | 4.91 | $Br_4$ |
| | I | Green | 5.09 | $I_4$ |
| Alkali-rich cobalt glass ($Na_2O{\cdot}3\ B_2O_3$) | — | Blue | 4.80 | $O_4$ |
| | F | Blue | 4.79 | $O_4$ |
| | Cl | Blue | 4.84 | $O_4$ |
| | Br | Blue | 4.85 | $O_4$ |
| | I | Blue | 4.89 | $O_4$ |
| Alkali-poor nickel glass ($K_2O{\cdot}8\ B_2O_3$) | — | Yellow-green | 3.29 | $O_6$ |
| | Cl | Blue | 3.65 | $Cl_4$ |
| Alkali-rich nickel glass ($K_2O{\cdot}2\ B_2O_3$) | — | Purple | 3.65 | $O_4$ |
| | Cl | Purple | 3.65 | $O_4$ |

metal. The color of the alkali-rich cobalt- and nickel-containing glasses remained unchanged. The absorption bands in the near infrared and in the visible agree with those of the halide-free glasses. Since these are the regions of the ligand field bands, the same assignment applies as for the corresponding halide-free glass. The magnetic moments of $Co^{2+}$ and $Ni^{2+}$ also remain constant. The ligand field in the $CoO_4$ coordination polyhedra is obviously stronger than in the $Co(Hal)_4$ polyhedra, so that $Co(Hal)_4$ structural groups cannot form in alkali-rich glasses. However, slight differences in the spectra occur in the charge-transfer region.

Alkali-poor glasses (base glass $Na_2O{\cdot}7B_2O_3$) behave quite differently: when an alkali-metal chloride, bromide, or iodide is incorporated with the melt, their colors change. Comparison of the spectra of these glasses (Fig. 13) with the spectra of $[Co(Hal)_4]^{2-}$ compounds [19] shows that tetrahedral cobalt-halogen coordination polyhedra must be present. Table 5 gives the bands and the proposed assignments of the three glasses. The band discussion is based on that for the alkali-rich, halide-free, cobalt-containing sodium borate glasses (cf. Fig. 2 and Table 2). The first transition $^4A_2 \rightarrow {}^4T_2(F)$ for all three $Co(Hal)_4$ polyhedra occur below 4000 $cm^{-1}$ [43a].

The splitting into three bands in the near infrared [the $^4A_2 \rightarrow {}^4T_1(F)$ transition] has the same causes as the splitting for the same transition in the alkali-rich halide-free glass.

[43a] Note added in proof: Subsequent measurements with a Beckman IR 9 spectrophotometer yielded 3100 $cm^{-1}$ for the glass containing chloride. There is a shift to lower wave numbers in the glasses containing bromide and iodide.

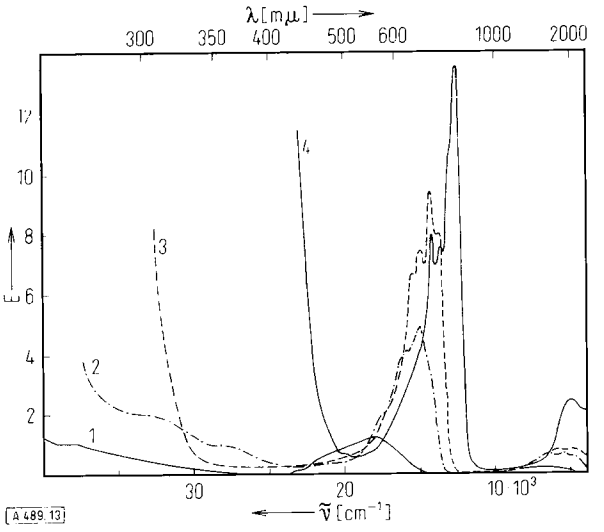


Fig. 13. Spectra of alkali-poor cobalt sodium borate glasses with added NaF (red-purple, curve 1), NaCl (blue, curve 2), NaBr (blue, curve 3), NaI (green, curve 4). Base glass $Na_2O{\cdot}7\ B_2O_3$.

Table 5. Band assignment in the spectra of alkali-poor halide-containing cobalt sodium borate glasses (base glass $Na_2O{\cdot}7\ B_2O_3$). (sh) = shoulder.

| Base glass with addition of | | | Assignment |
|---|---|---|---|
| $Cl^-$ $\tilde{\nu}$ ($cm^{-1}$) | $Br^-$ $\tilde{\nu}$ ($cm^{-1}$) | $I^-$ $\tilde{\nu}$ ($cm^{-1}$) | |
| 3100 [43a] | — | — | $^4A_2 \rightarrow {}^4T_2(F)$ |
| 4700 (sh) | 4400 (sh) | Broad band | $^4A_2 \rightarrow {}^4T_1(F)$ |
| 5400 | 5000 | beginning from < 4000, | |
| 6400 | 5800 | max. *ca.* 4800 | |
| *ca.* 14300 (sh) | 13800 | 12700 | $^4A_2 \rightarrow {}^4T_1(P)$ |
| 15050 | 14350 | *ca.* 13100 (sh) | |
| 15950 | 15000 | 13700 | |
| *ca.* 16400 (sh) | 15600 | 14300 | $^4A_2 \rightarrow {}^2G$ subs. level |
| *ca.* 17600 (sh) | 17100 (sh) | 15300 (sh) | |
| from *ca.* 37000 | from *ca.* 32000 | from *ca.* 22000 | Charge-transfer |

A very complex system of bands is found in the visible region. It is difficult to say which bands from the central part of this system are due to $^4A_2 \rightarrow {}^4T_1(P)$ transitions and which to $^4A_2 \rightarrow {}^2G$ subsequent level transitions, since according to calculations by *Cotton*, *Goodgame*, and *Goodgame* the levels $^2E(G)$ and $^2T_1(G)$ cross $^4T_1(P)$ even in the weak field with Dq = 300 or 320 $cm^{-1}$, in which, moreover, a multiplet splitting must also be taken into account [19].

The alkali-poor nickel potassium borate glass (base glass $K_2O{\cdot}8\ B_2O_3$) into which KCl was incorporated (blue) again shows an absorption spectrum (cf. Fig. 14) completely different from that of the halide-free glass (yellow-green): it is the spectrum characteristic of $NiCl_4$ coordination polyhedra. Table 6 gives the bands and the assignment proposed by the use of the energy-level diagram (Fig. 5). The $[NiCl_4]^{2-}$ complex has been thoroughly investigated both theoretically and experimentally in solution, in the solid state, and in melts. Nevertheless, the occurrence of three bands in the $^3T_1 \rightarrow {}^3T_1(P)$ region has not yet been finally explained [31,32,44].

[44] *D. M. L. Goodgame*, *M. Goodgame*, and *F. A. Cotton*, J. Amer. chem. Soc. *83*, 4161 (1961).

The fluoride containing alkali-poor cobalt glass occupies a special position. The spectrum agrees with that of the fluoride-free glass (cf. Fig. 13, curve 1), and from this it can be deduced that the $CoO_6$ octahedra are not destroyed by the addition of fluoride. The band assignment is the same as in the fluoride-free glass.

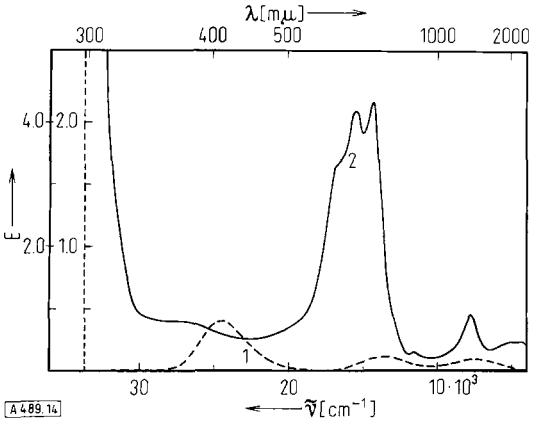


Fig. 14. Spectra of the alkali-poor nickel potassium borate glass (yellow-green, base glass $K_2O{\cdot}8\ B_2O_3$) without (curve 1) and with the addition of KCl (blue, curve 2).

Table 6. Band assignment in the spectrum of an alkali-poor, blue KCl-containing nickel potassium borate glass (base glass $K_2O{\cdot}8\ B_2O_3$).

| Ni-glass $\tilde{\nu}$ ($cm^{-1}$) | Assignment |
|---|---|
| 7700 | $^3T_1 \rightarrow {}^3A_2(F)$ |
| 11600 | $^3T_1 \rightarrow {}^1T_2(D)$ |
| 14200 | Region of $^3T_1 \rightarrow {}^3T_1(P)$ |
| 15300 | |
| 16400 (sh) | |

A further proof of the existence of cobalt-halogen bonds is offered by the charge-transfer bands (cf. Fig. 13 and Table 5), the rise of which in the sequence of the glasses with $Cl^-$, $Br^-$ and $I^-$ is displaced strongly to longer wavelengths. This shift corresponds to the law according to which "electron transfer" from $Hal^-$ to $Co^{2+}$ takes place more easily, and therefore at smaller wavelengths, with increasing oxidizability of the ligands ($Cl^- < Br^- < I^-$). There must be a comparatively high proportion of covalent bonding in the $Co(Hal)_4$ polyhedra, highest in the $CoI_4$ polyhedra. In these, therefore, the electrons coming from the ligands must be most strongly transferred into a molecular orbital that is predominantly concentrated on the metal ion.

The magnetic properties of the $Co^{2+}$ and $Ni^{2+}$ ions in the halide-containing glasses (cf. Table 4) also fit into the pattern obtained from the optical measurements. While in the alkali-rich glasses the moments are not changed by the incorporation of alkali-metal halides in the melt, the moment for the octahedral coordination changes into that for the tetrahedral coordination in the alkali-poor nickel-containing glass after the addition of halide. In the cobalt-containing glasses, a weak rise in the moments of the $Co^{2+}$ ion is found, in the sequence of $CoO_4$, $CoCl_4$, $CoBr_4$, and $CoI_4$ structural groups. This can be explained qualitatively by the fact that the distance between the non-degenerate $^4A_2$ ground terms of the $Co^{2+}$ ion (cf. Fig. 2) and the nearest triply degenerate $^4T_2$ state decreases because of the weakening of the ligand field in the direction of the $CoI_4$ complex, *i.e.* the $^4A_2 \rightarrow {}^4T_2$ excitation will occur more readily and therefore the participation of the triply degenerate T state in the state of the $Co^{2+}$ ion becomes greater.

The experiments with the halide-containing glasses are a good example of the influence of the ligand field. Thus it can be shown that, in the sense of *Tsuchida*'s sequence [13], $I^- < Br^- < Cl^- < H_2O$, an iodide-containing alkali-poor cobalt glass (green) becomes blue when chloride is incorporated in the melt, while the color of a chloride-containing glass does not change when iodide is added. In the same way, the $CoO_4$ complex cannot be destroyed by halide; the oxygen of the borate glass must therefore be inserted between $H_2O$ and $Cl^-$ in the above sequence. However, this comparison applies only if the coordination number is retained; when it changes, even the oxo complex $CoO_6$ can be converted into the halogeno complex $Co(Hal)_4$.

The spectroscopic results also permit a calculation of the ligand field strength $\Delta_t$ by Cotton and Goodgame's method [22] (Table 7).

Table 7. Ligand field strength $\Delta_t$ in some coordination polyhedra.

| Polyhedron | $CoI_4$ | $CoBr_4$ | $CoCl_4$ | $CoO_4$ | $Co(OH)_4$ |
|---|---|---|---|---|---|
| $\Delta_t$ ($cm^{-1}$) | 2750 | 2920 | 3190 [*] | 4060 | 4230 |

[*] Added in proof: Experimental value 3100 $cm^{-1}$ [transition $^4A_2 \rightarrow {}^4T_2(F)$].

The four values applying to the glasses are supplemented by the value calculated for $Co(OH)_4$ [19]. The non-bridging oxygen $^{\ominus}O-B\langle$ in the $CoO_4$ polyhedron therefore has a smaller field than the $OH^-$ ion. Similarly, the bridging oxygen $\rangle B-O-B\langle$ has a smaller ligand field than H–O–H, since the ligand field strength is calculated to be 7800 $cm^{-1}$ from the nickel-containing glass with $NiO_6$ polyhedra (transition $^3A_{2g} \rightarrow {}^3T_{2g}(F)$; cf. Fig. 6), while the $Ni(H_2O)_6$ polyhedra give the larger value of 8400 $cm^{-1}$ [25,26].

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# Madelung Constants

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*Dedicated to Prof. Wilhelm Klemm on the occasion of his 70th birthday*

*Madelung constants are simple numbers which depend on the type of structure investigated. They are needed for the calculation (using the Born-Haber cycle) of lattice energies and enthalpies of formation of ionic compounds. Each Madelung constant is the sum of partial Madelung constants which represent the contributions of the individual ions to the total lattice energy. The partial Madelung constants depend on the ionic charge and, clearly though not stringently, on the coordination number. On the other hand, each Madelung constant can be represented by a sum of Madelung constants for related simple primitive AB structures. Surprisingly, these Madelung constants are numerically interrelated in a simple manner, and are related to the partial Madelung constants of interstitial sites. – Madelung constants of parameter-dependent structures (e.g. of the rutile or anatase type) and their variations with the structure-determining quantities are of particular interest. Madelung constants also yield information in the case of complex compounds and – surprisingly – of non-metal compounds (e.g. $XeF_2$, $XeF_4$, $XeF_2 \cdot XeF_4$).*

For many problems both inside and outside the realm of inorganic chemistry, it is necessary or desirable to obtain reasonably reliable information about the free energy of formation of unknown compounds or of compounds that have not yet been subjected to thermochemical investigation. A very recent example of such a problem is that of the thermodynamic stability of xenon fluorides [1, 1a].

Entropies can nearly always be found with a high degree of accuracy from thermochemical data for analogous compounds. The calculation of enthalpies of formation, on the other hand, is difficult even today. An important aid to the calculation of enthalpies of formation, and one that is often used because of its fundamental simplicity, is the Born-Haber cycle. It can be seen from Fig. 1 that the two simple steps I and II, *i.e.* the formation of single atoms of the gaseous substances and the formation, from these atoms, of isolated gaseous ions, are followed by a third, more complicated step, in which all the ions combine to form the crystal structure

Even for compounds which can be considered as consisting largely of ions, it is difficult to calculate the enthalpy of formation $\Delta H^\circ$ corresponding to step IV (Fig. 1) with sufficient accuracy. There are several reasons for this. In the first place (and this is a fundamental weakness of the Born-Haber cycle), $\Delta H^\circ$ is a relatively small difference of values that are often very large (ionization potential $I_{Sp}$, electron affinity $E_A$, enthalpy of sublimation $\Delta H^\circ_{subl}$, dissociation energy $D_o$, lattice energy $U_g$), so that small individual errors can lead to a considerable absolute error. Secondly, the calculation of the lattice energy associated with step III (cf. Fig. 1) is not simple. This lattice energy can be broken down into three terms as shown in Equation (1),

$$U_g = [MF \times f(z_i) \times N_L \times e^2]/r_{KA} + E_{nC} + E_{corr} \qquad (1)$$

where $N_L$ is the Avogadro number, e is the unit charge, $r_{KA}$ is the shortest distance between cations and anions, and $f(z_i)$ is a function of the ionic charge, which is often written out in full for binary compounds [$f(z_i) = z_1 \times z_2$], but is better included in the Madelung constant MF in the case of more complicated compounds. (For the sake of simplicity, it is always assumed that T = 0 °K.)

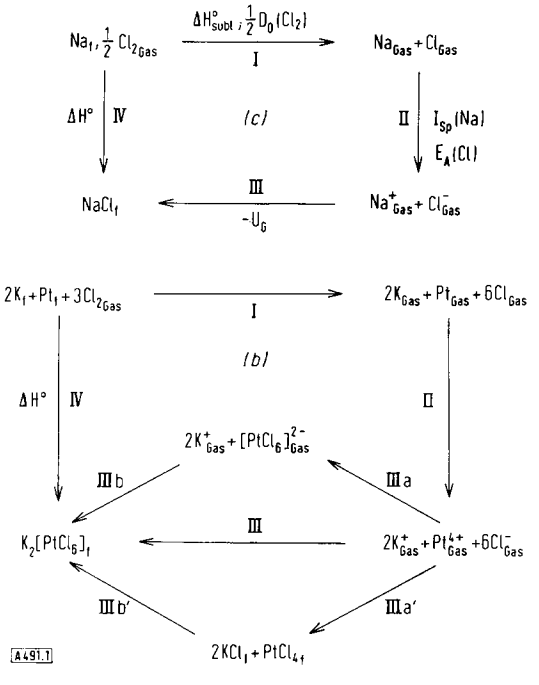


Fig. 1. Born-Haber cycle for NaCl (c) and $K_2[PtCl_6]$ (b). The index f denotes the solid state.

[1] *R. Hoppe, H. Mattauch, K.-M. Rödder,* and *W. Dähne,* Z. anorg. allg. Chem. *324,* 214 (1963); *N. Bartlett,* Endeavour *23,* 3 (1964).

[1a] *R. Hoppe,* Fortschr. chem. Forsch. *5,* 213 (1965).

In order to calculate the first term in Equation (1), *i.e.* the "Madelung component of the lattice energy", we must know the Madelung constant. This is determined by the charge on the ions and by their positions in the unit cell; in the remainder of this paper it will for binary compounds always be based on the shortest distance between cations and anions. The calculation of the Madelung constants is laborious without the aid of modern computers; consequently, Madelung factors have so far been calculated only for about 50 types of structures (most of which are very simple, often parameter-free structures) (cf. list in [3]).

The term $E_{nC}$, which takes into account the Born repulsion between the electron clouds that is due to non-Coulombic forces, must be present to explain the finite value of the equilibrium distances $r_{KA}$. Thus if we were to consider only the Madelung component of the lattice energy, this would reach its "optimum" value at $r_{KA} = 0$! Further correction takes into account the mutual polarization of the ions, the zero-point energy, lattice-energy components due to additional bonding forces (*e.g.* bonds within complex ions), *etc.* (cf. [2, 3]); these correction terms are combined in the term $E_{corr}$ in Equation (1). As can be seen from the review by *Waddington* [3], satisfactory accuracy in the calculation of lattice energies by means of Equation (1) can at present be achieved only for relatively few inorganic compounds, *e.g.* the alkali metal halides and alkaline earth metal chalcogenides. Impressive calculations have recently also led to the lattice energies of the higher alkali metal oxides [4].

## A. General

### I. The Madelung Constant and the Lattice Energy

Equation (1) can be used for the calculation of enthalpies of formation only if sufficient Madelung constants are known and if the uncertainty associated with the terms $E_{nC}$ and (in particular) $E_{corr}$ can be minimized. This makes the calculation of more Madelung constants desirable. The knowledge of Madelung constants is even more important in cases where the Madelung component of the lattice energy can be used alone, *e.g.* for investigating which modification of a compound (*e.g.* $TiO_2$) is thermodynamically stable under normal conditions, or why a parameter-dependent structure [*] (*e.g.* the rutile type) favors certain parameters (*e.g.* c/a $\approx \sqrt{2}/2$ and $x_O = 0.3$), instead of other "adjacent" values.

It can often be assumed in such cases that the terms $E_{Cn}$ and $E_{corr}$ are practically the same for "adjacent" modifications [**] of the same compound, so that differences in the enthalpies of formation are essentially due to differences in the Madelung components of the lattice energies. A similar argument applies to the variation of c/a or of the oxygen coordinates in isotypic compounds of the same structural type, such as $NaScO_2$, $NaYO_2$, $NaInO_2$, and $NaTlO_2$ [5].

### II. Partial Madelung Constants

It follows implicitly from *Ewald*'s method [6] for the calculation of Madelung constants that the Madelung constant, and hence the Madelung component of the lattice energy, can be expressed as a sum of terms which are due to the different ions in the unit cell [7]. We shall call these terms partial Madelung constants (PMF) [8, 9]. If in a compound $A_mB_n$ all the A particles occupy equivalent positions and if the same holds for all the B particles, Equation (2a) is valid:

$$MF(A_mB_n) = m \times PMF(A) + n \times PMF(B) \qquad (2a)$$

For example, for the NaCl type [$O_h^5$ – Fm3m, Z = 4, with $Na^+$ in 4(a) and $Cl^-$ in 4(b)], we have Equation (3),

$$MF(NaCl) = PMF(Na^+) + PMF(Cl^-) \qquad (3)$$

and similarly, for the $CaF_2$ type [$O_h^5$ – Fm3m, Z = 4, with $Ca^{2+}$ in 4(a) and F in 8(c)], we have Equation (4).

$$MF(CaF_2) = PMF(Ca^{2+}) + 2 \times PMF(F^-) \qquad (4)$$

If, on the other hand, the particles A occupy j different types of positions (multiplicity $z_j$), while the particles B occupy r different types of positions (multiplicity $z_r$), the general equation is (2b), where the factors $m_j = z_j/Z$

$$MF(A_mB_n) = \sum_{j=1}^{j} m_j \times PMF(A_j) + \sum_{r=1}^{r} n_r \times PMF(B_r) \qquad (2b)$$

and $n_r = z_r/Z$ ensure that the individual PMF values are correctly weighted (Z = number of formula units per unit cell). Thus for $Mn_2O_3$ [$T_h^7$ – Ia3, Z = 16, with $Mn_I$ in 8(a), $Mn_{II}$ in 24(d), and O in 48(e)], we obtain

$$MF(Mn_2O_3) = 1/2\, PMF(Mn_I) + 3/2\, PMF(Mn_{II}) + 3\, PMF(O) \qquad (5)$$

In contrast to the Madelung constants themselves, which offer only an overall picture of the energy relationships of a structural type, the partial Madelung constants provide information about the potential energies of the individual ions. For the calculation of partial Madelung constants, see [7–9].

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[2] *M. Born*: Atomtheorie des festen Zustandes. Teubner, Leipzig, 1923; Handbuch d. Physik, Springer, Berlin 1927, Vol. *24*, p. 420. M. *Born* and *A. Lande*, S.-B. preuß. Akad. Wiss., physik.-math. kl. *45*, 1048 (1918); *M. Born* and *A. Lande*, Verh. dtsch. physik. Ges. *20*, 210 (1918); *F. Haber*, ibid. *21*, 750 (1919); *M. F. C. Ladd* and *W. H. Lee*, Trans. Faraday Soc. *54*, 34 (1958); *E. Madelung*, Physik. Z. *19*, 524 (1918).

[3] *T. C. Waddington*: Advances in Inorganic Chemistry and Radiochemistry. Academic Press, New York 1959, Vol. 1, p. 157.

[4] *L. A. D'Orazio* and *R. H. Wood*, J. physic. Chem. *69*, 2550 (1965); *R. H. Wood* and *L. A. D'Orazio*, ibid. *69*, 2558 (1965); *69*, 2562 (1965).

[*] In a parameter-dependent structure, the dimensions of the unit cell (*e.g.* the ratio c/a for tetragonal or hexagonal crystals) or the coordinates of the particles in the unit cell can be altered without affecting the symmetry.

[**] "Adjacent" modifications differ only slightly in the structure-determining parameters.

[5] *R. Hoppe*, Bull. Soc. chim. France *1965*, 1115; Chem. Zvesti *19*, 172 (1965).

[6] *P. P. Ewald*, Ann. Physik *64*, 253 (1921).

[7] *R. Hoppe*, Dissertation, Universität Münster, 1954; Z. anorg. allg. Chem. *283*, 196 (1956).

[8] *R. Hoppe*, Habilitation Thesis, Universität Münster, 1958.

[9] *H. G. v. Schnering*, Habilitation Thesis, Universität Münster, 1963.

## III. Partial Madelung Constants as Structural Arguments [9,10]

The partial Madelung constants of the various ions can also be used as structural arguments:

Using modern Fourier methods, very accurate information about the position of the center of gravity of the particles in a crystal can be obtained by X-ray analysis of single crystals, often with an average error of only ±0.005 Å. It is only in special cases, however, that electron density distributions can be found from precision measurements and used as a basis for conclusions regarding the type of chemical bonding [10a].

It is therefore still useful to employ concepts such as ionic radius, sum of the radii, ratio of the radii, coordination number, *etc.*, in the interpretation of crystal structures (which are described only geometrically by the positions of the particles). Of course, there is a remarkable discrepancy between these concepts, which are often only vaguely defined, and the accuracy of modern methods of structural analysis. Thus in addition to attempts to obtain improved definitions of these fundamental crystal-chemical quantities (cf. *e.g.* [11]), every possibility of obtaining further information from the structural geometry should be examined. Such a possibility seems to be offered by the partial Madelung constants: A three-dimensional description of the potentials and potential energies of the individual particles corresponding to the three-dimensional network of the centers of gravity is obtained by calculation of the partial Madelung constants. This discontinuous "grid" of partial Madelung constants may then be made as "dense" as required by the calculation of partial Madelung constants for interstitial sites.

It has been found that even in the case of compounds with considerable non-ionic character, a better understanding of the reasons for the occurrence of certain structures is obtained by comparison of the partial Madelung constants with those of chemically related compounds (*e.g.* $BrF_3$, $XeF_4$, and $XeF_2$) [11a].

It has been known for some time that the Born-Haber cycle can also be applied in the case of compounds that do not consist of ions. Thus *Kapustinskii* [12] demonstrated that the lattice energies of non-ionic compounds can often be calculated with reasonable accuracy with the aid of the effective Madelung constants (cf. Section A.IX), which were introduced by *Klemm* [13]. (In favorable cases, the lattice energies of covalent compounds are found with an accuracy of about ±10 kcal/mole.)

[10] *R. Hoppe* and *H. G. v. Schnering*, unpublished work (1962–1964).

[10a] Cf. in particular *E. Wölfel et al.*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *63*, 891 (1959); Z. physik. Chem. N.F. *3*, 273, 296 (1955); *4*, 36, 65 (1955); *10*, 98 (1957).

[11] *R. Hoppe*, 18. IUPAC-Congress, Montreal (Abstracts of Scientif. Papers, page 73).

[11a] Cf. for example [1a].

[12] *K. F. Kapustinskii*, Z. physik. Chem. B *22*, 257 (1933); Zh. fiz. Khim. *5*, 59 (1943); Acta physicochim. USSR *18*, 370 (1943); Quart. Rev. chem. Soc. (London) *10*, 283 (1956); *A. F. Kapustinskii* and *K. B. Yatsimirskii*, Zh. obshch. Khim. *19*, 2191 (1949); *26*, 941 (1956).

[13] *W. Klemm*, Z. physik. Chem. B *12*, 1 (1931).

## IV. Madelung Constants of AB Types with Single Primitive Unit Cells [8,10,13a]

Simple relationships exist between Madelung constants of some compounds [7,14], for example:

$$MF(CaF_2) = MF(CsCl) + 2 \times MF(ZnS) \qquad (6)$$

In spite of reports to the contrary [15], there is an infinite number of such relationships for a given structure, since the Madelung constant represents the sum of all attractive and repulsive interactions of the ions in the crystal and can be broken down in an infinite number of ways into partial sums.

The Madelung constants of AB compounds with simple primitive unit cells (*e.g.* the CsCl type) are particularly important, since the Madelung constant of any structural type can be expressed as a sum of Madelung constants of single primitive (not necessarily isometric) AB types [*]. This follows from the fact that any structure can be derived by superposition of suitable, not necessarily isometric single primitive AB types. The Madelung constants of single primitive AB types are therefore "building units" for all other Madelung constants; they will be denoted in the remainder of this article by °MF.

For the sake of simplicity, we shall discuss only Madelung constants of single primitive AB types with cubic unit cells. However, similar relationships exist for non-cubic single primitive AB types.

For AB types with single primitive cubic unit cells, we shall always use the arrangement $A^+$ in 0,0,0 and $B^-$ in x,y,z, the corresponding Madelung constant being denoted by $^\circ MF(x,y,z)_k$; for example

$$MF(CsCl) \equiv {}^\circ MF(1/2,1/2,1/2)_k$$

When based on the shortest distance A–B, these Madelung constants all lie between 1 (the "Madelung constant" of the gaseous molecule AB) and MF(CsCl) = 1.76267... (cf. Table 1).

Table 1. $^\circ MF(x,y,z)_k$ for special values of x, y, z [8].

| x | y | z | $^\circ MF(x,y,z)_k = 2 \times PMF(x,y,z)_k$ |
|---|---|---|---|
| 1/2 | 1/2 | 1/2 | 1,7626747730... |
| 1/2 | 1/2 | 1/4 | $1{,}60742_5$... |
| 1/2 | 1/2 | 0 | $1{,}594367$ |
| 1/2 | 1/4 | 1/4 | $1.41251_3$... |
| 1/2 | 1/4 | 0 | $1.38825_9$ |
| 1/2 | 0 | 0 | $1.37068_1$ |
| 1/4 | 1/4 | 1/4 | $1.14177_4$... |
| 1/4 | 1/4 | 0 | $1.08778_1$... |
| 1/4 | 0 | 0 | $1.03580_8$... |

The variations of °MF(x,0,0), °MF(x,1/2,0), °MF(x,1/2,1/2) and °MF(x,x,x) in the range $0 \leqslant x \leqslant 1/2$ are shown in Figure 2. It can be seen that the variations follow roughly the same pattern, and are all characterized by the rapid fall-off from the maximum. The

[13a] *R. Hoppe* and *H. G. v. Schnering*, unpublished work (1965).

[14] *F. Bertaut*, J. Physique Radium *13*, 499 (1952); C. R. hebd. Séances Acad. Sci. *239*, 234 (1954); *P. Naor*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *110*, 2 (1958).

[15] *G. C. Benson*, Canad. J. Physics *34*, 888 (1956); *G. C. Benson* and *F. van Zeggeran*, J. chem. Physics *26*, 1083 (1957).

[*] The dimensions of the unit cells of these AB types need not be the same as those of the structural type, the Madelung constant of which is to be expressed as a sum.

Madelung constants of single primitive $A^+B^-$ types with non-cubic unit cells are also smaller than 1.76267..., but some are smaller than 1.0, and they may even be negative (cf. Section X).

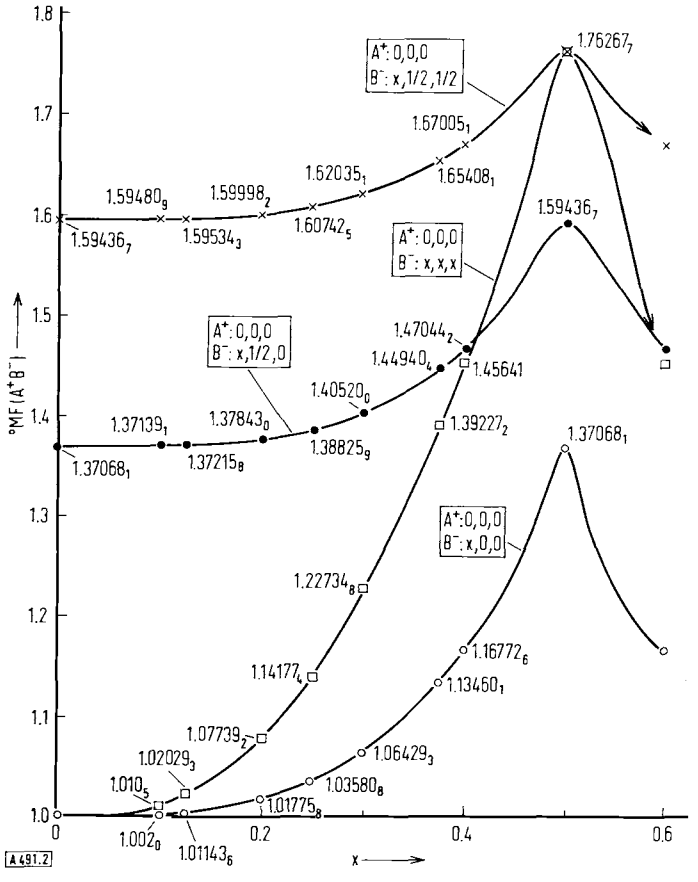


Fig. 2. Madelung constants (°MF) of cubic AB types with single primitive unit cells [arrangement: $A^+$ in (0,0,0) and $B^-$ in (x,y,z)].

## V. Partial Madelung Constants of Single Primitive AB Types

Single primitive AB types, irrespective of size and/or symmetry of their unit cell have commutative sub-lattices [7]. The partial Madelung constants of $A^+$ and $B^-$ are then numerically equal, each being half of the total Madelung constant. Where the ions are monovalent, $PMF(x,y,z)_k$ is between 0.5 and 0.88 (cf. Table 1). Moreover, some non-primitive AB structures, such as the rock salt, sphalerite and wurtzite types, also have commutative sub-lattices. In these cases the partial Madelung constants of the $A^+$ and $B^-$ particles are again numerically equal, each again being half of the total Madelung constant. An important example of a simple AB type with non-commutative sub-lattices is the NiAs type, in which the Madelung constant, as calculated by *Zemann* [16], is not a simple function of the partial Madelung constants of $A^+$ and $B^-$, which differ in their numerical values [*].

The partial Madelung constants of polyvalent ions in single primitive AB types are $z_i^2$ times as great as those of monovalent ions in the same lattice type ($z_i$ = number of unit charges on the ion in question).

[16] *J. Zemann*, Acta crystallogr. *11*, 55 (1958).

[*] They were recently calculated as functions of c/a; see [13a].

## VI. Relationships between the Madelung Constants of Single Primitive AB Types [17]

The Madelung constants of more complex structural types can all be expressed (cf. Section IV) as the sum of the Madelung constants of single primitive cells of the same size. It was assumed, therefore, that the Madelung constants of primitive AB types are not mutually related ("independent" Madelung constants) [8]; however, this assumption is wrong [17]:

Any single primitive AB structure, irrespective of the size and symmetry of its unit cell, can be described by a non-primitive pseudo-cell obtained by multiplication of one, two, or all three of the principal axes; this naturally does not change the Madelung constant, which can therefore be expressed as the sum of the Madelung constants of other single primitive AB types. If the non-primitive pseudo-cell is based on m times the a-axis, n times the b-axis, and p times the c-axis, we have

$$^{\circ}MF(x,y,z) = \sum_{r=0}^{m-1}\sum_{s=0}^{n-1}\sum_{t=0}^{p-1} \alpha_{rst}\ {}^{\circ}MF\left(\frac{x+r}{m},\frac{y+s}{n},\frac{z+t}{p}\right) - \sum_{r'=0}^{m-1}{\sum_{s'=0}^{n-1}}'{\sum_{t'=0}^{p-1}}' \alpha_{r's't'}\ {}^{\circ}MF\left(\frac{r'}{m},\frac{s'}{n},\frac{t'}{p}\right) \quad (7)$$

In this equation, the primes in $\Sigma'$, r', s', and t' indicate that the relationship r' = s' = t' = 0 must not be valid. The factors $\alpha_{rst}$ and $\alpha_{r's't'}$ are simple numbers depending on the geometry of the structure, and ensuring that the values of °MF are correctly weighted and normalized in the summation.

For example, if we describe the CsCl structure by eight times the primitive cell, we obtain

$$MF\left(\tfrac{1}{2},\tfrac{1}{2},\tfrac{1}{2}\right)_k = \tfrac{16}{3} \times MF\left(\tfrac{1}{4},\tfrac{1}{4},\tfrac{1}{4}\right)_k - \sqrt{3} \times MF\left(\tfrac{1}{2},0,0\right)_k - \frac{\sqrt{3}}{\sqrt{2}} \times MF\left(\tfrac{1}{2},\tfrac{1}{2},0\right)_k \quad (8)$$

These unexpected and surprising relationships between the Madelung constants of single primitive AB types, which exist in every case irrespective of size and symmetry of the unit cell, indicate that we are still far from a real understanding of the Madelung constants. They also suggest that other numerical relationships may exist between the Madelung constants of single primitive AB types with isometric unit cells.

## VII. Relationships between the Partial Madelung Constants of Primitive AB Types and of Interstitial Sites [17]

If we consider an infinitely large crystal of a primitive AB structure, and assume that only one interstitial site is occupied by an additional ion, the partial Madelung constant of this ion can be expressed as a sum of partial Madelung constants of single primitive AB types, and can then provide information about the energy of interstitial sites; defects can also be taken into account in this calculation by the use of additional terms.

For example, the partial Madelung constant of a cation $X^+$ occupying the position $^1/_2, ^1/_2, 0$ in one unit cell only of a CsCl-type crystal ($A^+$ in 0,0,0 and $B^-$ in $^1/_2, ^1/_2, ^1/_2$) is:

$$PMF(X^+) = PMF\left(\tfrac{1}{2},0,0\right) - \frac{\sqrt{2}}{2} \times PMF\left(\tfrac{1}{2},\tfrac{1}{2},0\right) = 0.2432946_6 \quad (9)$$

[17] *R. Hoppe*, unpublished work.

## VIII. Reduced Partial Madelung Constants

In isotypic compounds of the same formula type, but with different valences (*e.g.* $Cu^{+}Cl^{-}$, $Zn^{2+}S^{2-}$, $Ga^{3+}As^{3-}$), the partial Madelung constants of the "cations" are related as the squares of the valences $z_i^2$, if the valence factor $f(z_i)$ from Equation (1) is included in the Madelung constant. Similar relationships exist for more complex structures. In addition to the partial Madelung constants $PMF(A^{m+})$ and $PMF(B^{n-})$, it is therefore convenient to define reduced partial Madelung constants [10,18] as the partial Madelung constants divided by $z_i^2$, *i.e.*

$$*PMF(A^{m+}) \equiv \frac{PMF(A^{m+})}{m^2} \quad \text{and} \quad *PMF(B^{n-}) \equiv \frac{PMF(B^{n-})}{n^2}$$

These quantities enable us to compare the potentials in compounds of different types and with different ionic charges.

The reduced partial Madelung constants are strongly affected by the peculiarities of the crystal structures, and (unfortunately) are by no means constant. A number of typical values are given in Table 2, and Figure 3 shows how the reduced partial Madelung constants of cations vary with the coordination number and the ionic charge.

The reduced partial Madelung constants as found from Figure 3 are maximum values, and the values found for real structures are usually lower. For the "coordination number" in such cases, see Section IX.

Table 2. Reduced partial Madelung constants *PMF of the cations in typical binary crystal structures.

| Ion | Compound | Type | *PMF($A^{m+}$) |
|---|---|---|---|
| $Na^{+}$ | NaCl | NaCl | 0.874... |
| $Ca^{2+}$ | $CaF_2$ | $CaF_2$ | 0.819... |
| $Bi^{3+}$ | $BiF_3$ | $Li_3Bi$ | 0.797... |
| $Sc^{3+}$ | $ScF_3$ | $ReO_3$ | 0.685... |
| $Sn^{4+}$ | $SnF_4$ | $SnF_4$ | 0.657... |
| $A^{4+}$ | $AB_4$ | 8 B in: 0,0,0 | 0.701... |
| | 2 A in: $^1/_4, ^1/_4, ^1/_4$ | $^1/_2, 0, 0$ | |
| | $^3/_4, ^3/_4, ^3/_4$ | $0, ^1/_2, 0$ | |
| | | $0, 0, ^1/_2$ | |
| | | $^1/_2, ^1/_2, 0$ | |
| | | $^1/_2, 0, ^1/_2$ | |
| | | $0, ^1/_2, ^1/_2$ | |
| | | $^1/_2, ^1/_2, ^1/_2$ | |
| $Nb^{5+}$ | $NbCl_5$ | $NbCl_5$ | 0.551... |

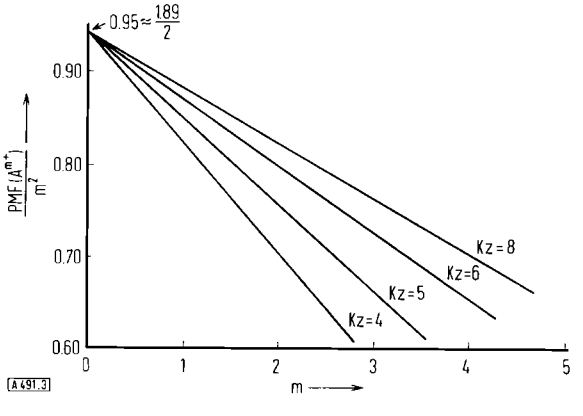


Fig. 3. Maximum values of reduced partial Madelung constants [13a] of cations as a function of charge (m) and coordination number (Kz).

[18] *D. H. Templeton*, J. chem. Physics *21*, 2097 (1953); *23*, 1826 (1955).

## IX. The Madelung Constant as a Function of Structure-Determining Factors such as Composition and Coordination Number

Many attempts have been made to estimate Madelung constants. *Klemm* [13], in his simplified expression (10) for the lattice energy, introduced an "effective" Madelung constant a'.

$$-U_{g(exp)} = \frac{a' \times N_L \times e^2}{r_{KA}} \qquad (10)$$

He showed that a' is practically constant for chemically similar compounds of analogous composition, but depends strongly on the formula type and on the bonds present. (The terms $E_{nC}$ and $E_{corr}$ of Equation (1) are here included in a').

*Kapustinskii* [12] then showed that the lattice energies of many compounds can be calculated from Equation (11), often with good accuracy.

$$U_g = \left[\frac{287.2 \times Z \times z_A \times z_B}{r_{KA}}\right]\left[1 - \frac{0.345}{r_{KA}}\right] \text{[kcal/mole]} \qquad (11)$$

($z_A$ and $z_B$ are the ionic charges of A and B, and Z is the number of atoms per formula unit.) In this case the Madelung constant is considered as independent of the coordination numbers of the particles A and B in the binary compound $A_mB_n$, since Equation (11) is based on Equation (12):

$$MF(A_mB_n) = \frac{z_A \times z_B \times Z \times \text{const.}}{2} \equiv \frac{z_A \times z_B \times Z \times MF(NaCl)}{2} \qquad (12)$$

It is surprising to find that (contrary to the results of calculations, which give a different Madelung constant for each structural type) MF(NaCl) may be used for all possible AB structures. For other binary structural types, a simple calculation with the aid of Equation (12) gives effective Madelung constants that should depend only on the composition, *i.e.* on the formula type, and not on structural pecularities! The explanation for this is as follows:

In binary compounds, we have:

$$z_A \times z_B \times Z \equiv \sum z_i^2. \qquad (13)$$

Thus, according to *Kapustinskii* [Equations (11) and (12)]:

$$MF(A_mB_n) = \sum z_i^2 \times \frac{MF(NaCl)}{2} = \sum z_i^2 \times PMF(Na^{+}_{NaCl}). \qquad (14)$$

It can be seen that, although *Kapustinskii* himself failed to notice it, this expression implicitly represents any Madelung constant as the sum of partial Madelung constants [10].

*Kapustinskii* also assumed that all compounds can be regarded as "NaCl derivatives" [in Equation (11) the shortest interionic distance $r_{KA}$ is assumed for the coordination number 6], a view that has also been expressed by other authors (cf. *e.g.* [19]).

To understand this apparently bold simplification, it must be remembered that a deviation from the coordination number 6

[19] *T. C. Waddington*, Trans. Faraday Soc. *56*, 305 (1960).

in a real structure rather frequently leads to *lower* coordination numbers, and nearly always results in lower partial Madelung constants, and hence in smaller Madelung components of the lattice energy. However, such a deviation can occur only if additional (*e.g.* covalent) bonds ensure that the decrease in the Madelung component of the lattice energy is overcompensated in some other way. If the overcompensation is comparatively slight, *Kapustinskii*'s equation (14) is applicable, even for compounds that cannot be considered as consisting predominantly of ions. For coordination numbers above 6, the Madelung component of the lattice energy again changes only slightly, as can be seen from a comparison of the Madelung constants of the NaCl and CsCl types. Moreover, the shortest distance $d_{KA}$, too, depends on the coordination number and always changes in the same direction as the Madelung constant. Thus alterations of the Madelung constant are in part "internally" compensated.

If one does not wish to calculate lattice energies from Equation (11), but to estimate Madelung constants from Equation (12), it is more convenient in the case of binary compounds [7] to use Equation (15)

$$MF(A_mB_n) = \frac{1}{2} \times \sum z_i^2 \times \beta \qquad (15)$$

in which $\beta$ = MF(NaCl) is replaced by the more accurate:

$$\beta + (\beta/p)^2 = 1.81 \qquad (16)$$

In Equation (16), $\bar{p}$ is the "average" coordination number of A and B [*i.e.* $^1/_3(8+2\times4)=5.33$ for the $CaF_2$ type].

*Templeton* [18] later also attempted to represent Madelung constants of binary compounds as functions of the coordination number; he used the empirical equation (17)

$$MF = 1.89 - 1/p_h \qquad (17)$$

in which $p_h$ is the weighted harmonic mean of the coordination numbers of A and B. The fact that all the straight lines in Fig. 3 meet at 1.89/2 is probably closely connected with Equation (17). The approximations used by *Hoppe* [Eq. (15)] and by *Templeton* give practically the same results, as can be seen from the examples in Table 3.

Table 3. Madelung constants MF of the CsCl, NaCl, and ZnS types.

| | *Hoppe* [7] | *Templeton* [18] | Exact value |
|---|---|---|---|
| CsCl | 1.761 | 1.765 | 1.7626... |
| NaCl | 1.727 | 1,723 | 1.7475... |
| $Zn^+S^-$ | 1.638 | 1.640 | 1.6380... |

However, there is no strict relationship between the Madelung constant and the coordination number! Such a functional relationship does not exist even in the case of the Madelung constants °MF of single primitive AB structures. The reason is the simplicity of the concept of the coordination number, *i.e.* the fact that only the nearest neighbors (with opposite charges) are counted for compounds considered as consisting of ions, whereas the partial Madelung constants take into account the interactions of one ion with all the others, however far away and whatever the sign of their charge. Furthermore, in the case of more complex structures (*e.g.* crystal structures of the NaSi type [20]), it is impossible to be completely objective in deciding

[20] *W. Klemm, J. Witte*, and *H. G. v. Schnering*, Z. anorg. allg. Chem. *327*, 260 (1964).

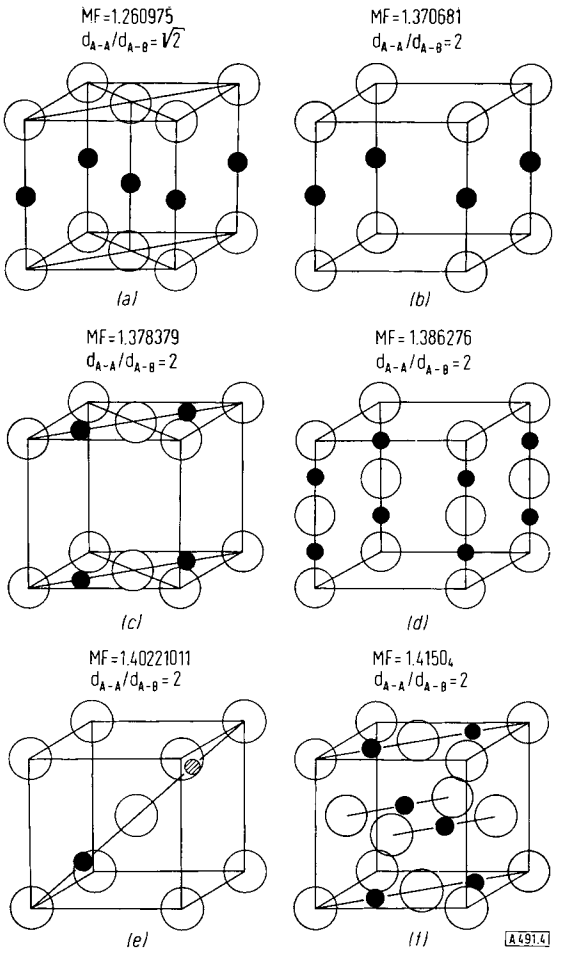


Fig. 4. Simple AB structures with the same "simple" coordination number, and the corresponding Madelung constants (sizes of the particles chosen arbitrarily).

which are the "nearest" neighbors. To illustrate this, Figure 4 shows some simple AB structures the coordination numbers of which, when counted on the basis of the simple definition, are the same. The Madelung constants [17] of these structures, on the other hand, show the influence of the arrangements of the A and B sub-lattices. From Figure 5 it can be seen how the Madelung constant is affected by the nature of the A and B sub-lattices (as a function of the coordination number) (cf. also Table 4).

Table 4. Madelung constants of simple cubic AB types. — C.N. = coordination number.

| C.N. | cubic primitive | cubic body-centered sub-lattices start in | cubic face-centered |
|---|---|---|---|
| 2 | $A^+$: 0,0,0<br>$B^-$: $^1/_2$,0,0<br>MF = 1.37068... | 0,0,0<br>$^1/_4$,$^1/_4$,$^1/_4$<br>MF = 1.40221... | 0,0,0<br>$^1/_4$,$^1/_4$,0<br>MF = 1.41504... |
| 3 | | $A^+$: 0,0,0<br>$B^-$: $^1/_2$,$^1/_8$,$^1/_8$<br>MF = 1.56968... | |
| 4 | $A^+$: 0,0,0<br>$B^-$: $^1/_2$,$^1/_2$,0<br>MF = 1.59436 | | 0,0,0<br>$^1/_4$,$^1/_4$,$^1/_4$<br>MF = 1.63804... |
| 6 | | | $A^+$: 0,0,0<br>$B^-$: $^1/_2$,0,0<br>MF = 1.74755... |
| 8 | $A^+$: 0,0,0<br>$B^-$: $^1/_2$,$^1/_2$,$^1/_2$<br>MF = 1.76267... | | |

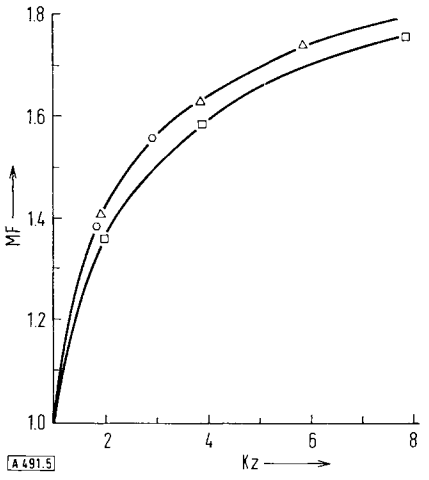


Fig. 5. Madelung constants and "simple" coordination numbers of simple cubic AB types with commutative sub-lattices. Primitive (□), face-centered (△), and body-centered (○) sub-lattices. Kz = coordination number.

The estimation of Madelung constants or the deduction of "effective coordination numbers" from calculated partial Madelung constants will always raise difficulties, since the precisely defined Madelung constant cannot be readily related to the rather vague though useful concept of the "coordination number".

Estimations of this nature are best carried out with the aid of Equation (18), in which $*PMF_i$ is the reduced partial Madelung constant and $z_i$ is the charge; $p_i$ corresponds to $m_j$ or

$$MF = \sum z_i^2 \cdot p_i \cdot *PMF_i \qquad (18)$$

$n_r$ of Equation (2b), and the summation is carried out as in Equation (2b). The $*PMF_i$ are found from comparable structures, or from graphs as in Figure 7.

## B. Special Part

The Madelung constant of a structural type is of interest for the discussion of enthalpies of formation. However, it acquires a more general importance only when considered in relation to other Madelung constants. An "observed" crystal structure is only one of many, since it is "surrounded" by a large number of other structures (*e.g.* thermodynamically less stable modifications) which are fundamentally possible, but which do not occur at thermodynamic equilibrium or have not so far been found.

It is particularly interesting in this connection to find how the Madelung constant of a structural type changes:

(a) when greater or smaller changes in the size and/or in the symmetry of the unit cell occur, while the coordinates of the particles remain constant in relation to the new axes, *i.e.* when the unit cell undergoes homogeneous affine transformations,

(b) when the coordinates of the particles change in parameter-dependent structural types, while the size of the unit cell remains unaltered, or

(c) when the changes described under (a) and (b) occur simultaneously.

In the following sections, therefore, we shall discuss, not only individual Madelung constants, but mainly their dependence on the variations mentioned.

### I. Madelung Constants of AB Types [10,17]

Homogeneous affine transformations lead to changes in the lengths of the axes and in the angles formed by them. For the sake of simplicity, the following examples are confined to special transformations in which the angle remains unchanged, and in which the changes in the principal axes can be expressed by one figure (the axial ratio c/a).

#### 1. Changes in the Madelung Constants on Tetragonal Compression or Elongation of a Cubic Unit Cell [8]

The following general rule is valid here, as for any other structure:

Any affine transformation of a structural type with a finite Madelung constant gives a new structure which also has a finite Madelung constant if the shortest distance $d_{A-B}$ remains smaller than the shortest distances $d_{A-A}$ and $d_{B-B}$. On the other hand, when the ratio $d_{A-A}/d_{A-B}$ or $d_{B-B}/d_{A-B}$ approaches zero, the Madelung constant approaches $-\infty$. It is assumed here that the Madelung constant is always based on the shortest distance $d_{A-B}$.

Table 5 contains some typical examples of Madelung constants of AB structures with single primitive unit cells derived from cubic unit cells by tetragonal compression or elongation. A characteristic feature is that

Table 5. Changes in the Madelung constants MF of cubic AB structures on tetragonal affine transformation of the unit cell [8]. $A^+$ in: 0,0,0; $B^-$ in: x,y,z [8].

| x,y,z \ c/a | 0 | 1/2 | 1 | 2 | ∞ |
|---|---|---|---|---|---|
| 0,0,1/2 | 1.386... | 1.386... | 1.770... | 0.774... | −∞ |
| 1/2,0,0 | −∞ | 1.127... | 1.370... | 1.378... | |
| 1/2,1/2,0 | −∞ | 1.095... | 1.594... | 1.615... | 1.615... |
| 1/2,1/2,1/2 | −∞ | 1.158... | 1.762... | 0.911... | −∞ |
| 1/2,0,1/2 | −∞ | 1.244... | 1.594... | 0.848... | −∞ |
| 1/4,1/4,0 | −∞ | 0.934... | 1.087... | | |
| 1/4,0,0 | −∞ | 0.971... | 1.035... | | |

the Madelung constant of the CsCl type falls off rapidly towards $-\infty$ on compression or elongation. That of the NaCl structure, on the other hand, remains finite, as can be seen from Table 6.

Table 6. The Madelung constant of the NaCl type on tetragonal affine transformation of the unit cell [8].

| c/a | MF |
|---|---|
| 0 | 1.3862... |
| 1 | 1.7475... |
| ∞ | 1.615... |

#### 2. Changes in the Madelung Constants on Hexagonal Compression or Elongation of a Cubic Unit Cell [10]

The CsCl and NaCl structures, which are fundamentally different in their cubic arrangements, are found to be

affinely transformed in the hexagonal arrangement (cf. Table 7).

Table 7. NaCl and CsCl types as affine transformations of the same structure. The letters A, a, B, b, C, c denote the positions of the particles with the coordinates given. The cation sites are denoted by capital letters and the anion sites by small letters.

| z | | |
|---|---|---|
| 1 | o o o o o o A | A (and a): 0,0,z |
| 5/6 | + + + + + + b | B (and b): 1/2, 2/3, z |
| 4/6 | o o o o o o C | C (and c): 2/3, 1/3, z |
| 3/6 | + + + + + + a | c/a = $\sqrt{6}$ : NaCl-type |
| 2/6 | o o o o o o B | c/a = $\sqrt{3/2}$ : CsCl-type |
| 1/6 | + + + + + + c | |
| 0 | o o o o o o A | |

As we pass from the CsCl type (c/a = $\sqrt{6}/2$) to the NaCl type (c/a = $\sqrt{6}$), the simple coordination number changes continuously from 8 to 6. If there were a direct relationship between the simple coordination number and the Madelung constant, the latter should change in the same direction as the coordination number, *i.e.* $\partial(MF)/\partial(c/a) \neq 0$ between the values given for c/a. However, it can be seen from Figure 6 that this is not the case. The two Madelung constants MF(CsCl) and MF(NaCl) are, in fact, separated by a minimum.

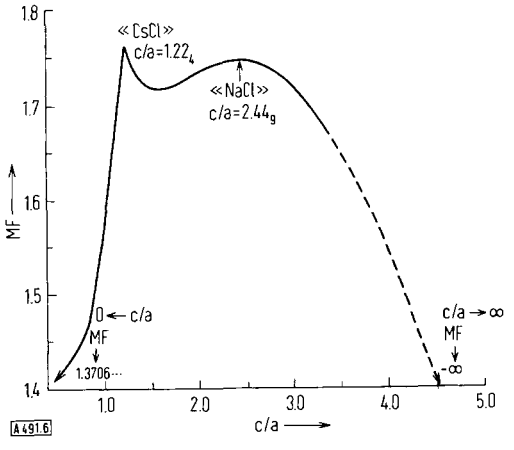


Fig. 6. Dependence of the Madelung constants of the CsCl and NaCl types on the ratio c/a in the hexagonal arrangement[10].

The change in the Madelung constants is also affected by the fact that during hexagonal elongation along [001], the shortest distance $d_{A-B}$ in the CsCl type increases rapidly for two (or six on analogous compression) of the original eight equally distant neighbors. The steep fall in MF(CsCl) for both larger and smaller values of c/a is directly related to this effect. Conversely, the relatively small decrease in MF(NaCl) on both sides of c/a = $\sqrt{6}$ is due to the fact that the six nearest neighbors do *not* split up into non-equivalent groups.

The characteristic changes in the Madelung constants of these two binary structural types are related to the fact that, although the structures of many ternary compounds (double oxides, double fluorides) are variants of the NaCl type (*e.g.* the important α-$NaFeO_2$ type), no corresponding variants of the CsCl type have so far been found.

The sphalerite type, in which the A and B sub-lattices are arranged somewhat differently (Table 8) also belongs to this group. Here the Madelung constant MF(ZnS) decreases monotonically on both sides of c/a = $\sqrt{8}/3$,

Table 8. Schematic representation of the ZnS structure. (For explanation of the symbols, see Table 7.)

| z | | |
|---|---|---|
| 1 | o o o o o o o o o o A | A (and a): 0,0,z |
| 11/12 | + + + + + + + + + + c | B (and b): 1/3, 2/3, z |
| | | C (and c): 2/3, 1/3, z |
| 8/12 | o o o o o o o o o o C | c/a = $\sqrt{6}$ : Zinc blende type |
| 7/12 | + + + + + + + + + + b | |
| 4/12 | o o o o o o o o o o B | |
| 3/12 | + + + + + + + + + + a | |
| 0 | o o o o o o o o o o A | |

Table 9. Schematic representation of the ZnO structure. (For explanation of the symbols, see Table 7.)

| z | | |
|---|---|---|
| 1 | o o o o o o o o o o A | A (and a): 0,0,z |
| 7/8 | + + + + + + + + + + b | B (and b): 1/3, 2/3, z |
| 4/8 | o o o o o o o o o o B | |
| 3/8 | + + + + + + + + + + a | c/a = $\sqrt{8/3}$: ideal ZnO type |
| 0 | o o o o o o o o o o A | |

approaching 1 for c/a → 0, and $-\infty$ for c/a → ∞ (cf. Figure 7). The Madelung constant of the wurzite type shows a similar dependence on c/a, although (as can be seen from Table 9) this type consists of hexagonally close-packed sequences of A and B particles.

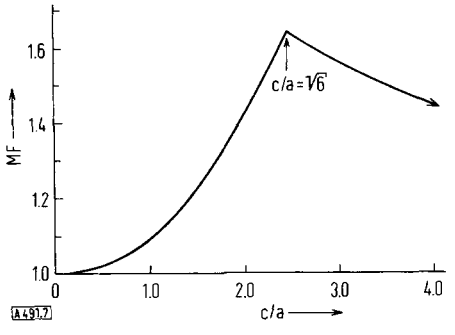


Fig. 7. Dependence of the Madelung constant of the sphalerite type on the ratio c/a in the hexagonal arrangement.

An example of an AB structure with non-commutative sub-lattices is the NiAs type (cf. Table 10), the Madelung constant of which (Fig. 8) also passes through a maximum[16], and approaches $-\infty$ for c/a → 0 and for c/a → ∞.

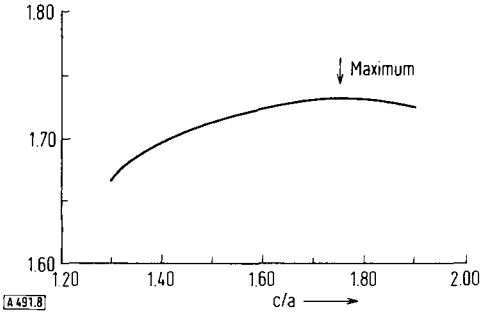


Fig. 8. Dependence of the Madelung constant of the NiAs type (non-commutative sub-lattices) on the ratio c/a [16].
Ordinate: Madelung constant.

Table 10. Schematic representation of the NiAs structure. (Ni: c; As: A, B; for explanation of the symbols, see Table 7).

| z | | |
|---|---|---|
| 1 | o o o o o o o o o o A | A: 0,0,z |
| 3/4 | + + + + + + + + + + c | B: 1/3,2/3,z |
| 1/2 | o o o o o o o o o o B | c: 2/3,1/3,z |
| 1/4 | + + + + + + + + + + c | |
| 0 | o o o o o o o o o o A | |

## II. Madelung Constants of Complicated Structural Types

Recently calculated Madelung constants of some important structural types are listed in Table 11 (see below).

### 1. The Madelung Constant of the Rutile Structure

In the rutile type $AB_2$, each cation A has only six equally distant neighbors B if the axial ratio c/a and the parameter x of the anion are related as

$$x = 1/4 + c^2/8a^2 \qquad (19)$$

*Bollnow*[21] has calculated MF(rutile) for a number of values of c/a and x that satisfy Equation (19). A recent detailed publication[22] suffers from the disadvantage that MF(rutile) is based, not on the shortest A–B distance (or some other simple difference), but on an undefined average of the distances to the six neighbors 4+ 2!), which are generally not all equal; the nature of this average cannot be deduced from the values given, but it is obviously not a simple mean. Moreover, since the difference between the Madelung constant and the Madelung component of the lattice energy is overlooked, some of the conclusions drawn are incorrect.

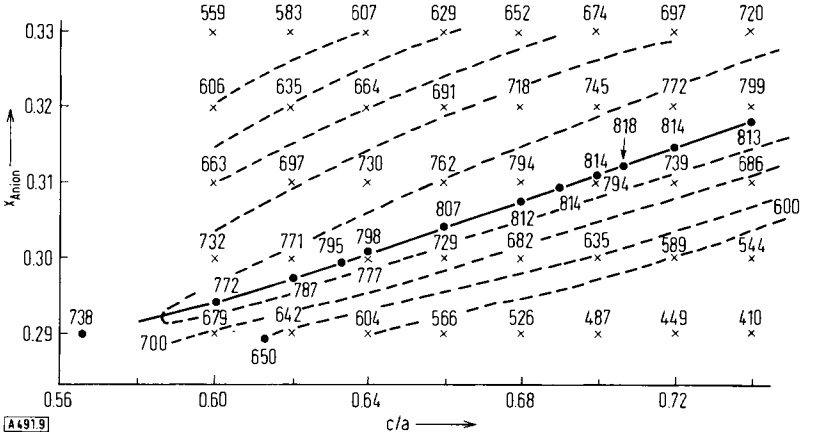


Fig. 9. Two-dimensional diagram of a three-dimensional representation of the Madelung constants of rutile as a function of $x_{anion}$ and c/a in accordance with Equation (19). The figures beside the curves are [MF(rutile)−4]× $10^3$.

Figure 9 shows MF(rutile) as a function of c/a and x[10]. The following points can be observed:

1. The Madelung constant has a maximum for c/a = $\sqrt{2}/2$ and x = 5/16 [in accordance with Equation (19)].

It became known only recently that this maximum is due to the structural geometry of the rutile type[17]. Thus if we start with a body-centered arrangement of the anions with regularly occupied quasi-octahedral holes (cf. Figure 10) the significance of the ratio c/a = $\sqrt{2}/2$ becomes immediately obvious: For this ratio the cubic sub-lattice (as indicated in Figure 10) and the favorable arrangement of the cations (with the charges +2 or +4) remain unchanged.

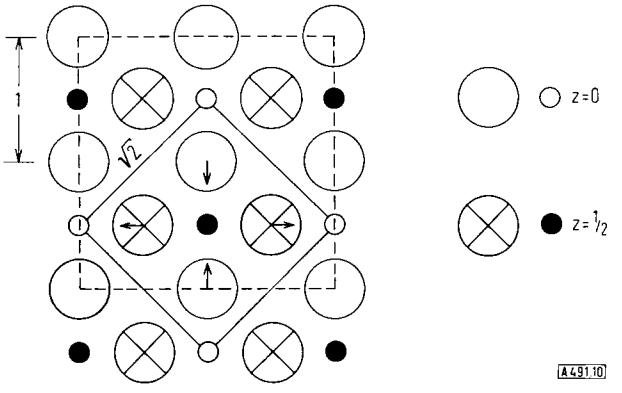


Fig. 10. Structural geometry of the rutile type. The lengths and directions of the arrows show the displacement of the anions to the true positions (sizes of the particles chosen arbitrarily).

2. No known compound with a rutile structure corresponds to this ideal case. This is at least partly due to the fact that the "grid" of Madelung factors (Figure 9) is calculated for point-shaped ions and does not take into account finite and even fixed ionic radii.

In typical rutile-type compounds $AB_2$, such as difluorides (*e.g.* $ZnF_2$) and dioxides (*e.g.* $SnO_2$), the ratio of the distances $d_{A-B}$ (1.9 to 2.1 Å) and $d_{B-B}$ (2.6 to 2.7 Å) is expected to be between 0.7 and 0.8. From the maximum of the Madelung constant at c/a = $\sqrt{2/2}$ and x = 5/16, it follows that $d_{A-B}/d_{B-B} = 0.83$ [by comparison, for c/a = 0.6 and x = 0.295, we find $d_{A-B}/d_{B-B} = 0.72$]; the deviations towards c/a < $\sqrt{2/2}$ are therefore understandable to some extent.

3. Even with a knowledge of the Madelung constants, it is not possible to discuss the question of why the parameters of a given rutile-type compound (*e.g.* $ZnF_2$) have the observed values (c/a = 0.666, x = 0.303: cf.[23]) instead of other values close to these.

Thus if these parameters are slightly changed, it can be assumed that the shortest distance $d_{A-B}$ [2.01$_5$ Å (2×) for $ZnF_2$] will remain constant as is required by the concept of

[21] *O. F. Bollnow*, Z. Physik *33*, 741 (1925).

[22] *W. H. Baur*, Acta crystallogr. *14*, 209 (1961).

[23] *W. H. Baur*, Acta crystallogr. *9*, 515 (1956); *11*, 488 (1958).

fixed ionic radii, or that the molar cell volume [20.87 cm³ for $ZnF_2$] will remain unchanged, as is to be expected if the volume increments of the various ions are constant. Examples are known which show that neither of these two concepts (which are mutually exclusive, cf. [24]) is strictly correct. This means that in the Madelung component of the lattice energy [Equation (1)] of "adjacent" rutile-type compounds, the numerator can be given accurately, but not the denominator (the shortest distance $d_{A-B}$). This difficulty is encountered with all parameter-dependent structures.

4. Finally it should be borne in mind that abnormally short distances $d_{B-B}$ are found in dioxides with rutile structures, such as $SnO_2$ and $TiO_2$ (the shortest O–O distance in $TiO_2$ is 2.53 Å). The only other cases in which such short distances are found are complex anions, *e.g.* $SO_4^{2-}$, $PO_4^{3-}$, or where strong hydrogen bonding occurs. These short distances are due to the strong polarization of the $O^{2-}$ particles by the highly charged cations ($Ti^{4+}$ *etc.*); they show that the picture of a compound consisting of rigid ions must be modified for these dioxides.

## 2. The Madelung Constant of the Anatase Structure

The anatase structure also depends on two parameters, namely the ratio c/a of the tetragonal unit cells (cf. Figure 11) and the parameter $z_O$ of the anions. For c/a = 2.0 and $z_O = 1/4$, we have a variant of the NaCl type in which half of the cation sub-lattice has been removed

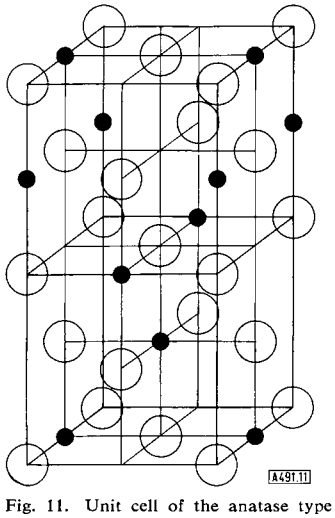


Fig. 11. Unit cell of the anatase type (sizes of the particles chosen arbitrarily).

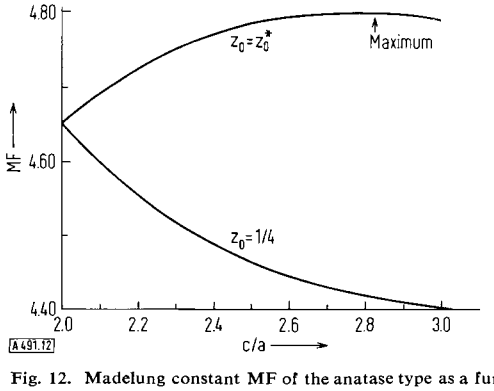


Fig. 12. Madelung constant MF of the anatase type as a function of c/a and $z_O$ [13a].

[24] *W. Biltz*: Raumchemie der festen Stoffe. W. de Gruyter, Leipzig 1934.

systematically. Figure 12 shows the variation of the Madelung constant MF(anatase), and Figure 13 shows the variation of the partial Madelung constants for two limiting cases: in the first case, c/a varies while $z_O$ (=1/4) remains constant [six originally equally distant B neighbors of each A particle become unequally distant (4+2) as c/a increases], and in the second case $z_O$ changes with c/a in accordance with Equation (20)

$$z_O^* = 1/8 + a^2/2c^2 \qquad (20)$$

(in this case, each A particle remains surrounded by six equally distant B particles). It is interesting to note that in compounds of the "filled-up" anatase type ($\alpha$-$LiFeO_2$ type), that have been studied so far, $z_O \approx z_O^*$, *i.e.* for any given c/a the arrangement of the O particles is such as to give the optimum Madelung constant [5, 24a].

## 3. Madelung Constants of Complex Structures

It can be seen from Figure 1b that in the case of coordination compounds, the Born-Haber cycle can be applied in various ways; the term "complexing energy" is also used with various meanings (it can be defined by steps IIIa or IIIb′ in Figure 1b [25]). In stating the Madelung constants of complex structures, therefore, it is particularly important to specify the reference distance. The values in Table 11 are based on the shortest central ion-ligand distance in each case.

Table 11. Madelung constants of other structural types.

| Compound | Type | Type | MF | Ref. |
|---|---|---|---|---|
| $SiO_2$ | High cristobalite | $A^{2+}B_2^-$ | $4.453_4$.. | [9] |
| | Low cristobalite | $A^{2+}B_2^-$ | 4.428 | [9] |
| $ZnF_2$ | Rutile type ($ZnF_2$ parameter) | $A^{2+}B_2^-$ | $4.765_6$.. | [10, 13a] |
| $NbCl_4$ | individual type | $A^{4+}B_4^-$ | $12.65_0$.. | [9] |
| $SnF_4$ | individual type | $A^{4+}B_4^-$ | $14.08_4$.. | [10, 13a] |
| $SnI_4$ | individual type | $A^{4+}B_4^-$ | $12.43_9$.. | [10] |
| $BiF_3$ | $Li_3Bi$ type | $A^{3+}B_3^-$ | $9.57_3$.. | [7] |
| $FeCl_3$ | individual type | $A^{3+}B_3^-$ | $8.26_1$.. | [9] |
| $TiI_3$ | individual type | $A^{3+}B_3^-$ | $7.73_8$.. | [9] |
| $MoCl_3$ | individual type | $A^{3+}B_3^-$ | $7.67_3$.. | [9] |
| $NbOI_2$ | individual type | $A^{4+}B^{2-}C_2^-$ | $13.54_2$.. | [9] |
| $NbOCl_2$ | individual type | $A^{4+}B^{2-}C_2^-$ | $14.31_4$.. | [9] |
| $MoOCl_2$ | individual type | $A^{4+}B^{2-}C_2^-$ | $14.09_9$.. | [9] |
| $KAlF_4$ | individual type | $A^+B^{3+}C_4^-$ | $10.09_3$.. | [9] |
| | | $A^{2+}B^{2+}C_4$ | $7.86_7$.. | [9] |
| $K_2NiF_4$ | individual type | $A_2^+B^{2+}C_4^-$ | $7.50_8$.. | [10] |
| $K_2GeF_6$ | individual type | $A_2^+B^{4+}C_6^-$ | 16.199.. | [9] |
| | | $A_2^{2+}B^{2+}C_4^-$ | 11,154.. | [9] |
| $Na_2Sn(OH)_6$ | individual type | $A_2^{2+}B^{4+}C_6^-$ | $16.18_8$.. | [9] |
| | individual type | $A_2^{2+}B^{2+}C_6^-$ | $11.55_3$.. | [9] |
| $Ba_2ZnF_6$ | individual type | $A_2^+B^{4+}C_6^-$ | $14.59_2$.. | [9] |
| | individual type | $A_2^{2+}B^{2+}C_6^-$ | $11.79_1$.. | [9] |
| $K_2PtCl_6$ | individual type | $A_2^+B^{4+}C_6^-$ | 15.873 | [9] |
| | individual type | $A_2^{2+}B^{2+}C_6^-$ | $11.79_2$.. | [9] |
| $K_2MnF_6$ | individual type | $A_2^+B^{4+}C_6^-$ | $15.98_4$.. | [9] |
| | individual type | $A_2^{2+}B^{2+}C_6^-$ | $11.03_1$.. | [9] |

## III. Madelung Constants of Molecular Lattices

Compounds such as $BrF_5$, $SiF_4$, $SbCl_3$, and $XeF_2$ form solids with structures in which the building units are individual molecules. Typical covalent bonds seem to

[24a] *R. Hoppe, B. Schepers, H. J. Röhrborn*, and *E. Vielhaber*, Z. anorg. allg. Chem. *339*, 130 (1965).

[25] *R. Hoppe*, Z. anorg. allg. Chem. *291*, 4 (1957).

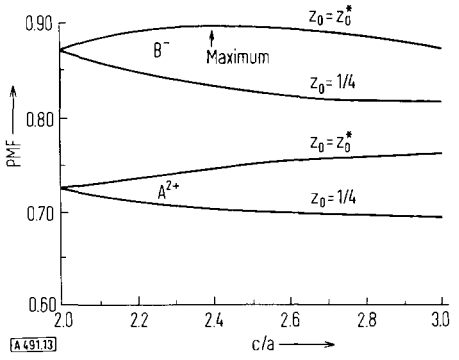


Fig. 13. Partial Madelung constants PMF of the anatase type as functions of c/a and $z_0$ [13a].

be present here. With the exception of *Klemm*'s effective Madelung constants [13], little was previously known about the Madelung constants of such structures. It is of interest, however, how these Madelung constants are related to those of typically ionic compounds. The Madelung constants of $XeF_2$, $XeF_2 \cdot XeF_4$, and $XeF_4$ are therefore briefly discussed in the following sections.

## 1. The Madelung Constant of the $XeF_2$ Structure [1a]

Linear F–Xe–F molecules are present in the tetragonal unit cell of xenon difluoride (cf. Figure 14). The PMF values and the Madelung constant of this structure are given in Table 12. PMF($Xe^{2+}$) for the coordination number 2 fits readily into the pattern of PMF($A^{2+}$) values for higher coordination numbers, as does the Madelung constant MF($XeF_2$) itself [*]. Thus $XeF_2$ is distinctly polar, in agreement with spectroscopic findings (cf. [1a]). This explains the apparently large enthalpy of sublimation (12.3 kcal/mole).

## 2. The Madelung Constant of the $XeF_2 \cdot XeF_4$ Structure

The composition of the double fluoride $XeF_2 \cdot XeF_4$, which still seems not to have been confirmed by analysis, was deduced from X-ray analysis (cf. Figure 15). Table 12 shows the individual PMF values and the Madelung constants for the components $XeF_2$ and $XeF_4$ in the addition compound. All values are of the expected magnitude.

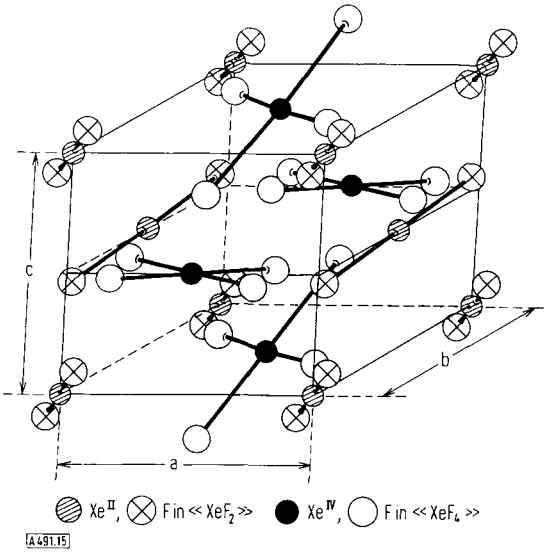


Fig. 15. Crystal structure of $XeF_2 \cdot XeF_4$ (a = 6.64 Å, b = 7.33 Å, c = 6.40 Å, β = 92°40') (sizes of the particles chosen arbitrarily).

Table 12. Comparison of Madelung constants and partial Madelung constants of $XeF_2$, $XeF_2 \cdot XeF_4$, and $XeF_4$ [1a].

| | $XeF_2 \cdot XeF_4$ | $XeF_2$ | "$XeF_2$" in $XeF_2 \cdot XeF_4$ | $XeF_4$ | "$XeF_4$" in $XeF_2 \cdot XeF_4$ | $SiF_4$ |
|---|---|---|---|---|---|---|
| Reference distance Xe–F[Å] | 1.909 | 1.983 | 1.995 | 1.932 | 1.909 | Si–F |
| PMF ($Xe^{2+}$) | 2.49848 | 2.4494 | 2.61051 | 9.4138 | | PMF($Si^{4+}$) = |
| PMF ($Xe^{4+}$) | 9.03938 | | | | 9.03938 | 8.8262 |
| PMF ($F_I^-$) | 0.60535 | 0.6749 | 0.63250 | | | PMF($F^-$) = |
| PMF ($F_{II}^-$) | 0.86372 | | | 0.8233 | 0.86372 | 0.9157 |
| PMF ($F_{III}^-$) | 0.86209 | | | 0.8184 | | |
| MF | 16.200 | 3.7992 | 3.87550 | 12.6972 | 12.4910 | 12.4889 |

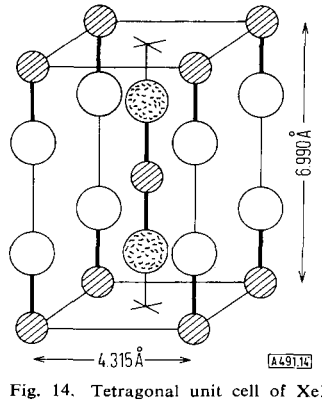


Fig. 14. Tetragonal unit cell of $XeF_2$ (sizes of the particles chosen arbitrarily).

[*] For details, see [1a].

## 3. The Madelung Constant of the $XeF_4$ Structure

The monoclinic unit cell of $XeF_4$ contains discrete, practically square $XeF_4$ groups (cf. Figure 16); the PMF values and the Madelung constant are given in Table 13. Comparison with the data for $XeF_2 \cdot XeF_4$

Table 13. Madelung constants and partial Madelung constants of a number of tetrahalides with respect to the shortest distance A–B=1 [1a, 9, 10].

| | [Xe[4]$F_4$] | $\frac{1}{\infty}$[Sn[6]$F_4$] | $\frac{2}{\infty}$[Nb[6]$Cl_4$] | [Si[4]$F_4$] |
|---|---|---|---|---|
| PMF ($A^{4+}$) | 9.4138 | 10.5153 | 8.9515 | 8.8262 |
| PMF ($F_I^-$) | 0.8233 | 1.0364 | 1.1102 | 0.9157 |
| PMF ($F_{II}^-$) | 0.8184 | 0.7480 | 1.0141 | |
| PMF ($F_{III}^-$) | | | 0.7874 | |
| MF | 12.6972 | 14.0841 | 12.6505 | 12.4889 |

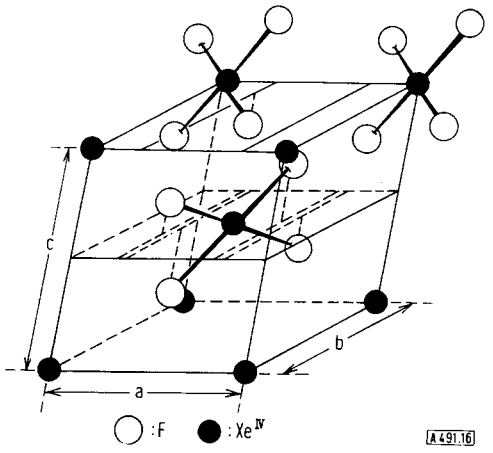


Fig. 16. Crystal structure of $XeF_4$ (a = 5.05 Å, b = 5.92 Å, c = 5.77 Å, $\beta$ = 99.6 °). For the sake of clarity, only some of the F atoms are shown (sizes of the particles chosen arbitrarily).

shows that the $PMF(F^-)$ values and the Madelung constant are of the expected magnitude. Comparison with the data for $SiF_4$ shows that the $PMF(F^-)$ values for $XeF_4$ are smaller than those for $SiF_4$. The reason is the electrostatically unfavorable planar shape of the $XeF_4$ unit. The smaller value of $PMF(Si^{4+})$ as compared with $PMF(Xe^{4+})$ indicates the more intimate entanglement of the $XeF_4$ groups. From the heats of sublimation ($SiF_4$: 6.15 kcal/mole, $XeF_4$: 15.3 kcal/mole) the Madelung constant of the $XeF_4$ type would be expected to be larger than that of the $SiF_4$ type. Table 13 shows that this is indeed the case. However, in considerations of this kind one has to be satisfied with modest accuracy.

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# Structure Formation and Molecular Mobility in Water and in Aqueous Solutions

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*Dedicated to Prof. W. Klemm on the occasion of his 70th birthday*

*The study of the structure of water and of aqueous solutions has recently received new impetus from the efforts at commercial desalineation of sea water and from developments in molecular biology. The current view that, apart from single molecules, water contains only one type of structural element, namely „flickering "network structures with tetrahedrally hydrogen-bonded water molecules (two-states model) is proving inadequate in the interpretation of new experimental data and in the calculation of thermodynamic functions. After a critical discussion of the basis of this model and of the concept of hydrogen bonds, a second kind of structural element, i.e. a third state, is suggested: small aggregates of molecules containing mainly non-tetrahedral hydrogen bonds as well as some tetrahedral ones, and packed more densely than allowed by the lattice-like structure. These aggregates – dimers to hexamers – can be regarded as the primary products of disruption of the network structures, and displace the latter as structural components in water with increasing temperature or concentration of solutes. This "combined" model allows a consistent interpretation of the properties of water and of the various effects of dissolved substances.*

## Introduction

Intermolecular structures have long been held responsible for the anomalies in the physicochemical properties of water, and are also used to explain its behavior as a solvent. The most important method up to a few years ago of detecting these structures was based on the radial distribution function of the intermolecular distances as found from X-ray diffraction photographs of liquid water. The development of microwave and in particular NMR spectroscopy now enables us to take a closer look at the interactions between neighboring $H_2O$ molecules and between dissolved particles and $H_2O$ molecules. Information about the mobility of $H_2O$ molecules, particularly with regard to rotary motion (reorientation), provides a better picture of the "structure", as well as a more sensitive means of determining the effect of solute particles on the short-range order of the $H_2O$ molecules.

In the following pages the development of current views will be discussed systematically and critically. It appears that we have been too ready to assume that the liquid structure of water is due to an intermolecular linkage of the same type as in ordinary ice (this will be referred to below as linkage by "tetrahedral" hydrogen bonds). Thus in addition to the larger structural units, *i.e.* the fluctuating networks or clusters, in which linkage is in fact mainly due to tetrahedral H bonds, too little attention has been paid to the possibility of a second, smaller type of aggregate, in which the molecules are held together by more dipolar non-tetrahedral hydrogen bonds.

## The Molecular Structure of Water

### 1. Structure of the $H_2O$ Molecule and of Ice

The geometrical structure of and the charge distribution in $H_2O$ are shown schematically in Fig. 1. In a free oxygen atom, in which the eletronic configuration of the L shell is $(2s)^2$ $(2p_z)^2$ $(2p_y)$ $(2p_x)$, the charge density of the $(2s)^2$ pair of electrons has a spherically symmetrical distribution about the inner-shell electrons; the charge densities of the $(2p_z)^2$ pair of electrons and of the two valence electrons $2p_y$ and $2p_x$ have rotationally symmetrical distributions about the three mutually perpendicular axes z, y and x. Two hydrogen atoms bound by $2p_y$ and $2p_x$ tend to widen the 90° angle owing to electrostatic repulsion. The electron configuration of the oxygen can accomodate this tendency to some extent by changing from pure p and s states to mixed electronic states (hybridization). As the s contribution to the states of the valence electrons increases, so also does the angle between the axes of maximum charge density; when this contribution reaches a certain level, the potential energy of the $H_2O$ molecule reaches a minimum (corresponding to a maximum in the bond energy), and the valence angle is the angle between the axes at this point. However, the hybridization of p and s states also leads to a change in the charge distributions of the two pairs of non-bonding electrons on the oxygen. Their charge clouds project unsymmetrically from the oxygen molecule on the side remote from the protons, so that the charge distribution in the $H_2O$ molecule can be described by an approximately tetrahedral four-point model (see Fig. 1a).

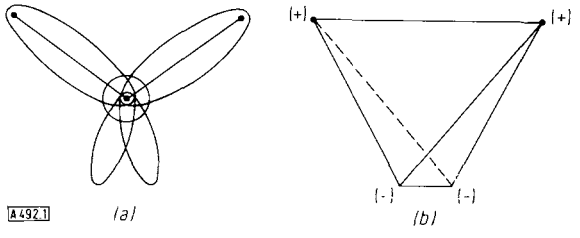



Fig. 1. Charge distribution in the $H_2O$ molecule according to *Bjerrum* [1]. (a) Electron distribution about the nuclei; (b) tetrahedral model of the $H_2O$ molecule.

For $H_2O$ molecules in the vapor state, where there is no interaction with neighbors, the valence angle is 104.5°, the O–H distance 0.96 Å, and the electrical dipole moment 1.84 D. It follows that in the isolated $H_2O$ molecule, each of the four centers of high charge density (see Fig. 1b) carries only 0.17 electronic charge; the protons are therefore largely surrounded and screened by electron clouds. If external influences cause the valence angle to increase beyond 104.5°, the accompanying increase in hybridization leads, within certain limits, to a further increase in the magnitudes of the four "point charges", and hence in the polarity and dipole moment of the molecule.

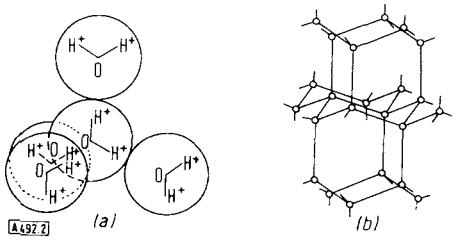



Fig. 2. Four-coordination of the $H_2O$ molecules with tetrahedral hydrogen bonds (a) and arrangement of the oxygen atoms in the ice structure (b). From *Samoilow* [2].

In the normal ice lattice, each proton forms a H-bond by interacting with a center of negative charge of a neighboring $H_2O$ molecule (cf. Fig. 2). This leads to the tetrahedral arrangement of the oxygen atoms found in ordinary, hexagonal ice, which corresponds to the silicon sub-lattice in β-tridymite (Fig. 2b). The bulkiness of the ice structure with its large, cage-like cavities is due to the low coordination number of 4. The distance between adjacent oxygen atoms linked by a hydrogen bond is 2.76 Å; the O–H distance (about 0.99 Å) is slightly greater than in isolated $H_2O$ molecules in the gas phase. There are two limiting possibilities for the H–O–H valence angle in the ice structure: (a) the H atoms lie on the lines joining the nuclei of the oxygen atoms, in which case the valence angle is increased from the value of 104.5° for the isolated water molecule to the tetrahedral angle of 109.5°; (b) the H–O–H angle in ice remains 104.5°, the hydrogen atoms lying to the side of the lines joining the oxygen atoms, *i.e.* the H-bonds are angular (bent). No definite conclusion can be reached on the basis of neutron diffraction measurements on solid $D_2O$, since the results are compatible with both possibilities [3]. It is possible, therefore, that the H–O–H valence angle in ice is slightly smaller than the tetrahedral angle and lies between the two limiting cases, *i.e.* the hydrogen bonds in the ice structure may be slightly "curved". However, since the valence angle is greater than 104.5°, the polarity of the $H_2O$ molecule in the ice structure should be greater than in the isolated state. From the high dielectric constant of ice (92 at the melting point), it is estimated that the dipole moment of the 4-coordinated water molecule in the ice structure is 2.5 D, compared to 1.84 D in the vapor [4]. These relationships, together with the fact that the O–H distance is greater in ice than in the gas phase, suggest that the hydrogen bonding in ice leads to considerable withdrawal of the protons from the screening electron cloud. Thus the "point charges" of the water molecules at the vertices of the tetrahedra in the ice structure are stronger than in "single" $H_2O$ molecules, *i.e.* molecules that are not involved in H bonding.

The well-known peculiarities of water, *i.e.* its density maximum at 4 °C, high heat of vaporization, surface tension, and specific heat in comparison with those of other liquids, and other anomalies such as those in the viscosity, thermal conductivity, and sonic absorption, led a long time ago to the view that bulky hydrogen-bonded structures also exist in the liquid state. Thus *Röntgen* and *Tammann* referred to "ice-like molecules", which they regarded as residual ice structure still present in water above the melting point. As the temperature increases, these "ice-like structures" dissociate into smaller aggregates and single molecules, and the resulting increase in the coordination number causes a decrease in volume. The density maximum at 4 °C can be explained by this tendency to closer packing, together with the opposing tendency of thermal expansion. With


[1] *N. Bjerrum*, Dan. Mat. Fys. Medd. *27*, No. 1, S. 3 (1951); Chem. and Ind. *1952*, 364.

[2] *O. J. Samoilow*: Die Struktur wäßriger Elektrolytlösungen und die Hydratation von Ionen. Teubner, Leipzig 1961.

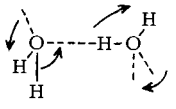
[3] *S. W. Peterson* and *H. A. Levy*, Physic. Rev. *92*, 1082 (1953); Acta crystallogr. *10*, 70 (1957); *R. Chidambaran*, *ibid. 14*, 467 (1961).

[4] *J. B. Hasted et al.*, J. chem. Physics *20*, 1452 (1952); cf. also *M. Weissmann* and *N. V. Cohan*, *ibid. 43*, 119 (1965).

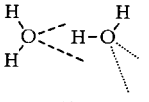
increasing thermal breakdown of the ice-like structure, the behavior of water approaches that of normal liquids. Similar "normalization" is observed under the influence of high pressures ($10^3$ to $10^4$ atm) and increasing electrolyte concentrations.

## 2. Types of Hydrogen Bonds

The breaking up of structures and of hydrogen bonds referred to below does not imply that the bonded atoms move away from each other along their center line, with the result that a hydrogen bond is stretched and ultimately broken; instead, in view of the close packing in the liquid state, we must imagine the rotation of $H_2O$ molecules out of the range of mutual orientation in which their interaction potential passes through a relative minimum [see Formula *(1)*]. This is generally



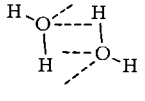
*(1)*



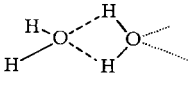
*(2)*

accompanied by an increase in the distance between the centers of gravity of adjacent molecules. Thus a hydrogen bond is regarded as broken or dissociated if the mutual orientation of the two $H_2O$ molecules is such that their interaction potential passes through a (relative) maximum. In general, an $H_2O$ molecule can get free from all hydrogen bonds to its neighbors only if it passes to practically free rotation.

Type *(1)*, which is suggested by the structure of ordinary hexagonal ice, is not the only orientation of two adjacent $H_2O$ molecules that gives a potential minimum; other orientations for which a minimum occurs include an open-chain structure *(2)*, a planar ring *(3)*, and a



*(3)*



*(4)*

"bifurcated" structure *(4)*. In these orientations, in contrast to type *(1)*, two negative charge centers of one $H_2O$ molecule are used to bind an adjacent molecule. Hence the total number of hydrogen bonds is lower, but the smaller aggregates with chain or ring structures, which are built up in this way, enable a closer packing of the molecules than in ordinary ice or in tetrahedrally constructed "clusters". The arrangements *(2)–(4)* have been repeatedly discussed as possible structures of $H_2O$ dimers [5]; type *(4)*, however, seems to be unfavorable for steric reasons.

Hydrogen bonds of type *(1)* will be referred to as "tetrahedral", and the types *(2)*, *(3)*, and *(4)* as "non-tetrahedral". In the types *(2)* and *(3)*, the polarity of the $H_2O$ molecules is not increased by spreading of the H–O–H valence angle. Moreover, the bridging protons are more strongly enveloped by the lone electron pair from the oxygen in types *(2)* and *(3)* than in type *(1)*. Thus with regard to their polarity, and above all to the electrostatic screening of their protons, non-tetrahedrally bound $H_2O$ molecules are between tetrahedrally bound $H_2O$ molecules and $H_2O$ molecules not involved in hydrogen bonding. The characteristic differences between these three types of $H_2O$ molecule and between the two types of hydrogen bond provide an interpretation for experimental findings that would otherwise be difficult to explain.

The bulky lattice of ordinary ice (ice I), which is characterized by straight or at most slightly bent tetrahedral bonds, changes at even moderate pressures into denser modifications. It exists in equilibrium with the much denser tetragonal ice III at 2050 atm and −22 °C, and with the still denser cubic ice II at 2100 atm and −34.5 °C. Altogether six denser modifications stable at high pressures are known [6]. The melting point-pressure curve of the so-called high-temperature modification, ice VII, has recently been measured up to 442 °C (200000 atm) [7].

This diversity of solid states suggests that the loose structure with the straight hydrogen bonds in ice becomes unstable at high pressure and rearranges to other ways of packing of the $H_2O$ molecules with higher coordination numbers and possibly shorter O···O distances, and hence with closer packing. Hydrogen bonds with remarkably short O···O distances (as short as 2.5 Å) have, in fact, been observed in a number of crystals containing OH groups [5, 6]. A number of cases of distinctly "curved" hydrogen bonds are also known, with O–H···O angles as small as about 165 ° [5]. Thus high pressures can lead to a closer packing in ice by bending and possibly compression of the hydrogen bonds. This is indicated, *e.g.*, by the results of an X-ray analysis of ice III, according to which the structural units are distorted oxygen tetrahedra [6, 8]. It is possible that other types of linkage, such as the non-tetrahedral hydrogen bonds described above, can also occur with further modification of the ice [*].

The arrangement in the structured regions (*i.e.* the "ice-like molecules") of liquid water need not be similar to that of ordinary ice, as has recently also been pointed out by *Frank* [9]. Arrangements such as that of ice III or cage structures of the type present in gas hydrates (Fig. 8) have been suggested (see also below); structures of this type cannot be ruled out as long as they agree with the results of the X-ray analysis of liquid water.

[5] *G. C. Pimentel* and *A. L. McClellan*: The Hydrogen Bond. Freeman, New York *1960*, pp. 100, 226, 255.

[6] *R. Brill*, Angew. Chem. *74*, 895 (1962), Angew. Chem. internat. Edit. *1*, 563 (1962).

[7] *C. W. F. T. Pistorius et al.*, J. chem. Physics *38*, 600 (1963).

[8] *W. B. Kamb* and *S. K. Datta*, Nature (London) *187*, 140 (1960).

[*] Note added in proof: Recent X-ray structure analysis of ice VI resulted in chains of distorted oxygen tetrahedra with some strongly bent hydrogen bonds (*B. Kamb*, Science *150*, 205 (1965)). Two structures having their chains mutually displaced by 90 ° fit into each other ("self-clathrate structure"), without being linked by H-bonds. The short distance between next-nearest neighbors (3.5 Å) leads to a high packing density (1.33 g/cm³).

[9] *H. S. Frank*: Desalineation Research Conference. Publication No. 942 Nat. Acad. Sci., Nat. Res. Conference (1962), p. 141.

## 3. Models for the Structure of Water

The concept of "ice-like molecules" was first treated quantitatively by *Eucken* in 1946[10]. This author regarded water as a mixture of different associates of definite stoichiometries, and set out to derive a quantitative description of the thermodynamic properties of water in extended ranges of state on the basis of the simplest possible assumptions about these associates. To compare the results of his calculations with experimental results, he chose parameters that are strongly influenced by association, *i.e.* the density (between −20 and about +100 °C, at 1 to 12000 atm) and the molar heat capacity (between 0 and 200 °C, at normal pressure). For the "ice-like molecules" postulated by *Röntgen* and *Tammann*, he took the smallest possible grouping, *i.e.* an associate of eight molecules forming a structure which, as shown in Fig.3, contains a cavity such as those occurring in the tridymite structure of ice (Fig. 2). *Eucken* assumed the volume occupied by these associates of eight molecules to be about 10 % greater, on average, than that occupied by the other components of water. He explained the anomalies in the equation of state of water by dissociation of these associates with increasing temperature and with increasing pressure.

Fig. 3. Model of an "ice-like" octamer with a cavity similar to that in tridymite, after *Eucken* [10].

In order to obtain a correct representation of the heat capacity of water as a function of temperature, it is necessary to postulate thermal changes in structure extending over wide temperature ranges. According to *Eucken*, the associates of eight molecules dissociate *via* two intermediates, one containing four molecules and the other containing two. He did not exclude the possibility that other associates (*e.g.*, one containing three molecules) exist, but neglected these in the calculations in order to keep the model as simple as possible; associates containing more than eight molecules were thought to be improbable. *Eucken*'s picture of individual associates was based on the assumption that the tendency of the $H_2O$ molecules to form hydrogen bonds and structures in liquid water could be saturated to some extent. In this model there is no differentiation between the various types of H-bonds, and it is not restricted to one distinct type.

For the above model it was necessary to use empirical values for seven quantities, *i.e.*, the molar fractions of the three types of associates in water at one given temperature (*e.g.* 0 °C), their heats of dissociation, and the increased volume of the associates containing eight molecules. These seven values permit the calculation of the proportions of the different species in water as a function of temperature and pressure, if the mixture is assumed to be ideal.

Figure 4 shows how the fractional amounts of these species vary with temperature between 0 and 100 °C and at normal pressure, as found by *Eucken*. Appreciable quantities of the two-molecule associates are still present at relatively high temperatures, and these may be responsible for the anomalous behavior of water at the critical point.

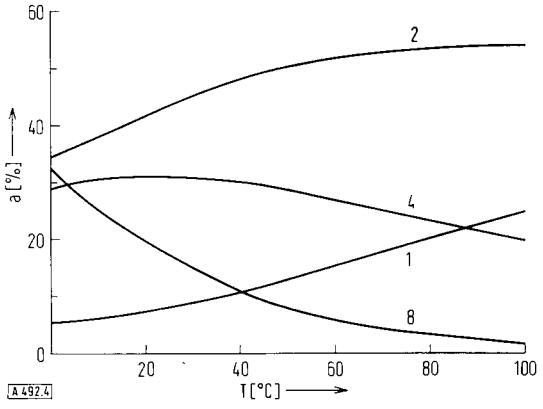



Fig. 4. Relative proportions a of octamers (8), tetramers (4), dimers (2), and single molecules (1) as a function of temperature, after *Eucken* [10].

Developments in England and in the United States took an entirely different course. The starting point for this development was *Bernal* and *Fowler*'s interpretation of the first reliable X-ray diffraction diagrams for liquid water[11].

Fig. 5 shows the radial distribution function of liquid water, *i.e.* the frequency distribution of the distances

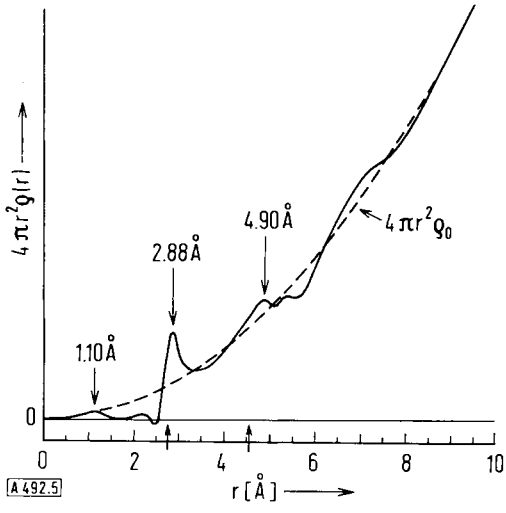



Fig. 5. Radial distribution function of the $H_2O$ molecules in liquid water from X-ray diffraction at 25 °C, after *Danford* and *Levy* [12]. The arrows on the abscissa at 2.75 and 4.50 Å indicate the distances of the nearest and next-nearest neighbors in the ice structure. The maximum at 1.10 Å is attributed by the authors to the O—H distance in the $H_2O$ molecules ($\varrho$ = number density of $H_2O$ molecules at distance r from a central molecule [Å$^{-3}$]; $\varrho_0$ = averaged number density of molecules in water [Å$^{-3}$].

[10] *A. Eucken*, Nachr. Akad. Wiss. Göttingen, math.-physik. Kl., IIa math.-physik.-chem. Abt. *1946*, 38; Z. Elektrochem. angew. physik. Chem. *52*, 255 (1948); *53*, 102 (1949).

[11] *J. D. Bernal* and *R. H. Fowler*, J. chem. Physics *1*, 515 (1933).

[12] *M. D. Danford* and *H. A. Levy*, J. Amer. chem. Soc. *84*, 3965 (1962).

between an arbitrarily chosen central molecule and the $H_2O$ molecules surrounding it, averaged over all directions in space. The maximum of the smallest average distance between adjacent molecules is remarkably sharp, and occurs at 2.88 Å, corresponding to a slightly elongated hydrogen bond of the type that occurs in the ice structure. A second maximum at 4.90 Å can be related to the distance between the second-nearest neighbors in ice.

From such and other analogies between the radial distribution functions of liquid $H_2O$ and of tridymite-like and quartz-like structures, *Bernal* and *Fowler* concluded that the $H_2O$ molecules in liquid water must be largely arranged in a four-coordinate pattern. The idea that water has a "loose" lattice structure was supported by considerations arising in the explanation of the high and very similar values found for the static dielectric constants of ice and water (92 and 88.5 at 0 °C, according to recent measurements). Thus according to *Bernal* and *Fowler*, the structure of supercooled water is essentially similar to the tridymite structure of ice, while at temperatures up to 200 °C, this gives way to a more densely packed quartz-like structure (in which however, the O–H···O bridges would have to be strongly bent [13a, 13b]). The density maximum of water at 4 °C is attributed to the transition to this quartz-like structure. Random close packing, as in normal liquids, is thought to predominate only at temperatures above 200 °C.

In this model of a tetrahedrally-coordinated, three-dimensional network, *Bernal* and *Fowler* provided the basis for the predominant view that the structure of water is due entirely to tetrahedrally oriented hydrogen bonds between adjacent $H_2O$ molecules. At the same time, by assuming that only one type of molecule, corresponding to the average of all the molecules, need be considered, they laid the foundations for the theories that *Frank* described as "uniformistic" [9] (to distinguish them from theories that regard the presence of different structural units as an essential characteristic of the structure of water).

It soon became clear, however, that the radial distribution function had been greatly overrated as a source of detailed information about the lattice-like arrangement of the $H_2O$ molecules in liquid water, particularly since the distances are averaged over all directions. This was demonstrated in 1938 by *Morgan* and *Warren* in the discussion of their new X-ray diffraction results for liquid water [14]. These authors also drew attention to a previously disregarded region of almost uniformly distributed distances (between 3 and 4 Å in Fig. 5) which have no correspondence in ordinary ice-like structures. From this they concluded that only part of the $H_2O$ molecules in liquid water can be linked tetrahedrally, that is a considerable part of the tetrahedral structure of ice should collapse immediately on melting; the contraction that accompanies melting is attributed to the filling of the cavities with $H_2O$ molecules that have broken away from the structure.

This criticism of *Bernal* and *Fowler*'s views was one of the factors that induced *Eucken* to set up a model with smaller molecular aggregates in which each $H_2O$ molecule forms only two or three hydrogen bonds, and which is consistent with the X-ray diffraction results.

The models subsequently developed in England and in the U.S.A., on the other hand, are still essentially based on *Bernal* and *Fowler*'s ideas, but further assumptions and corrections have been introduced to obtain agreement with the radial distribution function of *Morgan* and *Warren*.

On the basis of a purely electrostatic theory of (tetrahedral) hydrogen bonding, *Lennard-Jones* and *Pople* (1951) concluded that the angular orientation of two $H_2O$ molecules should be relatively flexible (small torsional forces for the transition from straight to bent O–H···O linkages; cf. *(I)*). The authors used this flexibility to fit the theory to experimental results, as mentioned above, and in this way developed a uniformistic model [15]. According to this model, the H-bridges even in ice bend as the temperature is raised, until the long-range lattice orientation breaks down, *i.e.* the ice melts. It is postulated that in liquid water, the four hydrogen bonds on each $H_2O$ molecule can bend or twist independently of one another. Thus the real difference between ice and water, according to this theory, is the mutual independence of the flexible orientations of the H-bonds. This would also explain how the cavities of the ice structure can become filled with $H_2O$ molecules in liquid water, without breakage of an appreciable fraction of the hydrogen bonds. Owing to the opposing effects of the thermal motion and the torsional strain of bending, the mean deflection of the H-bonds increases with temperature. By a suitable choice of values for the torsional force constants and for the numbers of nearest, second-nearest, and third-nearest neighbors ($N_1 = 4$, $N_2 = 11$, $N_3 = 22$) *Pople* obtained good agreement with *Morgan* and *Warren*'s radial distribution function, including the tendency of the frequency maxima to broaden with rising temperature. However, values found for the average bending angle were rather high (26 ° at 0 °C increasing to 30 ° at 100 °C). With this model, calculation of the dielectric constant of water by *Kirkwood*'s method [16] gave the correct temperature-dependence between 0 and 83 °C, but the absolute values were too low by about 20%.

Mixture models of the structure of water, with the exception of *Eucken*'s associate model, can be sub-divided into network or cluster models and cell or cage models. In the first type, liquid water is regarded as a mixture of "clusters" of $H_2O$ molecules, each molecule being linked to four others, and single $H_2O$ molecules, which occupy the spaces between the clusters (see Fig. 6). The clusters are continuously being built up and broken down, and single molecules are added on and split off in a rapid interchange (*ca.* $10^{-11}$ sec). However, this model

[13a] *L. Pauling* in *L. Hadži*: Hydrogen Bonding. Pergamon Press, London 1959, p. 1.

[13b] *L. Pauling*: Nature of the Chemical Bond. Cornell University Press, Ithaca, N.Y., 1960, p. 464.

[14] *J. Morgan* and *B. E. Warren*, J. chem. Physics *6*, 666 (1938).

[15] *J. Lennard-Jones* and *J. A. Pople*, Proc. Roy. Soc. (London) A *205*, 155 (1951); *J. A. Pople*, *ibid. 205*, 163 (1951).

[16] *G. Oster* and *J. G. Kirkwood*, J. chem. Physics *11*, 175 (1943).

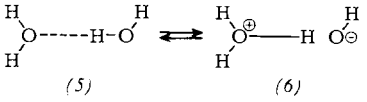
involves, not only two types of $H_2O$ molecules (single and four-coordinate), but five types, since $H_2O$ molecules with one, two, or three hydrogen bonds are also present at the surfaces of the clusters, although only as short-lived intermediate states.

The first model of this type was proposed by *Hasted et al.* in connection with dielectric relaxation measurements [4]. With such a model, they were able to explain the occurrence of a single, uniform, and remarkably fast relaxation process in water ($\tau_{liq} \approx 10^{-11}$ sec, as compared with $\tau_{solid} \approx 10^{-5}$ sec at the melting point). Assuming that only 9 % of the H-bonds in ice are broken on melting, and using a very rough estimate of the further breakdown with rising temperature, they obtained satisfactory results for the dielectric constant of water by *Kirkwood*'s method. The single molecules in the regions between the clusters were assumed to rotate almost freely.

Ten years later, *Némethy* and *Scheraga* attempted to obtain a more accurate picture of the breakdown of the clusters with rising temperature by means of statistical thermodynamics. Like *Eucken*, these authors used the thermodynamic data for water (instead of the dielectric constants) as a basis for comparison [17]. According to their calculations, the proportion of the H-bonds in ice that break during melting is not 10 %, but about 50 %. For regions with four-coordinated structures such as that in Fig. 6, they found an average of 90 $H_2O$ molecules per cluster at 0 °C, decreasing to about 25 at 70 °C. For less than 25 molecules per cluster, this model no longer has physical significance.

The development of the "flickering cluster" concept has been greatly aided by the fact that covalent as well as electrostatic bonding components must be taken into account for the (tetrahedral) hydrogen bonds. These covalent components can be approximately represented by the contribution made by the limiting resonance structures *(6)* to the hydrogen bonding. Theory shows that these limiting structures participate to the extent of a few per cent in hydrogen bonds of normal length (2.8 Å) [5], with the result that the tetrahedral orientation of the hydrogen bonds in the clusters is more rigid than had been assumed by *Lennard-Jones* and *Pople*.

*Frank* pointed out a special effect due to the covalent contributions [18, 19]: the charge separation associated with the limiting structure *(6)* increases the tendency of both $H_2O$ molecules to form hydrogen bonds with other neighbors, and these further hydrogen bonds then increase the energy of the original hydrogen bond by a kind of feedback effect. This possibility of co-operative behavior in the formation and breakdown of bridge structures is regarded as characteristic of tetrahedral



*(5)* *(6)*

hydrogen bonds and "flickering" clusters. In this connection, *Némethy* and *Scheraga* [17] emphasize that although the single $H_2O$ molecules shown in Fig. 6 exert strong dipole forces as well as van der Waals forces on one another, they are nevertheless "monomeric, unbonded water". Small aggregates such as dimers are unlikely to be present, and were disregarded in the calculations. In contrast to this cooperative behavior, the non-tetrahedral hydrogen bonds will to a certain extent be capable of saturation and therefore preferentially lead to the formation of smaller aggregates.

It is interesting to compare the above two cluster models with *Eucken*'s associate model. Fig. 7 shows the temperature-dependence of the average number of hydrogen bonds per $H_2O$ molecule for the three models. In the cluster and cage models, the ordinate values divided by 2 give the average "degree of cross-linking" of the $H_2O$ molecules (by tetrahedral hydrogen bonds). The Némethy-Scheraga cluster model and *Eucken*'s associate model differ remarkably little in the absolute values and temperature-dependence of the average number of H-bonds, the differences being much smaller than those between the two cluster models. This result is surprising at first, in view of the fundamentally different concepts on which the models are based; however, the Némethy-Scheraga cluster model is the only model, apart from *Eucken*'s, that gives reasonably good results for the molar heat capacity of water, though the values decrease a little too fast with rising temperature (from 21.5 to 13.7 cal mole$^{-1}$ deg$^{-1}$ between 0 and 70 °C, compared to experimental values of 18.1 to 16.9 cal mole$^{-1}$ deg$^{-1}$).

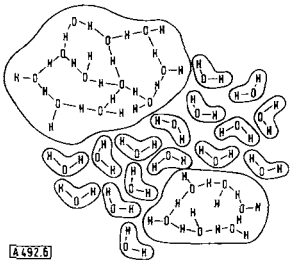



Fig. 6. Model of the structure of water as a mixture of clusters and single molecules. The $H_2O$ molecules in the clusters are assumed to be linked by tetrahedral hydrogen bonds and to have a coordination number of four. After *Némethy* and *Scheraga* [17].

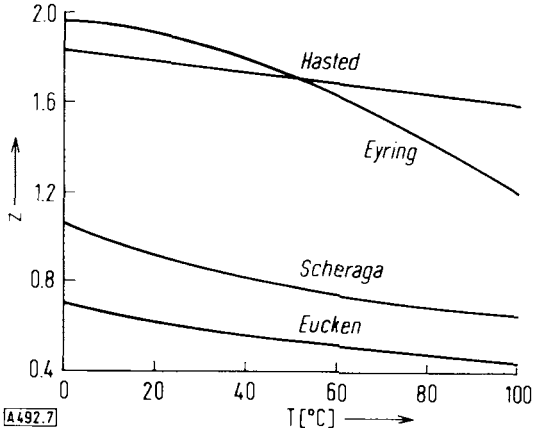



Fig. 7. Average number of hydrogen bonds (z) per $H_2O$ molecule as a function of temperature in various models for the structure of water.

[17] *G. Némethy* and *H. A. Scheraga*, J. chem. Physics *36*, 3382, 3401 (1962).

[18] *H. S. Frank* and *W. Y. Wen*, Discuss. Faraday Soc. *24*, 133 (1957).

[19] *H. S. Frank*, Proc. Roy. Soc. (London) A *247*, 481 (1958).

In the second type of mixture model, *i.e.* the cell or cage type, the mixture contains only two components. One of these components, in keeping with the views of *Bernal* and *Fowler*, is a bulky framework of tetrahedrally coordinated $H_2O$ molecules. The other component consists of single water molecules in the cavities of this framework, where they rotate without restraint, since they do not participate in hydrogen bonding. The structural parameters of the framework and the extent to which the cavities are filled can be chosen to give the correct density, dielectric constant, *etc.* of water. The first model of this type was proposed in 1946 by *Samoilov*, and consists of an ice-like structure with monomeric $H_2O$ molecules in interstitial sites (ref. 2, p. 44).

*Pauling* suggested a cage model for the structure of water in 1957 [13a, 13b]. The structural units in this model are two $H_2O$ polyhedra known from the gas hydrates (Fig. 8); one is a pentagonal dodecahedron comprising 20 $H_2O$ molecules with a cavity diameter of 5.2 Å, the other a polyhedron with fourteen faces containing 24 $H_2O$ molecules and with a cavity diameter of 5.9 Å. According to *Pauling*, these polyhedra can combine in various ways to give the framework structure of liquid water. For example, combination as in the methane hydrate illustrated in Fig. 8 (46 $H_2O$ molecules in the framework of the cubic unit cell, 8 $H_2O$ molecules in the cavities) gives a density (0.98 g/cm$^3$) close to that of water. *Pauling*'s choice of the gas hydrate polyhedra as models for the "cage" is based on the remarkable stability of these structural units: a pentagonal dodecahedron with one free $H_2O$ molecule in the cavity contains 21 $H_2O$ molecules and 30 (tetrahedral) hydrogen bonds, *i.e.* 71.5 % of the maximum possible (42); however, it is impossible to cut out a complex of 21 molecules with even 60 % of this maximum number of hydrogen bonds from the structure of ice. The cage model requires relatively high degrees of cross-linking; *Pauling* gives a value of 85 % at 0 °C, corresponding to the above example of methane hydrate. The author seems not to have published either calculations on the change in the degree of cross-linking or comparisons with the thermodynamic properties of water; however, *Frank* and *Quist* subsequently carried out calculations of this nature [21], and we shall return to these in the next Section.

The latest model for the structure of liquid water is the cage model proposed by *Marchi* and *Eyring* [20]. It assumes that when ice melts, the $H_2O$ molecules of the ordinary ice structure rearrange themselves into a new structure, which is about 20 % more dense than the ice structure, but in which the coordination is still tetrahedral; this new structure may resemble the tetragonal structure of ice III [8], or it may be similar to the cage models proposed by *Pauling* or *Danford* and *Levy* [12]. At the same time, "holes" characteristic of *Eyring*'s theory of liquids are formed in the liquid structure, leading to a 10 % increase in volume, so that the overall change in volume is a decrease of 10 %. The cavities in the framework contain freely rotating molecules, the proportion of which increases from about 2.5 % of all the $H_2O$ molecules present at the melting point to about 40 % at the boiling point (Fig. 7). Thus the structure of the framework must change within this temperature range, in order to accomodate the larger number of single molecules in its cavities; this change is thought to be related with the minimum in the heat capacity of water at 35 °C. Even with such a marked thermal dissociation of the H-bond structures (as demonstrated by the steeply descending curve in Fig. 7), however, the value obtained by the authors for the molar heat capacity of water is only about half (10 cal mole$^{-1}$ deg$^{-1}$) of the true value.

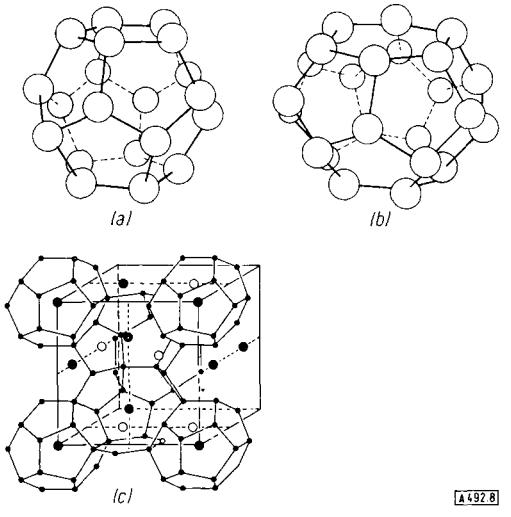



Fig. 8. Structure of solid methane hydrate, $(CH_4)_8(H_2O)_{46}$. Pentagonal dodecahedra (a) and polyhedra with 14 faces (b) consisting of tetrahedrally linked $H_2O$ molecules, and each containing one $CH_4$ molecule. (c) shows the arrangement of the polyhedra in the overall structure of the gas hydrate, illustrated by the front half of the cubic unit cell. After *von Stackelberg* and *Müller* [40].

### 4. Discussion of the Structural Models. — A Combined Structural Model

The models outlined above, with few exceptions, are characterized by the fact that only one type of structural element (*i.e.* networks of tetrahedrally coordinated $H_2O$ molecules) is considered in each case, and the elements of this type are assumed to exist in liquid water together with unbonded single molecules, the whole having a relatively high degree of cross-linking. Three arguments are used to support this assumption:

a) According to *Pauling* [13b], the sublimation energy of ice (12.2 kcal/mole) includes a contribution of 2.5 kcal/mole due to van der Waals forces. Thus each of the two hydrogen bonds formed by each $H_2O$ molecule in ice has a bond energy of about 5 kcal/mole. Thus the enthalpy of fusion of ice (1.44 kcal/mole) is sufficient to break only 0.3 hydrogen bond per molecule, so that the degree of cross-linking of water at the melting point must still be at least 85 %.

b) Relaxation processes in water, particularly dielectric relaxation, have been found to be uniform, one-step processes, indicating that water contains only one type of relaxing structural element.

[20] *R. P. Marchi* and *H. Eyring*, J. physic. Chem. *68*, 221 (1964).
[21] *H. S. Frank* and *A. S. Quist*, J. chem. Physics *34*, 604 (1961).

c) The fact that the dielectric constant of water at the melting point (88.5) differs only slightly from that of ice indicates that the degree of cross-linking in water is almost as high as that in ice.

Against point (a) it may be argued that the van der Waals contributions should be higher in water than in ice, owing to the higher average coordination numbers in water; thus the quantity of energy available for breaking hydrogen bonds is greater than the enthalpy of fusion. With regard to argument (b), uniform relaxation processes would also be expected if water contained several types of structural elements, the average lifetimes of which are so similar that they cannot be distinguished experimentally. Finally, while it is likely from argument (c) that the degree of cross-linking, at least at the melting point, is in fact high, it is possible that this is partly due to ordered states other than tetrahedrally coordinated frameworks or clusters.

*Frank* and *Quist* [21] have shown particularly clearly that it is necessary to consider a "third state" of $H_2O$ molecules in liquid water, in addition to the tetrahedrally coordinated networks and freely rotating single molecules. When these authors tried to reproduce the behavior of water with respect to density, compressibility, and molar heat capacity with the aid of *Pauling*'s cage model, they found that it was impossible to obtain a value higher than 12 kcal $mole^{-1}$ $deg^{-1}$ for the molar heat capacity. They concluded that there must be another state or group of states as intermediates between the $H_2O$ molecules in the cage structure and the monomers [*]. These states may only be present in small amounts at the melting point, but their concentration must increase with rising temperature in order to provide the required contribution to the heat capacity and to diminish other difficulties that generally arise with cage models as a result of their rigidity and insufficient adaptability to dissolved particles.

Some information about such a "third state" can be gained from results obtained by *Pimentel et al.* [22]. These authors condensed mixtures of nitrogen and water vapor at 20 °K on AgCl plates; the presence of a very large excess of nitrogen (1000:1 to 10:1) ensured that any $H_2O$ aggregates formed would be small (matrix isolation technique). They used the infrared absorption of the condensed layers in the regions of the $H_2O$ bending and stretching vibrations as a basis for conclusions as to the nature of the (smaller) aggregates $(H_2O)_n$ occurring in the condensed mixture at increasing water contents. The results indicate that the planar ring structure *(3)* is more likely under these conditions for the $H_2O$ dimer than the other types of dimers *(2)* and *(4)* mentioned in Section I.2. The authors also concluded from the infrared spectrum that the layers contained trimers and tetramers with non-tetrahedral hydrogen bonds, as well as higher polymers.

It seems reasonable to assume that aggregates of this type containing two, three, four and possibly up to six $H_2O$ molecules are the "third state" expected by *Frank* in liquid water. This "combined" model of the structure of water once more approaches *Eucken*'s views. However, instead of the "ice-like" octamers, it contains tetrahedrally coordinated networks; moreover, the average number of hydrogen bonds per $H_2O$ molecule is to be expected appreciably higher than in *Eucken*'s model. The correct curve in Fig. 7 should probably lie between those for the cluster models of *Scheraga* and *Hasted*. The structure of water accordingly is more complicated than assumed in the models concepted so far. Our knowledge of the water structure is in fact insufficiently detailed for a quantitative treatment. The following qualitative statements may, however, be made:

The networks with tetrahedral hydrogen bonds probably contain about 100 $H_2O$ molecules each in the neighborhood of 0 °C. The numerous molecules in the "surfaces" of these clusters already belong in part to the boundary regions between the clusters, in which the molecules are more closely packed (higher coordination numbers); in contrast to Fig. 6, however, the molecules of these regions are irregularly linked to one another, an appreciable proportion of the linkages being nontetrahedral hydrogen bonds. Both types of H-bonds have lifetimes of the order of $10^{-11}$ sec (the time taken for about 1000 OH stretching vibrations), and these lifetimes determine the frequencies of the fluctuations within and between the different structural elements. As the temperature is increased, the networks disintegrate rapidly; the number of smaller molecular aggregates at first increases with increasing temperature. The thermal breakdown of clusters, which are the main cause of the density anomalies, compressibility, and viscosity of water, is practically complete at 100 °C. This decay of the clusters is accompanied by cleavage of the larger molecular aggregates to form smaller ones; the shallow minimum in the heat capacity of water at about 35 °C may be related to the overlap of the thermal breakdown of the two types of structural units. It must be assumed that the thermal decay of the molecular aggregates takes place in several steps, which overlap to a considerable extent; this gives the high contributions of dissociation enthalpy, which are little dependent on temperature and which are required to explain the experimental values obtained for the heat capacity of water.

This concept of several thermal breakdown ranges, which are coupled together in such a way that no stages can be distinguished, follows the line developed by *Eucken* (Fig. 4).

Not only does this model allow for a replacement of the clusters that predominate at low temperatures by "molecular aggregates" as the temperature increases but, since these molecular aggregates contain a considerable proportion of non-tetrahedral hydrogen bonds, it also postulates a continuous increase in the relative amount of non-tetrahedral H-bonds with rising temperature.

**Addendum in Proof**

Since completion of the manuscript a number of publications on the structure of water have appeared, evaluating predominantly Raman and infrared spectroscopic results. In view of Raman spectra in the range of OH stretching bands

[*] The same conclusion has been drawn from difficulties encountered in the interpretation of "hydration of the second kind" on the basis of this model.

[22] *M. van Thiel, E. D. Becker*, and *G. C. Pimentel*, J. chem. Physics *27*, 486 (1957).

and of the radial distribution function from X-ray diffraction, a special "two-states model" was developed [23a]: puckered rings containing six $H_2O$ molecules (with tetrahedral H- bonds) forming an ice-like structure (structure I) or a more tightly packed structure (structure II). The relative proportions (structure I: 60 % at 0 °C; 30 % at 100 °C) can be chosen to fit the coefficient of thermal expansion and the compressibility of water. The model fails to explain the temperature dependence of the heat capacities; the authors remark that a further breakdown of structure II to a "third state" would be required. This is further confirmation of the inadequacy of a "two-states model".

With the treatment of a three-states model, *Vand* and *Senior* [23b] extended infrared studies of *Buijs* and *Choppin* [23c]. The latter authors divided the water band between 1.1 and 1.3 $\mu$, which is assigned to a combination $\nu_1 + \nu_2 + \nu_3$ of stretching frequencies and the bending vibration, into 3 sub-bands corresponding to $H_2O$ molecules the OH groups of which are involved in no, one, or two (tetrahedral) H-bonds. The change of concentration with temperature of the 3 molecular states was estimated from the temperature dependence of the intensities between 6 and 72 °C; the mean number of H-bonds per $H_2O$ molecule is close to the results of *Nemethy* and *Scheraga* [17] (cf. Fig. 7). (Size of the "flickering clusters": about 90 $H_2O$ molecules at 20 °C). The assignment of the absorption band and the analysis have, however, led to contradiction [23d] and controversy [23e]. *Vand* and *Senior* conclude that the thermodynamic properties of water cannot be computed, when discrete energy levels are assumed for the three molecular states suggested by *Buijs* and *Choppin*, but that Gaussian distributions of energy with correspondingly more adjustable parameters lead to reasonable results. Since, however, the three energy bands overlap strongly, the connection with the model is lost

From Raman spectra in the region of fundamental OH and OD stretching vibrations, *Wall* and *Hornig* [23f] also arrived at a continuous distribution of molecular states. In order to reduce the intramolecular coupling responsible for the broadening of the bands, they studied the OH band in a 10 % solution of HDO in $D_2O$ and the OD band in 10 % HDO in $H_2O$. Since under these conditions the bands also show no fine structure, the authors hold mixture models in which ordered lattice regions are the only structural units, apart from "monomeric" $H_2O$, to be unrealistic. The concept of mixture models in general has been reviewed by *Frank* [23g].

*Walrafen* [23h] studied the Raman and infrared spectra of $H_2O$ and $D_2O$, particularly in the range below 900 $cm^{-1}$. He assigned the bands in this long -wavelength region to intermolecular stretching and deformation vibrations, assuming $(H_2O)_5$ complexes with tetrahedral arrangement (symmetry $C_{2v}$). With increasing temperature the intensities of the bands decrease rapidly, particularly that of a band at 175 $cm^{-1}$, assigned to the stretching vibration (libration) of two $H_2O$ molecules linked by a hydrogen bond. Only a few tetrahedral bonds should thus remain in water at 100 °C.

The problem of the interpretation of the infrared bands of water has recently been resumed in detail by *Luck* [23i]: The sub-bands of the various species overlap almost completely, and the extinction coefficients, as well as their temperature dependence (influence of medium, dipole and dispersion forces) can only be estimated roughly. According to *Luck*, the combination band between 1.1 and 1.3 $\mu$ can be regarded as due to superposition of four vibrations: those of "free" OH groups in $H_2O$ molecules in which the other OH group also is free (1) or is part of a hydrogen bond (2), and those of OH groups in angular (3) or linear (4) H-bonds. Because of the difficulties mentioned, *Luck* makes use of the species (1) and (4) only to interprete his results (which extend to beyond the critical point). The average number of H-bonds follows the curve of *Hasted et al.* (Fig. 7) between 0 and 100 °C, in contrast to the results of *Buijs* and *Choppin*. In view of the approximations made, these values and the cluster sizes derived from them should be regarded as upper limits.

Most of the new experimental results confirm the "combined" structure model of water proposed in this article; no result in fundamental contradiction has been reported.

## II. The Influence of Dissolved Substances on the Structure of Water

### 1. General

The solvent properties of water depend on the interactions between the dissolved particles and the $H_2O$ molecules in the water structure. The diversity of the substances that dissolve in water indicate that this structure is sufficiently complex to be able to adapt itself in a characteristic manner to different types of solutes (non-polar, polar, or electrically charged).

The most familiar interaction of this type is the hydration of ions. The $H_2O$ molecules in the vicinity of the charged particles are kept in the potential trough of the ion-dipole interaction, and the depth of this trough corresponds to the hydration energy. The electric field of the ions decouples the H-bonds between the $H_2O$ molecules, and if its readjusting power is high enough, it may give rise to the formation of ordered hydration shells (cf. Fig. 9). It is not yet possible to determine the structures of such ordered regions by direct methods,

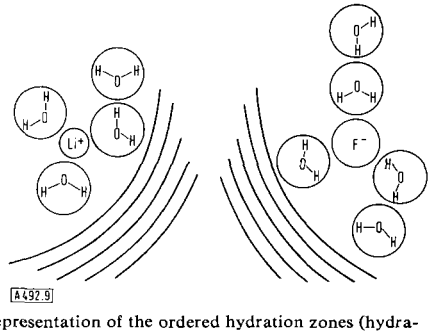



Fig. 9. Schematic representation of the ordered hydration zones (hydration shells) of the $Li^+$ and $F^-$ ions and fault zones of the water structure.

but this may become possible as a result of further development of X-ray diffraction methods, which may be applied to very concentrated electrolyte solutions [24]. Indirect information can be obtained from the viscosity and from relaxation times for the reorientation in space of $H_2O$ molecules. If the values of these parameters are higher for solutions than for pure water, it may be concluded that the solutions contain regions

[23a] *C. M. Davis* and *T. A. Litovitz*, J. chem. Physics *42*, 2563 (1965).

[23b] *V. Vand* and *W. A. Senior*, J. chem. Physics *43*, 1869, 1873, 1878 (1965).

[23c] *K. Buijs* and *G. R. Choppin*, J. chem. Physics *39*, 2035, 2042 (1963).

[23d] *D. F. Hornig*, J. chem. Physics *40*, 3119 (1964).

[23e] *K. Buijs* and *G. R. Choppin*, J. chem. Physics *40*, 3120 (1964).

[23f] *T. T. Wall* and *D. F. Hornig*, J. chem. Physics *43*, 2079 (1965).

[23g] *H. S. Frank*, Federat. Proc. *24*, No. 2, Part III, March-April 1965.

[23h] *G. E. Walrafen*, J. chem. Physics *40*, 3249 (1964).

[23i] *W. Luck*, Ber. Bunsenges. physik. Chem. *69*, 626 (1965); *67*, 186 (1963).

[24] *G. W. Brady*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *28*, 464 (1958).

in which the $H_2O$ molecules are more rigidly oriented with respect to one another than in pure water, *i.e.* in which the distances and angles between the molecules remain fixed for longer periods. These regions that are "rigid" in comparison with pure water are referred to as "ordered" or "structured" regions. At greater distances from the ions, the electric field is just strong enough to prevent the mutual orientation of the $H_2O$ molecules, and hence also the formation of the structural units of water. This region in which the water structure is broken down is shown in Fig. 9 as a fault zone. The average number of H-bonds between $H_2O$ molecules in this zone is smaller than that in pure water, and the $H_2O$ molecules are consequently more mobile. These relatively "fluid" regions are known as regions of "structure breaking".

This characterization of the hydration of ions by two concentric domains of water molecules in which the degree of order is higher and lower, respectively, than in pure water corresponds to the currently accepted picture, the development of which is due mainly to *Frank* and *Wen* [18]. One apparent deficiency of this picture is that although it takes into account the influence of the electric field, it ignores all other interactions between the ions and the $H_2O$ molecules in the water structure, *e.g.* volume or displacement effects, which also occur with neutral particles.

The simplest interaction of this kind, which can be imagined, is the separation of $H_2O$ molecules by dissolved particles, leading to reduced H-bond formation between the $H_2O$ molecules. This interaction should affect the association equilibria of the water in such a way as to give lower degrees of association. *Eucken* referred to this as (pure) "dilution effect" [25]. Here we shall use the terms boundary effect or break-off effect, since the phenomenon is due to the break off of the structure-forming elementary processes of pure water at certain positions; similar effects should also occur at macroscopic boundaries, such as the walls of a container or the surface of the liquid. However, this largely non-specific interaction does not generally occur alone, but is masked by other, more specific effects. There are two particularly important cases to considered:

(a) Loosening of the water structure as a result of break-off effects is to be expected mainly at the "surfaces" of non-polar or weakly polar dissolved particles. However, $H_2O$ molecules adjacent to these surfaces will try to screen their charge centers as much as possible in order to minimize the electric field extending into the non-polar environment, since relatively large amounts of electrostatic energy would otherwise have to be introduced into these regions of low dielectric constant. Particularly effective screening can be achieved by charge compensation of neighboring $H_2O$ molecules with formation of non-tetrahedral hydrogen bonds, as described in Section I.2. The nonpolar particles or groups are then surrounded, not by the expected loose "fluid" regions, but by a zone of more intense structure formation in which the orientation of the $H_2O$ molecules is relatively rigid. This phenomenon is known as hydration of the second kind [46b], and will be described in greater detail below.

[25] *A. Eucken*, Nachr. Akad. Wiss. Göttingen, math.-physik. Kl., math.-physik.-chem. Abt. *1947*, 33.

(b) The opposite behavior is to be expected where the $H_2O$ molecules are adjacent to strongly polarizable "surfaces" of dissolved particles, such as are formed by ions with an extended charge distribution. This is found mainly with large anions such as $Br^-$, $I^-$, $NO_3^-$, and $ClO_4^-$, the charge clouds of which screen $H_2O$ molecules in contact with them or (with their protons) "immersed" in them, so that the break-off effect can be fully active. Particularly strong structure-breaking effects are observed with these ions, and the fault zones indicated in Fig. 9 extend almost to the "surfaces" of the ions, *i.e.* ordered hydration shells are no longer formed ("ordered" in relation to water).

These break-off effects, which are due to displacement, are accompanied by the above-mentioned decoupling of hydrogen bonds by the electric field of the ions. Owing to the concerted action of these two effects, large cations such as $Rb^+$ and $Cs^+$ also have strong structure-breaking influences. Thus the $H_2O$ molecules adjacent to singly charged large anions and cations are, on average, more "mobile" in the potential troughs of the hydration regions (*i.e.* they can rotate and be displaced more easily) than in pure water. This type of hydration of ions has been pointed out mainly by *Samoilow* [26], who suggested that it should be called "negative hydratation". We shall refer in the present paper to "predominantly disordered" hydration of ions, and the $H_2O$ molecules in this case will be described as relatively "fluid".

In the case of LiF (Fig. 9), the ordering effects predominate over the structure-breaking effects. The same is true of practically all ions with multiple charges. The hydration of these ions is "predominantly ordered"; the orientation of the $H_2O$ molecules, averaged over the entire surroundings of the ion, is relatively "rigid" in comparison with pure water.

Thus the interactions discussed above can be summarized as follows:

*Structure forming*: formation of structured ion hydration shells; hydration of the second kind;

*Structure breaking*: decoupling of H-bonds in the electric field of the ions; break-off effects; fault zones; negative hydration.

In the above context "structure breaking" by solutes means the breakdown of the water structure from the flickering clusters, *via* the higher aggregates, to the dimeric and single molecules, as described in Section I for the thermal breakdown of the structure of pure water. "Structure forming", on the other hand, is simply the formation of ordered regions with relatively "rigid" dynamic behavior of the $H_2O$ molecules; this ordering need not obey the rules governing the structure of liquid water.

## 2. Experimental Results

Results of studies on the heat capacities and infrared absorption spectra of electrolyte solutions will now be discussed, as well as those of microwave and nuclear magnetic resonance spectroscopy, which have made an important contribution to the development of the combined model of the structure of water and to the development of the above views on the effects of dissolved particles on this structure.

[26] *O. J. Samoilow*, Discuss. Faraday Soc. *24*, 141 (1957).

### a) Heat Capacities and the Hydration of Ions

On the basis of *Eucken*'s views on the hydration of ions [26a] the heat capacities of many electrolyte solutions at various concentrations were measured between about 10 and 130 °C by precision calorimetric methods [27–30]. The results were extrapolated to infinite dilution to find the partial molar heat capacities of the dissolved electrolytes in the standard state. This eliminates the influence of ion-ion interactions, whereas the extrapolated values contain the influence of the ion-water interactions, because they include the total difference between the molar heat capacity of the water in the solution and that of pure water.

Figures 10 and 11 show the (extrapolated) partial molar heat capacities of alkali halides and of HCl and NaOH in aqueous solution. If influence of the ions on the structure of water could be neglected, these electrolytes would have practically the same partial molar heat capacity at infinite dilution, *i.e.* about +12 cal mole$^{-1}$ deg$^{-1}$. The values obtained, however, are all negative and generally become more negative as the radius of the cation (Fig. 10a) or of the anion (Fig. 10b) is increased. At higher temperatures, this trend apparently is reversed, as is clearly shown by the fact that the curves intersect, even though the error in the (extrapolated) points may be up to ±3 cal/mole·degree. With increasing temperature, the partial molar heat capacities pass through a maximum, which for all electrolytes falls within the remarkably narrow range of 50 to 80 °C.

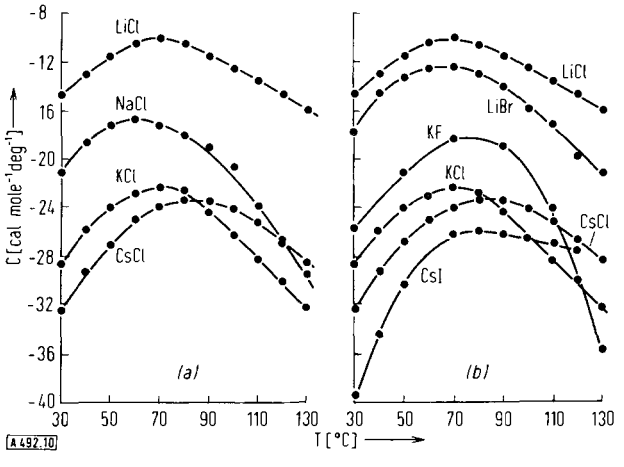



Fig. 10. Partial molar heat capacities C of alkali metal chlorides in aqueous solution (in the standard state), for demonstration of the influence of various cations (a) [27, 29, 30] and anions (b) [27, 30].

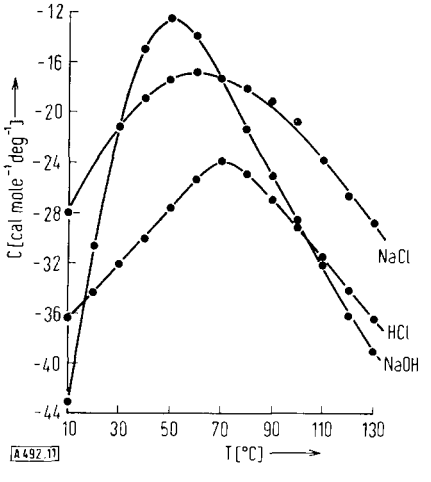



Fig. 11. Partial molar heat capacities C of HCl, NaOH, and NaCl in aqueous solution (standard state) [27–29].

The negative partial molar heat capacities of the dissolved electrolytes show that the heat capacity of water is much lower in these electrolyte solutions than in the pure state. Since the abnormally high heat capacity of water is due to the thermal decay of hydrogen bonds, this means that there are fewer hydrogen bonds present in the electrolyte solution, *i.e.*, that a large number of hydrogen bonds have already been broken during the dissolution of the electrolyte.

This is not due only to structure breaking. Many hydrogen bonds are also removed during the formation of ordered hydration shells, since the $H_2O$ molecules used must be withdrawn from the water structure. This process is important in the case of univalent ions, particularly $Li^+$, $F^-$, and the water ions $H^+$ and $OH^-$. The partial molar heat capacities of HCl and NaOH in Fig. 11 are at some temperatures much more negative than those of NaCl; this is mainly due to the fact that the protons and the hydroxide ions form special hydration structures in water (Fig. 12).

Several factors are responsible for the decrease in the partial molar heat capacities with increasing ionic radii of the alkali metal and halide ions. The relatively large differences between the LiCl and NaCl curves in Fig. 10a and between the KF and KCl curves in Fig. 10b are probably due mainly to the fact that the thermal splitting-off from the ordered hydration shells of $Li^+$ and $F^-$ in this temperature range makes a higher dissociation contribution to the molar heat capacity than in the case of $Na^+$ and $Cl^-$. On the other hand, the steps from $K^+$ to $Cs^+$ and from $Cl^-$ to $Br^-$ and $I^-$ are due to the increase in the structure-breaking action with increasing ionic radius, the principal factor in this case being the break-off effect (see Section II.1.).

The maximum in the curve of partial molar heat capacity against temperature can be correlated with the breakdown ranges of the two types of structural unit in water, *i.e.* the clusters and the molecular aggregates. Near room temperature, the structure-breaking action affects mainly the clusters; this explains the strongly negative molar heat capacities in this temperature range. When the temperature is increased, this effect decreases parallel with the number and size of clusters still present in pure water. Above about 60 °C, the breakdown of molecular aggregates by the electric fields of the ions becomes more important, and the partial molar heat capacities again become more negative, the steepness of the decrease depending on the size of the ion. Thus the molecular aggregates are more strongly broken down by smaller ions with their higher field strengths, *i.e.*, the order of the curves is reversed above 100 °C. The lithium ion behaves exceptionally, since in this case the thermal decay of the ordered hydration shell still makes an appreciable positive contribution to the partial molar heat capacity even at 130 °C.


[26a] *A. Eucken*, Z. Elektrochem. angew. physik. Chem. *52*, 6 (1948).

[27] *M. Eigen* and *E. Wicke*, Z. Elektrochem. angew. physik. Chem. *55*, 354 (1951).

[28] *E. Wicke*, *M. Eigen*, and *Th. Ackermann*, Z. physik. Chem. N.F. *1*, 340 (1954).

[29] *Th. Ackermann*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 411 (1958).

[30] *Th. Ackermann et al.*, unpublished work.

The heat capacities of aqueous solutions of simple electrolytes can be understood in this way. Many of the details still remain to be clarified, but it can already be seen that a combined model is required for the structure of water, and that the ion-water interactions considered in Section II.1 must be taken into account.

From the partial molar heat capacities of HCl shown in Fig. 11, and from the densities of aqueous hydrochloric acid solutions, it was concluded about ten years ago that the proton is primarily hydrated with four $H_2O$ molecules. The model shown in Fig. 12 was then proposed for this hydration shell. According to this model, the hydronium ion $H_3O^+$ and three $H_2O$ molecules form a complex $[H_9O_4]^+$, which can add on further $H_2O$ molecules to form an outer hydration layer [28]. Within the $[H_9O_4]^+$ complex, the proton can move (or jump) rather freely along the hydrogen bonds, the resulting fluctuations giving rise to a strong continuous absorption in the infrared spectra of aqueous solutions of acids. *Ackermann* has measured the absorption in the fundamental vibration range of $H_2O$ with the aid of special cells [31]. Fig. 13 shows the strong additional continuous absorption of 5 N hydrochloric acid, which extends from the broad double band of the OH stretching vibration to beyond the deformation band at 1640 $cm^{-1}$. Since then, various other authors have observed $[H_9O_4]^+$ complexes under different conditions. *Beckey* found $[H_9O_4]^+$ complexes in the course of mass-spectroscopic studies with a field-emission ion source operated in the presence of water vapor [32]. *Rudolph* and *Zimmermann* recently measured the infrared absorption of solid hydrogen bromide tetrahydrate at −170 °C, and concluded from the analysis of the spectrum that the substance has the structure $[H;O_4]^+Br^-$, with $[H_9O_4]^+$ as shown in Fig. 12 [33].

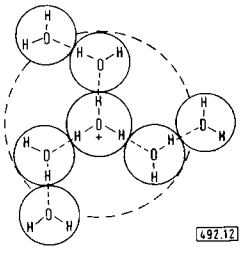



Fig. 12. Hydration of the proton in aqueous solution with formation of the $[H_9O_4]^+$ complex [28].

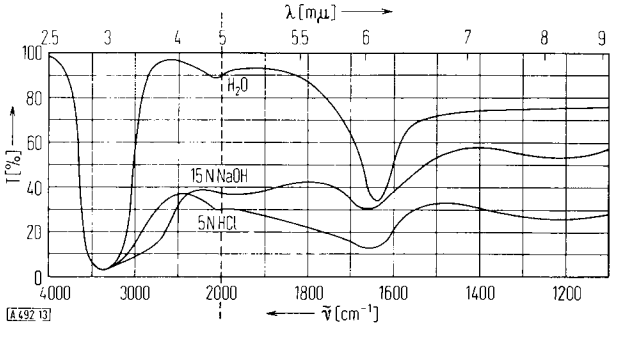
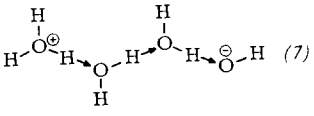



Fig. 13. Infrared absorption of aqueous 5 N HCl and 15 N NaOH in comparison with pure water in the fundamental vibration region of $H_2O$ [31].

Analogously it has been shown that the hydration shell of the hydroxide ion probably has a similar structure [34], again involving fluctuation of protons along hydrogen bonds. Concentrated aqueous NaOH solutions have been found to give a continuous additional absorption similar to that found for hydrochloric acid (cf. Fig. 13) [31]. The mobility of the protons in these hydrate structures contributes to the extreme rapidity of neutralizations. Thus when $H^+$ and $OH^-$ ions approach each other so closely that the structures of their hydration shells coalesce, the proton spontaneously closes the remaining gap by jumping along hydrogen bonds. *Eigen* and *De Maeyer* measured the rate of neutralization with the aid of the dissociation field effect [35], and found that the last 5 to 8 Å (*i.e.* two to three H-bond lengths) between the proton and the hydroxide ion are covered by proton jumps as described above [see formula *(7)*].



(7)

Structure formation and transport mechanisms of this nature are generally of considerable importance to protolytic reactions in aqueous media; they are particularly important to the influence of the pH on rates of reaction in biological systems (acid-base and enzyme catalysis [36]).

### b) Heat Capacities and Hydration of the Second Kind

The (extrapolated) partial molar heat capacities of a number of organic salts are shown in Fig. 14 [37]. Most of the values are positive, unlike those of simple electrolytes (Figs. 10 and 11). This is chiefly due to the con-

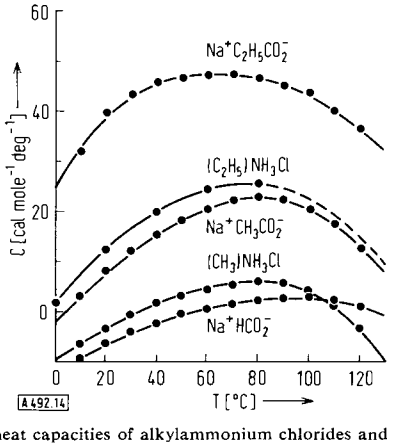



Fig. 14. Partial molar heat capacities of alkylammonium chlorides and of sodium salts of fatty acids in aqueous solution (standard state) [37].

[31] *Th. Ackermann*, Z. physik. Chem. N.F. *27*, 253 (1961).

[32] *H. D. Beckey*, Z. Naturforsch. *14a*, 712 (1959); *15a*, 822 (1960).

[33] *J. Rudolph* and *H. Zimmermann*, Z. physik. Chem. N.F. *43*, 311 (1964).

[34] *Th. Ackermann*, Discuss. Faraday Soc. *24*, 180 (1957).

[35] *M. Eigen* and *L. De Maeyer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 986 (1955).

[36] *M. Eigen*, Angew. Chem. *75*, 489 (1963); Angew. Chem. internat. Edit. *3*, 1 (1964).

[37] *Th. Ackermann* and *F. Schreiner*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 1143 (1958); *F. Schreiner*, Dissertation, Universität Hamburg, 1959.

tributions of the vibrations and internal rotations in the organic ions. However, the increment of 15 to 20 cal $mole^{-1}$ $deg^{-1}$ resulting from the introduction of one additional $CH_2$ group into the alkylammonium or fatty acid ion is surprisingly large; the same increment per $CH_2$ group was found by measurements on aqueous solutions of the free fatty acids [37]. In the corresponding hydrocarbons, or in the pure liquid acids, one additional $CH_2$ group contributes with its thermal degrees of freedom only 5 to 10 cal/mole degree to the molar heat capacity. In aqueous solution, therefore, the greater part of the increment observed, corresponding to about 10 cal/$mole^{-1}$ $deg^{-1}$, must be due to other causes. It is, in fact, due to "hydration of the second kind", *i.e.*, an intensified hydrogen-bond structure in the vicinity of the hydrocarbon groups; the extra contribution to the heat capacity comes from the thermal decay of this structure with rising temperature. The maximum in the curve of the partial molar heat capacity of the dissolved organic electrolytes against temperature (Fig. 14) is due to the contributions of the ions, as explained earlier for monatomic ions.

The structure formation of water in the vicinity of non-polar groups, *i.e.*, the greater rigidity of the mutual orientation of adjacent $H_2O$ molecules (short-range order) provides an explanation for the fact that non-polar gases such as hydrocarbons dissolve exothermically in water, the entropy of the system simultaneously undergoing an abnormally large decrease. This explanation was first offered by *Frank* and *Evans* [38]; however, the term "iceberg formation" coined by these authors has often led to the view that the structure formation in the vicinity of non-polar particles consists in the enlargement and stabilization of the flickering clusters with their framework of tetrahedral hydrogen bonds (see, *e.g.*, *Némethy* [17]) [*]. In reality, however, the chemical shift of the proton resonance of water (Section II.4d) indicates that the structure in this case is not one with tetrahedral hydrogen bonds, but involves predominantly non-tetrahedral linking of neighboring $H_2O$ molecules.

Structure formation in the vicinity of non-polar dissolved particles has also been correlated with the structure of gas hydrates, in which $H_2O$ molecules form crystalline cages around non-polar and weakly polar molecules such as hydrocarbons or halogenated hydrocarbons (cf. Fig. 8). These hydrogen-bond structures, which were elucidated by *Claussen* [39] and *v. Stackelberg* [40], resemble a particularly bulky modification of ice. Water molecules can be separated from salt solutions by the formation of solid hydrates with gases (*e.g.* propane) under pressure, even above the normal freezing-out temperature; this procedure, termed gas hydrate process, has been suggested for the desalineation of sea water [41]. However, these strictly ordered cage structures in the solid state have relatively little connection with hydration of the second kind in the case of dissolved non-polar particles. On the other hand, an intensified short-range order analogous to hydration of the second kind can be assumed to occur at water surfaces. It is due to similar electrostatic factors (boundary effects) and is responsible for the anomalously high surface tension of water. Thus structure formation in the vicinity of non-polar groups may be regarded as the origin on a molecular scale of the development of an interface between water and a non-polar medium [37].

If two non-polar groups (*e.g.*, alkyl side-chains) surrounded by $H_2O$ molecules with an intensified short-range order approach each other, the regions of short-range order tend to coalesce to form a hydration zone of the second kind surrounding both groups (this reduces the number of $H_2O$ molecules involved in this ordered zone, and so leads to a gain in entropy). The result is an effect similar to surface tension: the non-polar groups tend to form micelles, and behave as if the strength of the attractive forces between them were increased.

This effect is often discussed in connection with the stabilization of the tertiary structure of proteins in aqueous solution; the so-called "hydrophobic bonds" between non-polar side groups of the polypeptide chains are thought to assist the hydrogen bonds in maintaining the protein structures [42].

### c) Microwave Spectroscopy. Dielectric Relaxation

The close agreement between the dielectric constant of water at 0 °C and that of ice is an important argument in favor of the assumption that regions of order similar to that in ice still exist in the liquid state. The rapid reorientation of the $H_2O$ dipoles in the electric field (which, according to *Hasted*, has a relaxation time of $0.8 \times 10^{-11}$ sec in water at 25 °C [4,42a]) suggest that these zones are not very large, and that they are constantly being broken down and re-formed in a rapid sequence of thermal-statistical fluctuations, *i.e.* they are "flickering clusters". The decrease in the dielectric constant with increasing temperature up to about 100 °C can be correlated with the thermal breakdown of the clusters. Since the molecular aggregates with predominantly non-tetrahedral H-bonds replacing these clusters also are strongly polarizable, the dielectric constant and its temperature coefficient remain remarkably large (55.5 at 100 °C; 34.5 at 200 °C) even at higher temperatures.

Aqueous solutions exhibit a region of dielectric dispersion at wavelengths between 1 and 10 cm in the same region as pure water (characteristic wavelength for pure

[38] *H. S. Frank* and *M. W. Evans*, J. chem. Physics *13*, 507 (1945).

[*] Note added in proof: *A. Ben-Naim*, J. phys. Chem. *69*, 1922 (1965) has shown that a preference for larger clusters in the vicinity of non-polar molecules results from calculations of the energetic interaction if it is assumed that the clusters are "compact", *i.e.* that they do not incorporate the non-polar groups – as is assumed by *Nemethy* and *Scheraga* – but interact with these groups only at their "surfaces". The calculation shows a stabilization of larger at the expense of smaller clusters because in the former the surface/volume ratio is lower.

[39] *W. F. Claussen*, J. chem. Physics *19*, 259, 662, 1425 (1951).

[40] *M. v. Stackelberg* and *H. R. Müller*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *58*, 25 (1954); *62*, 130 (1958).

[41] *W. G. Knox et al.*, Dechema-Monographien, Vol. *47*. Verlag Chemie, Weinheim/Bergstr. 1962, p. 839.

[42] *H. A. Scheraga*, Ber. Bunsenges. physik. Chem. *68*, 838 (1964).

[42a] *J. B. Hasted et al.*, J. chem. Physics *29*, 17 (1958).

water: $\lambda_w$ = 1.56 cm at 25 °C). *Hasted et al*[4, 42a] showed the existence of groups of substances (see Table 1) whose solutions give dispersion curves that can be regarded (as in the case of pure water) as a uniform relaxation process with a single relaxation time. The dipole molecules listed in Table 1, the smallest of which is propionic acid, are aligned relatively slowly with the field direction; the dielectric dispersion range due to this reorientation process, is situated at considerably longer wavelengths. Thus in the microwave region, *i.e.* from 1 to 10 cm, there is no dipole contribution from the solute molecules to the dielectric constant of the solution. Since the effect of displacement polarization of the solute can be readily estimated, it is possible to study the dielectric behavior of the water alone. This is an advantage of dielectric relaxation methods in the study of the effects of solutes on the structure of water.

The measurements yield the limiting value of the dispersion stage towards long wavelengths, *i.e.* the "static" dielectric constant $\varepsilon_{st}$, which, as described above, contains no dipole component due to the solvent. On the other hand, the frequency of the maximum of absorption can be determined, and hence the characteristic wavelength $\lambda_s$, which is related to the relaxation time by: $\lambda_s/2\pi c = \tau$, where $c$ is the speed of light. This dielectric relaxation time $\tau$ is closely related to the reorientation of the $H_2O$ molecules as a result of thermal motion of the molecules, and can be approximately (*i.e.* disregarding the effects of the local fields) identified with the average reorientation time, which is found by averaging over all the states of $H_2O$ molecules that exist in the solution. $\varepsilon_{st}$ and $\lambda_s$ vary linearly with the concentration c of the solutions up to c = 1 to 2 mole/*l*. Table 1 shows the gradients of the experimental curves for a representative selection of solutes. The negative values of $[\varepsilon_{st}(c) - \varepsilon_w]/c$ in the second column of the Table show that the static dielectric constant is reduced by the solutes studied.

Table 1. Influence of solutes on the static dielectric constant, $\varepsilon_{st}(c)$, and on the characteristic wavelength, $\lambda_s(c)$, of water in solutions of molarity c at 25 °C [4]. $\varepsilon_w$, $\lambda_w$ are reference values for pure water.

| Solutes | $(\varepsilon_{st}(c) - \varepsilon_w)/c$ [l/mol] | $100\cdot(\lambda_s(c) - \lambda_w)/c$ [*] [cm·l/mol] |
|---|---|---|
| Dioxane | −8 | +20 |
| t-Butyl alcohol | −7 | +40 |
| Aniline | −8 | +15 |
| Propionic acid | −7 | +20 |
| NaF | −10 | − 5 |
| NaI | −17 | −25 |
| LiCl | −15 | −10 |
| RbCl | −13 | −20 |
| HCl | −20 | ≈ 0 |
| $MgCl_2$ | −30 | −10 |
| Na propionate | −14 | +15 |
| $(C_3H_7)NH_3Cl$ | −14 | +15 |
| $(C_2H_5)_4NCl$ | −22 | +30 |

[*] For pure water at 25 °C: $\lambda_w = 1.56$ cm; $\tau_w = 0.83 \times 10^{-11}$ sec. A value of +10 corresponds to an increase of $0.05 \times 10^{-11}$ sec in the relaxation time of a 1 M solution over that in pure water.

This is due to three effects, all of which act in the same sense: (a) when the solution is formed, regions that previously contained a strongly polarizable water structure are occupied by the much less polarizable particles of the solute; (b) strong electrostatic fields fix the orientations of the water dipoles in ordered hydration shells; (c) structure-breaking effects preferentially break down the clusters, which make a large contribution to the dielectric polarization. Since several effects are simultaneously present, it is difficult to draw definite conclusions from the results. It can be stated, however, that the results show no evidence of effects that increase the dielectric constant, such as formation or stabilization of frameworks with tetrahedral H-bonds (*e.g.* clusters).

It can be seen from Table 1 that the differences in the relaxation times are more specified than the differences in the static dielectric constants. The values in the third column of the Table can be divided into three groups. The first group comprises weakly polar neutral substances and weak organic electrolytes, which retard reorientation relatively strongly; the orientation of the $H_2O$ molecules in the vicinity of these dissolved particles is more rigid, on average, than in pure water (hydration of the second kind). This effect also prevails (as expected) in the third group, which includes salts of fatty acids and alkylammonium salts. Owing to the influence of the ionic charge, however, the effect is weaker in this case. In the second group (alkali metal halides), on the other hand, the average relaxation time is reduced, *i.e.* the $H_2O$ dipoles can reorient themselves more easily; the value obtained for hydrochloric acid was the same as that for pure water.

The fact that in these cases the structure formation in the ordered hydration shells of $H^+$, $Li^+$, $Mg^{2+}$, and $F^-$ does not outweigh the structure-breaking effect, so leading to an increase in the average relaxation time, probably is due to the method of averaging inherent in the relaxation measurements. The various states of the $H_2O$ molecules are assigned weighting factors that increase with the contribution made by the state in question to the total dielectric polarization. The contribution made by $H_2O$ molecules in ordered ion-hydration shells decreases as the molecules become more firmly fixed so that their relatively long relaxation times have no marked influence on the average.

The order in which the electrolytes listed in Table 1 facilitate the reorientation of the $H_2O$ molecules (HCl < NaF, LiCl < RbCl, NaI) is the same as the order in which their structure-destroying action increases. However, the "origin" of the structure forming-structure breaking scale is displaced here towards the side of structure breaking compared to other methods.

### d) Chemical Shift of the $H_2O$ Proton Resonances in Aqueous Solutions

The most important advances of recent years on the problem of the structure of water and aqueous solutions have been achieved with the aid of nuclear magnetic resonance spectroscopy. Only a representative selection of the results obtained will be discussed here. The chemical shift is a measure of the difference in polarity of the $H_2O$ molecules in various bonding states, *i.e.* a measure of the extent to which the proton is shielded. The relaxation measurements mentioned below give the most reliable information available at present about the dynamic behavior of the $H_2O$ molecules (reorientation times)[*].

[*] For the principles and the methods of measurement of nuclear magnetic resonance, see *H. Strehlow* [43].

[43] *H. Strehlow*: Magnetische Kernresonanz und chemische Struktur. Steinkopff, Darmstadt 1962; Ber. Bunsenges. physik. Chem. 67, 250 (1963).

The chemical shift of the proton resonances of the water in various diamagnetic electrolyte solutions in relation to pure water was first studied by *Hertz* and *Spalthoff*[44, 45], by means of the "internal standard" method. A little tert.-butyl alcohol was added to the solutions or to the pure water, and the methyl protons of the alcohol were used as internal standard. The results are shown in Figs. 15 and 16. Only one resonance line was obtained

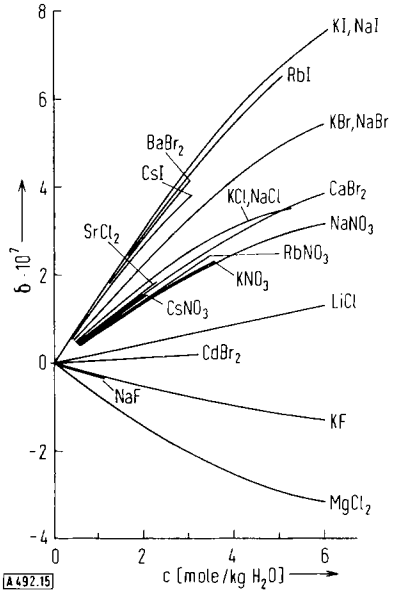



Fig. 15. Chemical shift $\delta$ relative to pure water of the $H_2O$ protons in aqueous solutions of inorganic electrolytes, as a function of concentration at 25 °C. $\delta = (H_c - H_0)/H_0$ ($H_c$ = resonance field of the $H_2O$ protons in a solution of concentration c; $H_0$ = resonance field in pure water) [44].

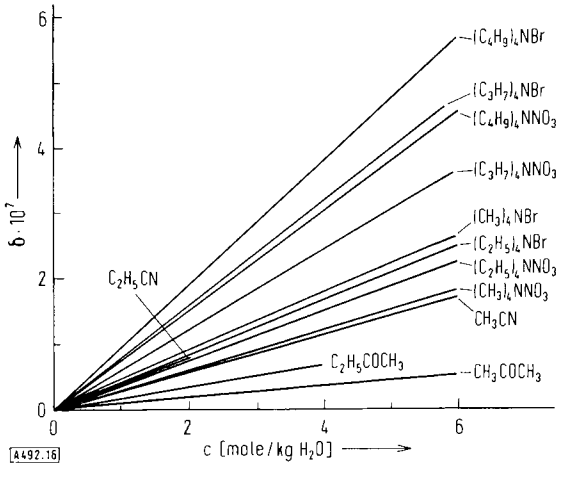



Fig. 16. Chemical shift of the $H_2O$ protons in aqueous solutions of substances containing hydrocarbon groups, at 25 °C [44].

for the $H_2O$ protons in every case. It may therefore be concluded that the $H_2O$ molecules change so rapidly from one state to another that the chemical shift obtained is an average for all these states (exchange takes less than $10^{-7}$ sec even in the ordered hydration shells of the alkaline earth ions).

It can be seen from Figs. 15 and 16 that in nearly all the solutions studied, these average chemical shifts are positive in relation to pure water, *i.e.* a higher external magnetic field is required for resonance of the $H_2O$ protons than in the case of pure water. This means that in these solutions, the contribution of such molecules to the chemical shift predominates in which the diamagnetic screening of the protons by the electron clouds is stronger than in pure water. A negative chemical shift, on the other hand, would indicate that the contributions of $H_2O$ molecules predominate whose protons are less strongly shielded and which are therefore more polar than in pure water. This is the type of behavior expected in $H_2O$ molecules that are built into the ordered hydration shell of ions, and should therefore be particularly noticeable in solutions containing $Li^+$, $F^-$, and alkaline earth ions.

In fact, the only solutions studied that give negative chemical shifts (see Fig. 15) are those of NaF, KF, and $MgCl_2$. Even LiCl solutions give positive chemical shifts, while the positive shifts are still stronger for solutions of $SrCl_2$, $CaBr_2$, and $BaBr_2$. In these cases the influence of the ordered hydration shell around the cations is evidently outweighed by opposing effects. The only effects of this type that could be involved are those of the halide ions $Cl^-$, $Br^-$, and $I^-$, so that these must cause a strong positive shift of the resonances of neighboring water protons. This positive shift increases stepwise in the above order, as can be seen from the values for the alkali metal chlorides, bromides, and iodides in Fig. 15 (the behavior of the nitrates is almost the same as that of the chlorides). The effects of the alkali metal ions from $Na^+$ to $Cs^+$ differ only slightly. The phenomenon is therefore characteristic of large, highly polarizable anions, and is obviously the same as the effect discussed in Section II.1 in connection with the break-off of the water structure; thus protons of adjacent $H_2O$ molecules are embedded in and shielded by the charge cloud of the ions, and the positive chemical shift is due to the (internal) diamagnetism of the shielding electronic charges.

A positive proton resonance shift has also been observed for pure water with increasing temperature; the chemical shift increases linearly with temperature, at 100 °C it is $\delta = 7 \times 10^{-7}$ relative to pure water at 25 °C [44]. This shows that the water molecules, on average, become less polar as the temperature is raised, *i.e.* as the thermal dissociation of the structural units in the order clusters – molecular aggregates – single molecules progresses. Since the molecular aggregates contain many non-tetrahedral hydrogen bonds, the $H_2O$ molecules in this state are less polar (*i.e.* their protons are more strongly shielded) than in the tetrahedral hydrogen bonds of the flickering clusters; in the unbonded state, *i.e.* as monomers, the $H_2O$ molecules are even less polar than in the molecular aggregates. (Measurements on water vapor and on very dilute solutions of $H_2O$ in carbon tetrachloride indicated a strong positive shift ($\delta = 4.3 \times 10^{-6}$) relative to pure water at 25 °C.)

The surprising linearity of the changes in the proton resonance shift with temperature in the case of pure water

[44] *H. G. Hertz* and *W. Spalthoff*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *63*, 1096 (1959).

[45] *H. G. Hertz*, Ber. Bunsenges. physik. Chem. *67*, 311 (1963).

is probably connected with the superposition of these two effects. Thus ice, in which the number of tetrahedral hydrogen bonds is a maximum (two per $H_2O$ molecule), should give a relatively strong negative shift in relation to liquid water. This cannot be verified by measurement, since the resonance signals for ice (as for most solids) are so broad that it is impossible to determine the resonance frequencies with the required accuracy (±1 c/s for the examples in Fig. 15). However, if the number and stability of the "ice-like" clusters in water were increased by solutes, this would lead to a negative chemical shift of the proton resonance of water in the solutions in question. *Hertz* and *Spalthoff*[44] carried out measurements on quaternary ammonium salts and on organic substances that give neutral solutions in water in an effort to detect this "iceberg formation" (*Frank* and *Evans*[38]).

It can be seen from Figure 16 that the shifts obtained are always positive in relation to pure water, and increase with the length of the alkyl group. This indicates that the intensified structure of water in the neighborhood of non-polar groups, *i.e.* hydration of the second kind, does not involve ice-like structures. Instead, the adjacent $H_2O$ groups must be joined by linkages with stronger electrostatic screening of the protons, *i.e.* linkages such as the non-tetrahedral hydrogen bonds described in Section I.2.

### e) Nuclear Magnetic Relaxation Rate

When the thermal equilibrium distribution of the nuclear spins over the energy states in a magnetic field is temporarily disturbed, the disturbance decays with a time constant $T_1$. The reciprocal $1/T_1$ is known as the relaxation rate. *Hertz* and *Zeidler*[46a] have shown that the relaxation rate for the proton nuclear spins of the $H_2O$ molecules in water and in aqueous solutions and provide information about the average time required for the $H_2O$ molecules to execute one (hindered) rotation. These "reorientation times" are approximately proportional to the measured relaxation rates for the proton nuclear spins. The values obtained as a result of this averaging over states of $H_2O$ molecules with different "mobilities" are more reliable with regard to structure forming and breaking in electrolyte solutions than the values obtained by the dielectric method involving the average reorientation times of $H_2O$ dipoles. It can be seen from Fig. 17 that the relaxation rates, and hence the reorientation times, are lower on average in the solutions of the chlorides, bromides, iodides (also nitrates) of potassium, rubidium, and cesium than in pure water. Thus breakdown of structure predominates in these cases; the hydration of the ions is predominantly disordered, and the dynamic behavior of the solvent water is relatively "fluid". On the other hand, the average reorientation times of the $H_2O$ molecules in the solutions of the Li and Na salts, of KF, and of the alkaline earth halides are greater than in pure water,

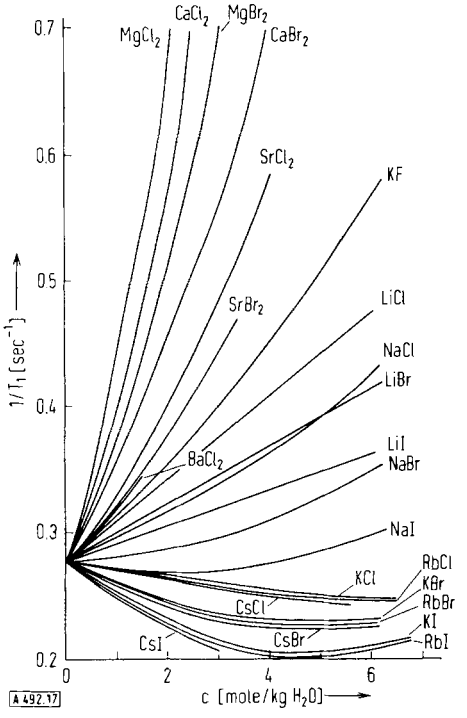



Fig. 17. Relaxation rate $1/T_1$ of the nuclear resonance of the $H_2O$ protons in aqueous solutions of inorganic electrolytes as a function of concentration at 25 °C ([45] and personal communication from *H. G. Hertz* and *M. D. Zeidler*).

indicating that the hydration of the ions in these cases is predominantly ordered, and the dynamic behavior of the water is relatively "rigid" [*].

This method was specially adapted by *Hertz* and *Zeidler* for the study of the hydration of non-polar groups in aqueous solution[46b]. To avoid interference due to the protons of solutes, only deuterated solutes were used in one method; the results are illustrated in Fig. 18 for dimethyl sulfoxide, potassium acetate, and tetramethylammonium nitrate. The average reorientation time of the $H_2O$ molecules increases steadily with the concentration of these substances (similar behavior is found with potassium oxalate).

Another method for solutes containing hydrogen involves the use of deuterium oxide as solvent; the reorientation times of the $D_2O$ molecules are then studied by means of the deuteron nuclear quadrupole resonance signal. Experimental results obtained with quaternary ammonium salts are shown in Fig. 19. It can be seen that the orientation of the $D_2O$ molecules becomes increasingly rigid on passing from methyl through ethyl to propyl groups. With butyl groups, the effect decreases again, probably owing to coiling or

[46a] *H. G. Hertz* and *M. D. Zeidler*, Ber. Bunsenges. physik. Chem. *67*, 774 (1963); *M. D. Zeidler*, Dissertation, Universität Münster, 1963.

[*] Note added in proof: *D. W. McCall* and *D. C. Douglas*, J. phys. Chem. *69*, 2001 (1965), using the NMR spin-echo method, have studied the self-diffusion of $H_2O$ in pure water and in electrolyte solutions at 23 °C. The measured (average) self-diffusion coefficient generally decreases with increasing electrolyte concentration; an increase was found, however, for KBr, KI, CsI, and $KNO_3$. The concentration dependence is essentially analogous to that of the solution viscosity. The authors correlate their results with the proton chemical shifts (Fig. 15); they agree much better, however, with the concentration dependence of the relaxation rates in Fig. 17.

[46b] *H. G. Hertz* and *M. D. Zeidler*, Ber. Bunsenges. physik. Chem. *68*, 821 (1964).

micelle formation. The same qualitative results were obtained in the homologous series of fatty acids and their salts in deuterium oxide [46b]. Further, from the increase of the relaxation rates with temperature (which was studied up to 80 °C), it can be concluded

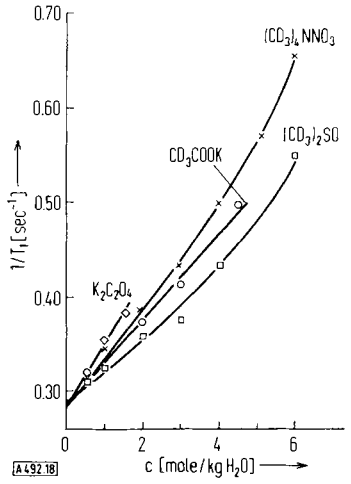



Fig. 18. Relaxation rate $1/T_1$ of the nuclear resonance of the $H_2O$ protons in aqueous solutions of organic substances that contain no protons, as a function of the molal concentration at 25 °C [46b].

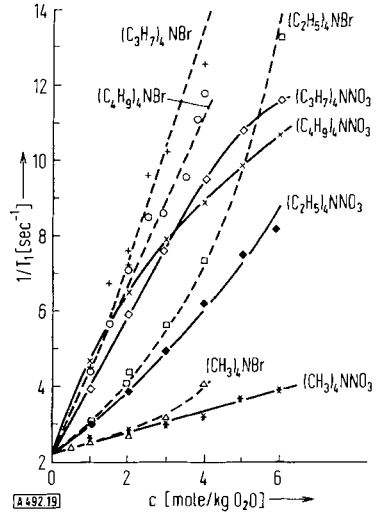



Fig. 19. Relaxation rate $1/T_1$ of the nuclear quadrupole resonance of the $D_2O$ deuterons in solutions of tetraalkylammonium salts in $D_2O$ at 25 °C [46b].

that these solutions contain $H_2O$ molecules whose reorientation is much more strongly restricted than in pure water. These measurements have given the most direct evidence so far obtained for structure formation by $H_2O$ molecules in the neighborhood of non-polar groups [47].

Some typical results of nuclear magnetic relaxation measurements are given in Fig. 20 for an aqueous solution of tetraethylammonium bromide. The hydration zone of the ions is indicated in every case. The values beside the curved arrows show the reorientation times of the particles in question, while those near the straight arrows are the average times spent by the particles at a given site between two jumps. These residence times were found from the self-diffusion of the particles. Both the reorientation time and the residence time can be taken as $10^{-11}$ sec in pure water. In the hydration sphere of the bromide ions, the reorientation and transposition take $7 \times 10^{-12}$ sec, *i.e.* the $H_2O$ molecules are more mobile than in pure water; in the neighborhood of the tetraethylammonium ion, the molecules take $2 \times 10^{-11}$ sec for one reorientation, *i.e.* they are rather more

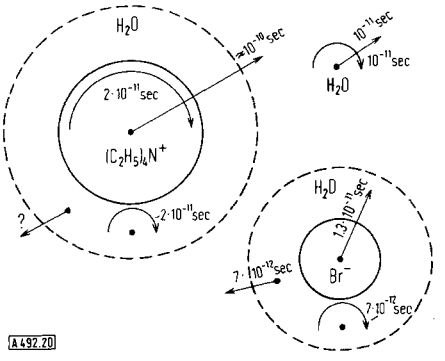



Fig. 20. Reorientation and residence times of the $H_2O$ molecules in various zones and of the ions in an aqueous solution of tetraethylammonium bromide at 25 °C. Concerning the division into zones and the time values, cf. *H. G. Hertz* and *M. D. Zeidler* [46a, 46b].

rigidly bound than in pure water. The same reorientation time is found for the quaternary ammonium ion itself. This remarkably low value for such a large, bulky particle shows that the ion experiences little hindrance to rotation inside its "hydration sphere of the second kind"; this is expected, since there are no specific (orientation-dependent) interactions between the alkyl groups and the adjacent $H_2O$ molecules. The residence time of the bromide ion inside its hydration zone ($1.3 \times 10^{-11}$ sec) is remarkably short, obviously owing to the increased mobility of the $H_2O$ molecules in this zone.

It follows from Fig. 20 that it is only a crude approximation to describe the interactions between dissolved particles and $H_2O$ molecules in water by regions of "structure breakdown" and "structure formation". Beyond this the physicochemical properties of the solutions are strongly dependent on the dynamic behavior of the $H_2O$ molecules within the various structure regions, *i.e.* their mobility in reorientation and transposition. Some apparent contradictions reported in the literature may be explained by the different ways of averaging – which are inherent in different experimental methods – the short-lived intermediate states.

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[47] *H. G. Hertz*, Ber. Bunsenges. physik. Chem. *68*, 907 (1964).

## Reaction of Alkyldichloroamines with Nickel Tetracarbonyl [1]

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On reaction with *N,N*-dichloro-t-butylamine or -cyclohexylamine in benzene at 0 °C, nickel tetracarbonyl evolves three moles of carbon monoxide per mole. A colorless precipitate *(1)* is formed that has a Ni:N ratio of 1:1 and is insoluble in the usual solvents.

$$2\ RNCl_2 + 2\ Ni(CO)_4 \rightarrow 2\ [RNCl_2Ni(CO)] \quad (1)$$

$$H_2O \xrightarrow{\text{excess of } H_2O} 2\ RNH_2 + 2\ NiCl_2 + 2\ CO_2$$

$$\xrightarrow{1\ \text{mole } H_2O} RHN{-}CO{-}NHR + 2\ NiCl_2 + CO_2$$

Addition of the complex *(1)* to water gives equimolar amounts of the original amine and nickel(II) chloride (carbon dioxide was determined qualitatively). However, cautious hydrolysis of *(1)* with moist benzene or moist diethyl ether permits isolation of the *N,N'*-dialkylurea in yields of 80 % calculated on the amount of nickel carbonyl that reacted; the stoichiometric amount of nickel(II) chloride remains on evaporation of the reaction mixture. Cautious deuteriolysis of the complex *(1)*, $R = C(CH_3)_3$, gives the *N*-deuteriated urea, whose $^1$H-NMR spectrum shows, as expected, only one type of proton.

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German version: Angew. Chem. *78*, 114 (1966)

[1] 2nd Communication on *N*-Halogenoamines. – Part I: *H. Bock* and *K. L. Kompa*, Angew. Chem. *74*, 327 (1962); Angew. Chem. internat. Edit. *1*, 264 (1962).

## Conformational Analysis of Bicyclopropyl by Vibrational Spectroscopy

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A large number of conformational analyses of open-chain and cyclic aliphatic compounds have been carried out, especially on derivatives of ethane and cyclohexane [1]. However, no studies have been carried out on molecules in which two aliphatic rings are linked by a single bond. We have therefore commenced a systematic investigation of the conformations of the compounds in the homologous series

$$(H_2C)_n\ CH\text{-}CH\ (CH_2)_n \qquad n = 1, 2, \ldots 5$$

*(1)*

in order to find out whether these compounds show rotational isomerism around the central C–C single bond and to determine the extent to which this isomerism depends on the strain in the rings, the spatial requirements of the rings, and the hybridization of the two central carbon atoms.

The following observations on bicyclopropyl were made:

1. The infrared spectra of the gas and liquid contain the same number of bands.

2. The number of bands in the infrared and Raman spectra is approximately halved on transition from the liquid to the solid state.

3. Most of the vibrational frequencies in the infrared and Raman spectra of liquid bicyclopropyl agree, but there is no such coincidence of spectral bands in the crystalline state (see Fig. 1).

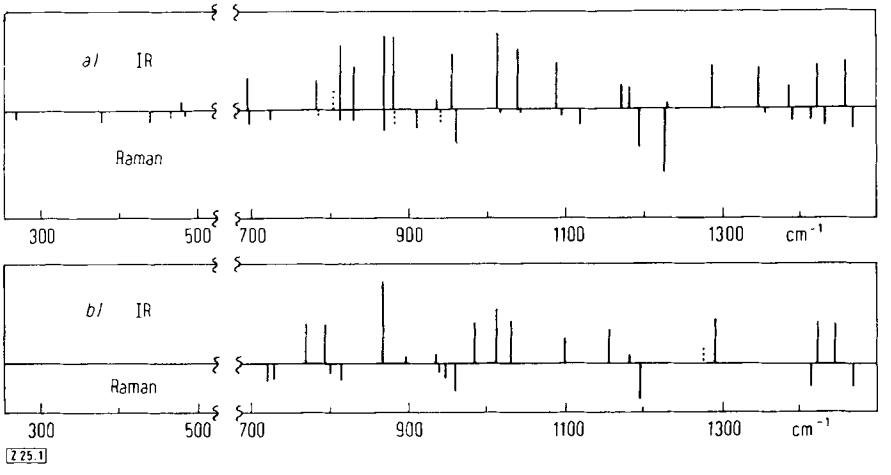


Fig. 1. Infrared and Raman spectra of (a) liquid and (b) crystalline bicyclopropyl.

Hence the solid strictly obeys the rule of mutual exclusion, *i.e.* in the crystal lattice the molecule occurs in a form with a center of symmetry. Of all the conformational isomers possible, this can only be the s-*trans*-form (see Fig. 2) which belongs to the $C_{2h}$ point group. Accordingly, all the bands in the spectra of the crystalline form can be assigned without difficulty to the normal vibrations of the s-*trans*-form and can be included in the series of spectra of cyclopropane monoderivatives ("spectral sequence" [2]).

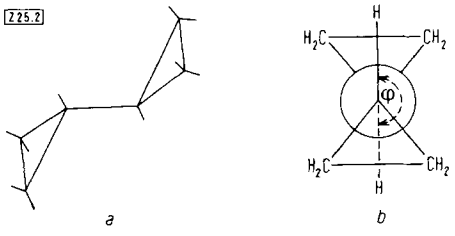


Fig. 2. s-*trans*-Conformation of bicyclopropyl.
a) Perspective; b) Newman projection (φ = angle of torsion).

When the substance is melted, numerous other bands appear in its spectra; hence there must be a rotationally isomeric form in equilibrium with the s-*trans*-form in the *liquid* phase. Preliminary measurements of the intensities revealed that both forms are present in comparable concentrations and that the position of the equilibrium changes only slightly with temperature. The coincidence of most of the infrared and Raman absorptions indicates that the rotational isomer does not have a center of symmetry.

We have also prepared 1-methyl- and 1,1'-dimethylbicyclopropyl and examined them analogously. The infrared and Raman spectra of the monomethyl derivative did not permit a definite decision as to the nature of the rotational isomers because this compound has only low symmetry (s-*trans*- and s-*cis*-forms have $C_s$, other forms have $C_1$ symmetry). The dimethyl derivative has a symmetry corresponding to that of the unsubstituted compound and gives infrared spectra in the liquid and crystalline states containing the same number of bands (apart from crystal field splittings). The infrared and Raman spectra of the liquid dimethyl derivative obey the rule of mutual exclusion. Consequently dimethylbicyclopropyl also occurs in the s-*trans*-form ($C_{2h}$); here intramolecular rotation is restricted by steric hindrance.

Similar spectroscopic measurements with 1,3-butadiene, which is formally the first member of the series *(1)*, showed that it behaves exactly like dimethylbicyclopropyl. Within the accuracy of our concentration measurements (3–4 %), there is no s-*cis*-butadiene present in any of the three states of aggregation of the compound between −160 and 30 °C; this is in agreement with findings from another approach [3].

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[1] *E. L. Eliel, N. L. Allinger, S. J. Angyal,* and *G. A. Morrison*: Conformational Analysis. Interscience, New York-London, 1965.

[2] *K. W. F. Kohlrausch*: Ramanspektren, Hand- und Jahrbuch der Chemischen Physik. Akademische Verlagsgesellschaft, Leipzig 1943, Vol. 9/VI.

[3] *D. R. Lide*, J. chem. Physics *37*, 2074 (1962); *R. A. Beaudet*, ibid. *42*, 3758 (1965); *D. J. Marais, N. Sheppard,* and *B. B. Stoicheff*, Tetrahedron *17*, 163 (1961); *A. Almenningen, O. Bastiansen,* and *M. Traetteberg*, Acta chem. Scand. *12*, 1221 (1958).

## Conformations of Bicyclopropyl and Bicyclobutyl by Electron Diffraction

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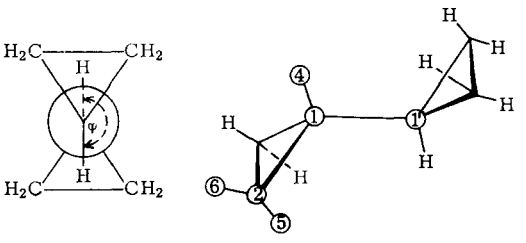
The problem of the shapes of the rotational isomers of bicyclopropyl[1] can be solved by a study of the electron diffraction of the substance in the gaseous state.

The diffraction diagrams were obtained by the sector microphotometer method and were treated in the usual way[2, 3]. All the bond lengths and valence angles (Table 1) were obtained from the experimental radial distribution curves. The forms of the rotational isomers were determined from the same data. For this purpose radial distribution curves were calculated for numerous models having various torsion angles and for mixtures thereof, and compared with the experimental curve. The best agreement was obtained for a mixture of 60 % of a non-rigid *gauche* form with 40 % of a non-rigid *s-trans*-form *(1)*; a torsion amplitude of ± 18 ° about the equilibrium angle φ was assumed for the non-rigid

Table 1. Bicyclopropyl.

| Bond | Length [Å] | u [Å] [a] |
|---|---|---|
| C–C (in the ring) | 1.517 ± 0.005 | 0.048 ± 0.002 |
| C–C (between rings) | 1.517 ± 0.01 | 0.048 ± 0.004 |
| C–H | 1.094 ± 0.02 | 0.089 ± 0.006 |
| C(2)–C(1') | 2.634 ± 0.02 | 0.070 ± 0.005 |
| C(1)–H(5) = C(1)–H(6) | 2.235 ± 0.03 | 0.118 ± 0.008 |
| ∢ H–C–H | 117.3 ± 1.5 ° | |
| ∢ H(4)–C(1)–C(1') | 115.2 ± 1.5 ° | |
| ∢ C(2)–C(1)–C(1') | 120.5 ± 1.5 ° | |

[a] u = root mean square amplitude of vibration. The values were refined by matching the theoretical to the experimental intensity curve by the least squares method.



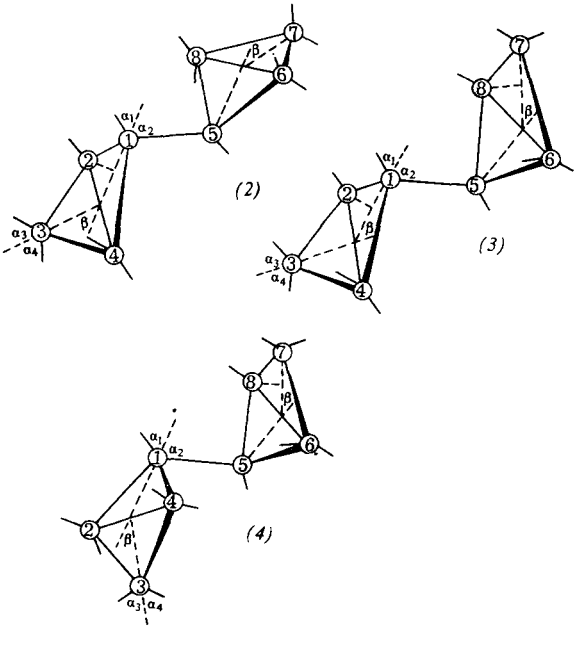

*(1a)* *(1b)*, φ = 180°

*gauche* form, the angle φ being between 35 and 40 ° because of the unusual geometry of the molecule. For the non-rigid *s-trans*-form an amplitude of ± 80 ° about the equilibrium angle φ = 180 ° had to be assumed, *i.e.*, rotation about the central C–C bond of bicyclopropyl is almost unhindered in the region 100 to 260 °. This behavior can be understood if the potential curve V(φ) of internal rotation is calculated with consideration merely of the H···H interaction[4].

The same procedure was applied for bicyclobutyl. Table 2 shows the structural parameters obtained. In this case, as the cyclobutyl ring is not planar[5], three conformations must be considered, independent of the rotational isomerism about the central C–C bond: dependent on the folding of the cyclobutane ring an equatorial (*e*) and an axial (*a*) position

Table 2. Bicyclobutyl.

| Bond | Length [Å] | u [Å] (cf. Table 1) |
|---|---|---|
| C–C (in the ring) | 1.548 ± 0.004 | 0.052 ± 0.003 |
| C–C (between rings) | 1.536 ± 0.016 | 0.051 ± 0.005 |
| C–H | 1.104 ± 0.01 | 0.085 ± 0.006 |
| C(4)–C(5) | 2.625 ± 0.02 | 0.075 ± 0.005 |
| ∢ H–C–H = $\alpha_3 + \alpha_4$ | 110.0 ± 4.0 ° | |
| $\alpha_3 = \alpha_4$ | 55,0 ± 2.0 ° | |
| $\alpha_2$ | 51.6 ± 2.0 ° | |
| $\alpha_1$ | 58.5 ± 2.0 ° | |
| β | 33.0 ± 2.0 ° | |



can be distinguished for the C(1)–C(5) and the C(5)–C(1) linkages relative to the two rings. The existence of the three forms, *ee-s-trans* ($\varphi$ = 180°) *(2)*, *ea-s-trans* ($\varphi$ = 180°) *(3)*, and *ee-gauche* ($\varphi$ = 60°), can be proved from the experimental radial distribution curve. The contribution from the *ea-gauche* form ($\varphi$ = 60 °C) is only just observable, whereas the presence of small amounts of the *aa-s-trans* ($\varphi$ = 180 °C) *(4)* and the *aa-gauche* form ($\varphi$ = 77 °C) can only be justified by statistical considerations. The best agreement between the theoretical and the experimental curve was obtained for the following composition (the amounts in brackets were not directly determinable): *ee*-form ($\varphi$ = 180 °C) 31 %, *ee*-form ($\varphi$ = 60 °C) 26 %, *ea*-form ($\varphi$ = 180 °C) 24 %, *ea*-form ($\varphi$ = 63°)[6] 12 %, [*aa*-form ($\varphi$ = 180°) 5 %], [*aa*-form ($\varphi$ = 77°) 2 %][6].

Although the relative error in the percentages is estimated as ± 10 %, the relative proportions give provisional values for the energy differences between the forms. From such calculations the non-rigid *s-trans*-form of bicyclopropyl is favored over the non-rigid *gauche* form by less than about 500 cal/mole. For bicyclobutyl the *ee-s-trans*-form is energetically the most favored, the energy difference from the *ee-gauche* and the *ea-s-trans*-form being about 550 cal/mole, and from the *ea-gauche* form about 1400 cal/mole.

Received: October 29th, 1965 [Z 97/930 IE]
German version: Angew. Chem. *78*, 142 (1966)

[1] *W. Lüttke* and *A. de Meijere*, Angew. Chem. *77*, 141 (1965); Angew. Chem. internat. Edit. *4*, 123 (1965).

[2] *O. Bastiansen* and *P. N. Skancke*, Advances chem. Physics *3*, 323 (1961).

[3] *A. Almenningen, O. Bastiansen, A. Haaland*, and *H. M. Seip*, Angew. Chem. *77*, 877 (1965); Angew. Chem. internat. Edit. *4*, 819 (1965).

[4] For applicability of this potential see *L. S. Bartell*, J. chem. Physics *32*, 827 (1960).

[5] *O. Bastiansen* and *P. N. Skancke*, Acta chem. scand. *15*, 711 (1961).

[6] The angle $\beta$ = 22° was used for these forms.

## Synthesis of 4-Methylosthenolic Acid by the Willgerodt-Kindler Reaction[1]

By Dr. K.-H. Boltze and Dr. H.-D. Dell

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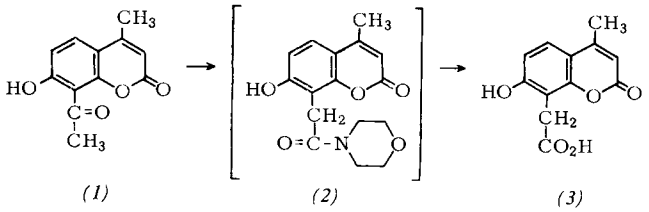
The Willgerodt-Kindler reaction (conversion of ketones into ω-carboxamides of the same chain length[2]) has previously not been used for the preparation of carboxylic acid derivatives of coumarin. Such derivatives of umbelliferone have, however, been obtained by degradation of natural products.

We have prepared 4-methylosthenolic acid *(3)* from 8-acetyl-4-methylcoumarin *(1)*[3] by a Willgerodt-Kindler reaction.



*(1)* *(2)* *(3)*

A mixture of 0.03 mole of *(1)*, 0.045 mole of morpholine, and 0.06 g-atom of sulfur was heated at 140 °C for 4 h. After addition of 32 ml of a mixture of glacial acetic acid, concentrated $H_2SO_4$, and water (80:12:18 v/v) the whole was heated for 4–6 h at the boiling point, poured while hot into 500 ml of hot water, boiled, and filtered hot. The acid *(3)* separated on cooling (crude yield: 81 %). After repeated recrystallization from water the yield of pure product was about 50 %. The acid *(3)* crystallizes as pale pink needles of m.p. 240–242 °C.

If the synthesis is carried with the 7-*O*-methyl derivative instead of *(1)*, the same acid *(3)* is formed and not its 7-*O*-methyl derivative, owing to ether cleavage.

4-Methylumbelliferone-8-propionic acid, m.p. 167–170 °C, can be obtained analogously from 8-allyl-4-methylumbelliferone[4]. In accordance with *Mansfield*'s modification[5] of the Kindler reaction of aminomethylated phenols, 8-dimethylaminothiocarbonyl-4-methylumbelliferone [needles of m.p. 250–260° (decomp.)] was obtained from 8-dimethylaminomethyl-4-methylumbelliferone, and thence 4-methylumbelliferone-8-carboxylic acid, m.p. 254–257 °C (from ethanol/dimethylformamide).

Received: October 4th, 1965 [Z 101/935 IE]
German version: Angew. Chem. *78*, 114 (1966)

[1] Part 1 of Experiments in the Coumarin Series.

[2] *F. Asinger, W. Schäfer, K. Halcour, A. Saus*, and *H. Triem*, Angew. Chem. *75*, 1050 (1963); Angew. Chem. internat. Edit. *3*, 19 (1964).

[3] Synthesis: Org. Syntheses, Coll. Vol. III, p. 283.

[4] Synthesis: *W. Baker*, J. chem. Soc. (London) *1935*, 628.

[5] *R. C. Mansfield*, 146th Meeting Amer. Chem. Soc. 1964, Abstracts of Papers 26C, 49.

## Conversion of Cobinamide into Cobyric Acid

By Dr. Gerhard Müller and Priv.-Doz. Dr. Otto Müller

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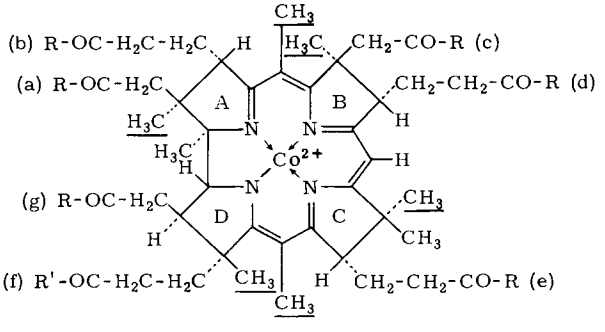
Cobyric acid *(1)*[1] is a valuable starting material for the preparation of potent antagonists of vitamin $B_{12}$[2], but so far has been isolated in substantial amounts only from a corrinoid mixture found in sewage sludge[1].

We have found that cobinamide *(2)* or vitamin $B_{12}$ obtained from fermentation mixtures can also be converted into cobyric acid.



*(1)*, R = $-NH_2$, R′ = $-OH$
*(2)*, R = $-NH_2$, R′ = $-NH-CH_2-CH(OH)-CH_3$
*(3)*, R = $-NH_2$, R′ = $-O-CH(CH_3)-H_2-NH_2$

In anhydrous hydrofluoric acid the amide group f of cobinamide rearranges, by way of the hydroxyoxazolidine derivative, to yield the cobyric ester *(3)* of 1-aminopropan-2-ol. After acylation of the amino group by acetic anhydride, the ester *(3)* is hydrolysed to cobyric acid *(1)* by piperidine/water. Vitamin $B_{12}$ is also suitable as starting material since it is rapidly degraded to cobinamide *(2)* by hydrofluoric acid. The ester *(3)* regenerates the amide *(2)* when kept in an alkaline reaction medium (*e.g.* 0.05 M $Na_2HPO_4$).

*Cobyric Acid from Cobinamide*: A solution of 1 g of cyanocobinamide (dried for 24 h at 80° over $P_2O_5$) in a mixture of 15 ml of anhydrous hydrofluoric acid and 5 ml of absolute methanol is set aside at 30 °C for 3 days. The solvent

is removed in a vacuum and the residue is taken up in 200 ml of 0.1 % aqueous hydrocyanic acid and added to a column (40 mm diameter by 100 mm) of carboxymethylcellulose.

Most of the unchanged cyanocobinamide runs through the column; the rest is eluted with 2 % acetic acid, and immediately thereafter the cobyric ester *(3)* of 1-aminopropan-2-ol is eluted with a 1:1 mixture of 2 % acetic acid and 2 % ammonium acetate solution. This ester is purified by extraction with phenol[3], taken up in 100 ml of water, and acetylated by slow, dropwise addition to 5 ml of acetic anhydride at 0 to 2 °C with stirring. After an hour the product is washed twice with 10 ml of chloroform, and the corrinoid is purified by extraction with phenol. For cleavage, the ester is kept at 0 °C for 2 h in 200 ml of 1 M aqueous piperidine solution. The mixture is washed three times with 30 ml of 2:1 isopropyl ether/1-butanol and brought to pH 5.5 by dilute hydrochloric acid. After a further phenol extraction and cellulose-column-chromatography with sec-butanol/water (10:3) the cobyric acid is obtained in pure form; yield 20–22 %.

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Publication delayed at the authors' request

[1] *K. Bernhauer, H. Dellweg, W. Friedrich, G. Gross, F. Wagner,* and *P. Zeller,* Helv. chim. Acta *43*, 693 ,696 (1960).

[2] *H. C. Heinrich* and *E. E. Gabbe* in: Vitamin $B_{12}$ und Intrinsic Factor, 2. Europ. Symp., Hamburg 1961. Enke-Verlag, Stuttgart 1962; *H. C. Heinrich, W. Friedrich,* and *P. Riedel,* Biochem. Z. *334*, 284 (1961); *W. Friedrich, H. C. Heinrich, E. Königk,* and *P. Schulze* in: Conference on $B_{12}$-Coenzymes, New York Academy of Sciences, New York 1963.

[3] *W. Friedrich* u. *K. Bernhauer,* Z. Naturforsch. *9b*, 755 (1954).

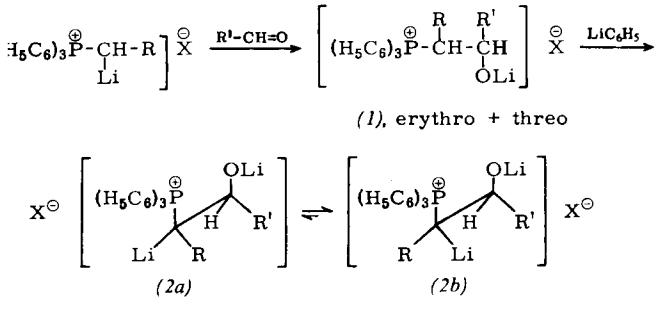
## Trans-Selective Olefin Syntheses

By Dr. M. Schlosser and K. F. Christmann

Organisch-Chemisches Institut
der Universität Heidelberg (Germany)

Usually only mixtures of *trans*- and *cis*-olefins can be obtained by the Wittig reaction. A few examples are known yielding predominantly *trans*-[1] or *cis*-[2] olefins. *trans*-Selective olefination can be expected if equilibration of the *erythro*- and *threo*-betaines *(1)*[1c] can be accelerated.

We have now found that interconversion of the diastereoisomeric betaine ylides *(2)*[3] is extremely rapid[4]. These ylides are formed if the betaine-LiX adduct *(1)* is treated with phenyl-lithium or n-butyl-lithium in ether/tetrahydrofuran (1:1) at −30 °C, and with proton donors (*e.g.*, hydrogen chloride or t-butyl alcohol) they regenerate the betaine-LiX adducts *(1)*.



*(1)*, erythro + threo



*(2a)* *(2b)*

The equilibrium between the diastereoisomeric betaine ylides lies far to the side of form *(2b)*, so that protonation gives mainly the *threo*-betaine [*threo*-*(1)*]. Subsequent treatment with potassium t-butoxide then liberates almost pure *trans*-olefin (cf. Table).

| Olefin | R | R' | Yield [%] | *trans*: *cis* |
|---|---|---|---|---|
| 2-Octene | $CH_3$ | n-$C_5H_{11}$ | 70 [b] | 99: 1 |
| 2-Octene | n-$C_5H_{11}$ | $CH_3$ | 60 [b] | 96: 4 |
| 4-Octene | n-$C_3H_7$ | n-$C_3H_7$ | 72 [b] | 98: 2 |
| 1-Phenyl-1-propene | $CH_3$ | $C_6H_5$ | 69 [a] | 99: 1 |
| 1-Phenyl-1-butene | $C_2H_5$ | $C_6H_5$ | 72 [a] | 97: 3 |
| 1-Phenyl-1-hexene | n-$C_4H_9$ | $C_6H_5$ | 75 [a] | 96: 4 |
| 1-Phenyl-1,3-pentadiene | $CH_3$ | *trans*-$C_6H_5$–CH=CH | 63 [b] | 97: 3 |
| 2-Phenyl-2-butene | $CH_3$ | [c] | 55 [a] | 89:11 |

[a] Determined gas-chromatographically.

[b] Isolated in substance.

[c] With acetophenone as carbonyl component, *i.e.*, R' = $C_6H_5$, and with $CH_3$ in place of H.

*Procedure*

The phosphonium salt (30 mmole) is suspended in 50 ml of tetrahydrofuran and 30 ml of ether and stirred with 30 mmole of ethereal phenyl-lithium solution until the Gilman test is negative (about 10 min). The solution is cooled to −70 °C and 30 mmole of aldehyde (dissolved in 20 ml of ether) is added; the mixture is stirred vigorously. As soon as decolorization is complete (5 min at −70 to −40 °C), a further 30 mmole of phenyllithium solution is added and the whole kept at −30 °C until the Gilman test is again negative (about 5 min). This solution is treated with 33 mmole of ethereal hydrogen chloride and with 45 mmole of potassium t-butoxide (as 1:1 complex with t-butyl alcohol). The mixture is stirred at room temperature for 2 h, centrifuged, and the clear supernatant liquor is poured off, washed with water until neutral, and dried. After evaporation of the solvent, the olefin is fractionated in a vacuum.

For comparison the olefins listed were prepared in parallel experiments by the conventional Wittig reaction. The *trans*:*cis* ratio (determined gas-chromatographically) varied between 75:25 (phenylhexene) and 20:80 (2-octene).

Received: October 14th, 1965 [Z 91/922 IE]
German version: Angew. Chem. *78*, 115 (1966)

[1] a) *H. O. House* and *G. R. Rasmusson,* J. org. Chemistry *24*, 4278 (1961). – b) *H. J. Bestmann* and *O. Kratzer,* Chem. Ber. *95*, 1894 (1962). – c) *M. Schlosser* and *K. F. Christmann,* Angew. Chem. *77*, 682 (1965); Angew. Chem. internat. Edit. *4*, 689 (1965).

[2] *H. Pommer,* Angew. Chem. *72*, 811 (1960), particularly p. 817; *L. D. Bergelson, V. A. Vaver, L. I. Barsukov,* and *M. M. Shemyakin,* Tetrahedron Letters *1964*, 2669; *H. Machleidt* and *R. Wessendorf,* Liebigs Ann. Chem. *674*, 1 (1964); *P. A. Chopard, R. F. Hudson,* and *R. J. G. Searle,* Tetrahedron Letters *1965*, 2357.

[3] It is uncertain whether the betaine ylides actually have the conformation shown. This representation is used merely for clarity.

[4] Cf. the rapid racemization of optically active organolithium compounds: *R. L. Letsinger,* J. Amer. chem. Soc. *72*, 4842 (1950).

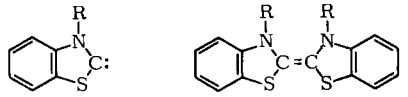
## Elimination of Hydrogen Halide from Benzo- and Naphtho-thiazolium Halides [1]

By Prof. Dr. H.-W. Wanzlick, Dr. H.-J. Kleiner, Dipl.-Ing. I. Lasch, and Dipl.-Chem. H. U. Füldner

Organisch-Chemisches Institut
der Technischen Universität Berlin (Germany)

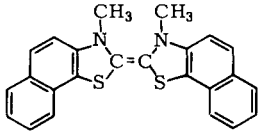
Hydrogen halide can be removed from benzothiazolium halides by heating them with triethylamine[2] or by treating them with triethylamine (or other tertiary amine) in polar solvents at room temperature[3,4], with sodium in dioxane[4], or with triethylamine in boiling acetone[5]. This leads to dimers *(2)*, of as yet unknown configuration, by way of the short-lived nucleophilic carbenes *(1)*[6]. Contrary to our pre-

vious assumption[3], the carbene moieties *(1)* cannot be isolated in substance.



*(1)* *(2)*

*N*-Methylnaphtho[2,1-*d*]thiazolium iodide (obtained from naphtho[2,1-*d*]thiazole and methyl iodide in dimethylformamide in 92 % yield, m.p. 203–204 °C), when treated with triethylamine in dimethylformamide (preferably under nitrogen) gives the brilliant red dimer *(3)* (87 %; decomp. above *ca.* 195 °C; configuration not yet known) within a few seconds even at 0 °C.



*(3)*

Like *(2)* and related systems, the compound *(3)* reacts as a "half-molecule" (cf.[1]). Thus with diazo compounds they give azines.

Whereas the compounds of type *(2)* studied so far do not show evidence of dissociation in mass spectroscopy[7], the mass spectrum of the dimer *(3)* shows the peak due to the half-molecule (m/e = 199) as well as the comparably intense peak of the molecule-ion (m/e = 398)[8].

Received: October 19th, 1965 [Z 90/921 IE]
German version: Angew. Chem. *78*, 115 (1966)

[1] Part 9 of Chemistry of Nucleophilic Carbenes. – Part 8: *H.-W. Wanzlick, B. Lachmann,* and *E. Schikora,* Chem. Ber. *98*, 3170 (1965).

[2] *J.-J. Vorsanger,* Bull. Soc. chim. France *1964*, 119.

[3] *H.-W. Wanzlick* and *H.-J. Kleiner,* Angew. Chem. *75*, 1204 (1963); Angew. Chem. internat. Edit. *3*, 65 (1964).

[4] *H. Quast* and *S. Hünig,* Angew. Chem. *76*, 989 (1964); Angew. Chem. internat. Edit. *3*, 800 (1964); cf. also *H. Quast* and *E. Frankenfeld,* Angew. Chem. *77*, 680 (1965); Angew. Chem. internat. Edit. *4*, 691 (1965).

[5] *J. Metzger, H. Larivé, R. Dennilauler, R. Baralle,* and *C. Gaurat,* Bull. Soc. chim. France *1964*, 2857.

[6] *H. Balli,* Angew. Chem. *70*, 442 (1958), formula V; *76*, 995 (1964); Angew. Chem. internat. Edit. *3*, 809 (1964).

[7] We thank Dr. *H. Rehling* (Farbwerke Hoechst) for these measurements.

[8] Cf. *H. Prinzbach, H. Berger,* and *A. Lüttringhaus,* Angew. Chem. *77*, 453 (1965); Angew. Chem. internat. Edit. *4*, 435(1965).

## Synthesis of 2-Alkyl-1,3-dilithiobenzenes and 2-Alkylisophthalic Acids

By Dr. F. M. Stoyanovich and Prof. Dr. B. P. Fedorov

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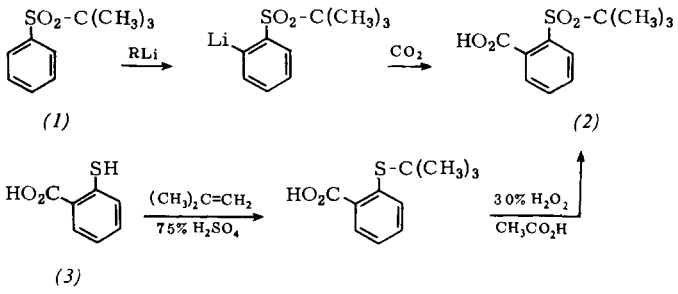
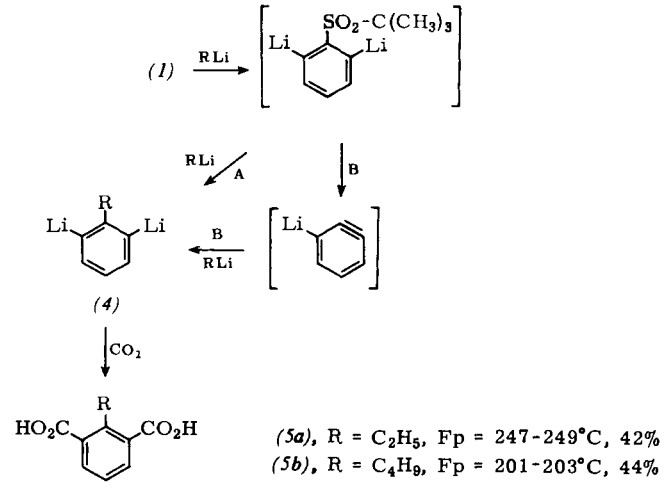
When t-butyl phenyl sulfone *(1)* is metalated in ether/tetrahydrofuran (1:1) at −60 °C for 8–10 h with an excess of an alkyl-lithium or at −10 °C for 3 h with 1 mole of the alkyl-lithium and then carbonated, *o*-(t-butylsulfonyl)benzoic acid *(2)* is formed in 40–45 % yield. The structure of the acid was proved by synthesis from thiosalicylic acid *(3)*.



*(3)*

If the reaction is carried out with an excess (3 moles or more) of the alkyl-lithium (alkyl = ethyl or butyl) for 15–20 h at 20 °C, the t-butylsulfonyl group is removed from *(1)* and the 2-alkyl-1,3-dilithiobenzene is formed, which can be recognized by formation of the previously unknown 2-alkylisophthalic acids *(5)* on carbonation. The acids *(5)* are



*(4)*

*(5a)*, R = $C_2H_5$, Fp = 247–249 °C, 42 %
*(5b)*, R = $C_4H_9$, Fp = 201–203 °C, 44 %

very stable and can be recrystallized from hot concentrated $HNO_3$ and sublimed without decomposition at 200–220 °C/1 mm. Their structure is proved by oxidation of *(5a)* with concentrated $HNO_3$ (sealed tube, 160–180 °C, 5 h) to hemimellitic acid[1].

The formation of the acids *(5)* can be explained by nucleophilic substitution of the t-butylsulfonyl group (route A) or intermediate occurrence of 3-lithiobenzyne (route B).

Received: October 20th, 1965 [Z 92/926 IE]
German version: Angew. Chem. *78*, 116 (1966)

[1] *C. Graebe* and *M. Leonhardt,* Liebigs Ann. Chem. *290*, 217 (1896).

## Synthesis of Bicyclo[3.1.1]heptane

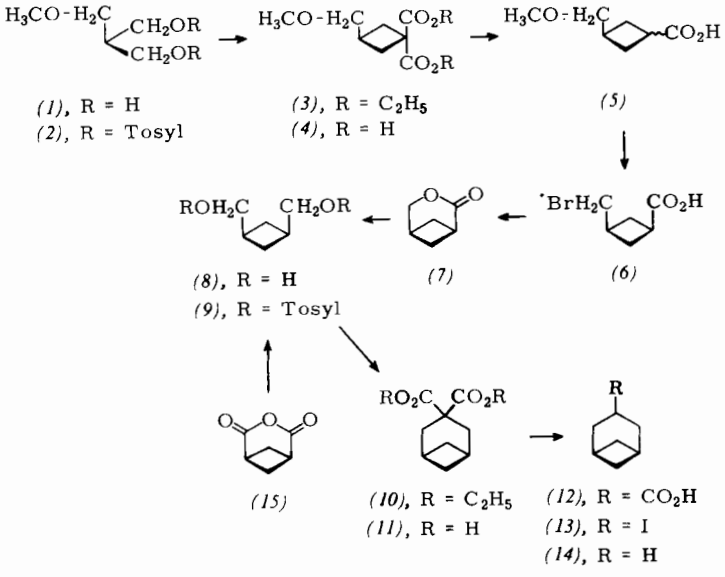
By Prof. Dr. H. Musso and Dipl.-Chem. K. Naumann

Chemisches Institut der Universität Marburg and Chemisches Institut der Ruhr-Universität Bochum[11] (Germany)

Attempts to synthesise bicyclo[3.1.1]heptane (norpinane) *(14)* have previously failed[2]. We have now prepared this compound by the following method, in order to study the 1,4 interaction in the boat form of cyclohexane.

Ethyl (methoxymethyl)malonate was reduced with $LiAlH_4$ to 2-methoxymethyl-1,3-propanediol *(1)* (b.p. 139 °C/12 mm, 59 %), whose di-*p*-toluenesulfonate *(2)* (m.p. 166 °C, 81 %) was condensed with ethyl malonate by *Buchta*'s method[3], giving diethyl (3-methoxymethyl)-1,1-cyclobutanedicarboxylate *(3)* (b.p. 97–99 °C/0.7 mm, 63 %). The acid *(4)* (m.p. 123 °C, 100 %) obtained therefrom on hydrolysis was de-

carboxylated when heated at 160 °C, yielding a mixture of *cis*- and *trans*-3-(methoxymethyl)-1-cyclobutanecarboxylic acids *(5)* (b.p. 140 °C/11 mm, 93 %) in which, according to the gas-chromatogram of the methyl esters, the *cis*-acid was present in excess (55 %). Treatment with hydrogen bromide converts *(5)* into a mixture of *cis*- and *trans*-3-(bromomethyl)-1-cyclobutanecarboxylic acid *(6)* (b.p. 100 °C/0.8 mm, 65 %) [4]. Silver oxide readily converts the *cis*-component of the acids *(6)* into the bicyclic lactone *(7)* (m.p. 75 °C), which can be isolated in 63 % yield. Reduction of the lactone *(7)* with $LiAlH_4$ affords *cis*-1,3-cyclobutanedimethanol *(8)* [5a] (b.p. 92 °C/1 mm, 79 %), which can also be prepared analogously from *cis*-1,3-cyclobutanedicarboxylic anhydride *(15)* [5]. The di-*p*-toluenesulfonate *(9)* (m.p. 79 °C, 71 %) of *(8)* is treated again with malonic ester, yielding diethyl norpinane-3,3-dicarboxylate *(10)* (b.p. 98 °C/1 mm, 54 %), and the derived




acid *(11)* (m.p. 172 °C, 89 %) was decarboxylated to norpinane-3-carboxylic acid *(12)* (m.p. 48 °C, 99 %). This acid *(12)* was converted by lead tetraacetate, iodine, and light [6] into 3-iodonorpinane *(13)* (b.p. 210 °C, crude yield 90 %), from which the iodine was removed by reduction. Dehalogenation by $LiAlH_4$ in boiling tetrahydrofuran is incomplete, but lithium in t-butyl alcohol or hydrogen in presence of Raney nickel and triethylamine affords an iodine-free product from which bicyclo[3.1.1]heptane (norpinane) *(14)* was separated as pleasant-smelling, colorless crystals (m.p. 54 °C) by gas chromatography [7].

Retention times on the gas chromatogram at 95 °C were: n-pentane 3.5, norbornane 5.3, *(14)* 5.7 min [8].

All the new compounds gave satisfactory elemental analyses and infrared and NMR spectra.

Received: October 25th, 1965 [Z 94/927 IE]
German version: Angew. Chem. *78*, 116 (1966)

[1] Present address: Marburg, Bahnhofstraße 7.

[2] *S. Beckmann* and *O. S. Ling*, Chem. Ber. *94*, 1899 (1961); *97*, 2407 (1964).

[3] *E. Buchta* and *K. Geibel*, Liebigs Ann. Chem. *648*, 36 (1961); *E. Buchta* and *W. Theuer*, *ibid.* *666*, 81 (1963); *E. Buchta* and *S. Billenstein*, Naturwissenschaften *51*, 383 (1964).

[4] The acid *(6)* has previously been prepared by *K. B. Wiberg*, *D. S. Connor*, and *G. M. Lampman*, Tetrahedron Letters *1964*, 531, but was not characterized.

[5] *E. R. Buchmann* and *D. H. Deutsch*, Techn. Rep. Calif. Inst. Technol. *1951*, 120.

[5a] Added in proof: *(8)* and *(9)* were also prepared recently *via (15)* by *N. L. Allinger* and *L. A. Tushaus*, J. org. Chemistry *30*, 1945 (1965).

[6] *D. H. R. Barton* and *E. P. Serebryakov*, Proc. chem. Soc. (London) *1962*, 309.

[7] Preparative: Wilkens Autoprep, column SE 30, 100 °C, $H_2$.

[8] Analytical: Perkin-Elmer F6, column 1 G 1, 90 °C, $N_2$.

## Synthesis of 1,3-Cyclotetradecanediones by Ring Enlargement [1]

By Dr. H. J. Buysch and Prof. Dr. S. Hünig

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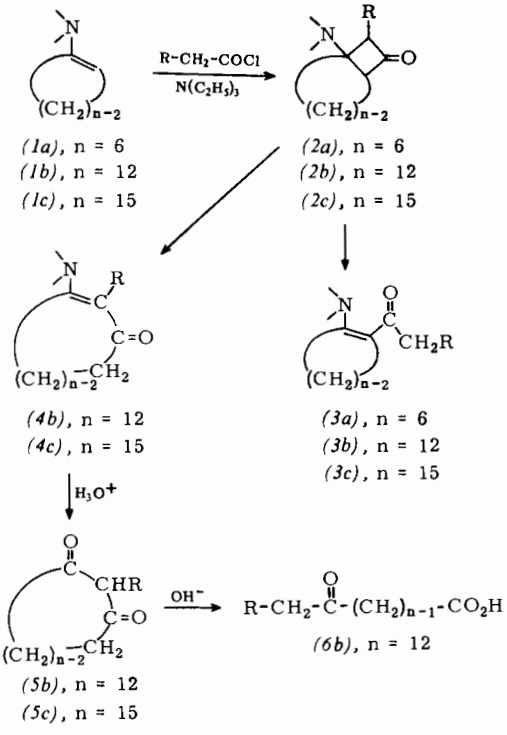
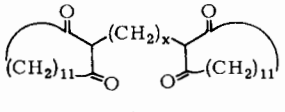
The acylation of tertiary enamines by aliphatic acid chlorides in presence of triethylamine proceeds by way of ketenes, which in the case of enamines derived from aldehydes lead, by addition, to isolable cyclobutanone derivatives [2]. Easy opening of the cyclobutane ring gives acylenamines [2]. The intermediate *(2a)* from 1-morpholinocyclohexene *(1a)* can be detected ($\nu_{C=O}$ = 1770 to 1780 $cm^{-1}$) in the reaction medium for a short time, but only the product *(3a)* [3] can be isolated [2a].

We have now found that the intermediate *(2b)* for med from 1-morpholinocyclododecene *(1b)* isomerizes spontaneously in two ways: products *(3b)* and, by ring expansion by two carbon atoms, *(4b)* are obtained. Acid hydrolysis of the latter gives 1,3-cyclotetradecanediones *(5)* (yields: R = H, *ca.* 20 %, R = alkyl, *ca.* 80 %), which can be purified through their Cu chelates.



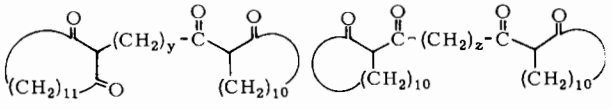

"Acid cleavage" of the diketones *(5)* by alkali affords the keto acids *(6)*, whereas loss of the acyl group is the preponderant reaction of the 2-acylcyclododecanones [4].

The ring expansion in reaction of the enamine *(1b)* with acyl chlorides explains why this reaction is suitable for extension



*(7)*

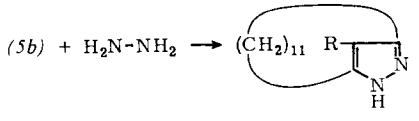
x = 4, m. p. = 183-184 °C



*(8)* *(9)*

of the chain of monocarboxylic acids by 12 carbon atoms (yields 70 to 75 %) and of dicarboxylic acids from $C_8$ onwards by 24 carbon atoms (yields 40 to 50 %)[5]. From the enamine *(1b)* and dicarboxylic acid dichlorides [$C_8$, $C_{10}$, $C_{22}$, $C_{32}$] we obtained 50 to 60 % yields of the tetraketones *(7)* corresponding to *(5)* [x = 4, 6, 18, 28], their structures following from homogeneous alkaline ring fission to diketo dicarboxylic acids. Compounds *(8)* and *(9)* were by-products in the formation of *(7)*. Alkaline fission of product *(8)* affords a keto acid mixture and cyclododecanone (> 10 % yield), whereas the tetraketone *(9)* gives cyclododecanone in about 70 % yield.

Compounds *(5)* and *(7)–(9)* are suitably characterized by reaction with hydrazine to give pyrazoles, *e.g. (10)*.



*(10)*

Experiments are in progress to test the generality of the ring expansion reaction. The reaction sequence has meanwhile been reproduced for *(5b)*, R = H and $CH_3$, and applied to *(1c)* whose ring is thereby expanded to cycloheptadecanedione *(5c)*[6].

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| Compound | Groups |
|---|---|
| *(1)* $[\{p\text{-}(CH_3)_2N\text{–}C_6H_4\}_nR^1_{3-n}PR^2]^{\oplus}\ Hal^{\ominus}$ | $R^1$ = $C_6H_5$, (also $CH_3$ for n = 1)<br>$R^2$ = Alkyl, (also $p$-$(CH_3)_2N$–$C_6H_5$ for n = 3)<br>Hal = Br, I |
| *(2)* $\{p\text{-}(CH_3)_2N\text{–}C_6H_4\}_nR^1_{3-n}PX$<br>*(3)* | X = O, $R^1$ = $C_6H_5$, (also $CH_3$ for n = 1)<br>X = S, $R^1$ = $C_6H_5$ |
| *(4)* $\{p\text{-}(CH_3)_2N\text{–}C_6H_4\}_n(C_6H_5)_{3-n}P$ | |
| *(5)* $p$-A–$C_6H_4(C_6H_5)_2P$<br>*(6)* $p$-A–$C_6H_4(C_6H_5)_2PX$<br>*(7)* | A = *(a)*: COOH, *(b)*: $COOCH_3$, *(c)*: $CON(CH_3)_2$<br>X = O *(d)*: $COCH_3$, *(e)*: CN, *(f)*: CHO<br>X = S *(g)*: $NO_2$ |

Results of the various methods of investigation are not immediately comparable for the two series of compounds; in order to test the results for the *P*-substituted dimethylanilines *(1)* to *(4)* by an independent method, and to relate them to those for the compounds *(5)* to *(7)*, we determined the half-neutralisation potential (HNP)[6] of the dimethylamino groups of compounds *(1)* to *(4)* by potentiometric titration in chloroform/glacial acetic acid at 20 ± 1 °C with 0.02 N $HClO_4$ in glacial acetic acid; therefrom we calculated the Hammett σ′ constants of the phosphorus-containing *para*-substituents (cf. Table) by using Eq. (a), which was obtained from the half-neutralisation potentials (determined under the same conditions) of reference substances of known σ′[10] by the method of least squares.

$$\sigma' = 3.47 + (5.30\times10^{-3})\mathrm{HNP} \qquad (a)$$

When several $(CH_3)_2N$ groups were present in one molecule, they gave rise to only one potential jump; protonation of the phosphorus did not interfere in the titration of the phosphines *(4)*[7]. Values of σ′ for comparison exist for three P substituents, obtained by alkali cleavage of substituted benzyltrimethylsilanes[8]; for two substituents [$(C_6H_5)_2$OP- and $(CH_3)_2$OP-] the σ′ values of +0.845 and +0.725, respectively, agree well with our results; the value for $(CH_3)_3P^{\oplus}$-, σ′ = +1.14, diverges considerably, but in view of the instability of phosphonium salts in an alkaline medium this may be due to decomposition of the trimethylphosphonium group.

As expected[1,3,5], phosphorus is a fairly strong electron acceptor in all cases; the σ′ values depend on the electron density at the phosphorus: $(\sigma'_{NO_2}>)\ \sigma'_{Phosphonium} > \sigma'_{Phosphinyl} \geqslant \sigma'_{Thiophosphinyl}$ $(> \sigma'_{COOCH_3})$; for *(1)* and *(2)*, n = 1, $\sigma'_{R^1=C_6H_5} > \sigma'_{R^1=CH_3}$[3]; for *(2)* and *(3)* [and for *(4)*, n = 2 or 3], $\sigma'_{n=1} > \sigma'_{n=2} > \sigma'_{n=3}$. The phosphines *(4)*, n = 2 or 3, behave analogously to the phosphine oxides *(2)*, n = 2 or 3, and thus, as in the u.v. spectra show no participation of the phosphorus 3p orbital; however, the compound *(4)*, n = 1, in which the donor effect exerted on the phosphorus is smaller resembles the phosphines *(5)* in having a smaller σ′ value[5]. The decrease in σ′ for the series where n = 1 is qualitatively similar to the decrease in Hammett constants calculated from dissociation constants of the benzoic acids *(5a)* to *(7a)* ($\sigma_{(C_6H_5)_2OP-}$ = +0.71; $\sigma_{(C_6H_5)_2SP-}$ = +0.70; $\sigma_{(C_6H_5)_2P-}$ = +0.31)[4,5], but, as is typical for a mesomeric effect[9], the numerical values are higher for the dimethylanilines. A similar dependence on the nature of the reaction center Y is known also for the substituent constants of a $p$-$(C_2H_5O)_2OP$- group in the series $(C_2H_5O)_2OP$–$C_6H_4$–$p$-Y, where Y = $NH_2$, OH, or COOH[9].

[1] Part 11 of Syntheses by means of enamines. – Part 10: *S. Hünig* and *M. Salzwedel*, Chem. Ber., in press.

[2] a) *G. Opitz* and *M. Kleemann*, Liebigs Ann. Chem. *665*, 115 (1963). – b) *G. Opitz* and *F. Zimmermann*, *ibid. 662*, 178 (1963). – c) *R. H. Hasek* and *J. C. Martin*, J. org. Chemistry *26*, 4775 (1961); *28*, 1468 (1963). – d) *G. A. Berchtold*, *G. R. Harvey*, and *G. E. Wilson*, *ibid. 26*, 4776 (1961).

[3] The formula is intended to indicate the ring size but not the position of the double bond.

[4] For instance, by acylation of the ketone enolate. Cf. *Ch. R. Hauser* and *B. O. Linn*, J. Amer. chem. Soc. *78*, 6606 (1956).

[5] *H. J. Buysch*, Dissertation, Universität Würzburg 1963: monocarboxylic acids $C_{15}$, $C_{18}$, $C_{24}$, $C_{30}$, dicarboxylic acids $C_{32}$, $C_{34}$, $C_{46}$, $C_{56}$. – For method see *S. Hünig*, *E. Lücke*, and *W. Brenniger*, Org. Synth. *43*, 34 (1963). – *C. Wakselman*, C. R. hebd. Séances Acad. Sci. *260*, 5056 (1964), has prepared heptacontanedioic acid by this procedure.

[6] *A. Kirrmann* and *C. Wakselman*, personal communictaion; C. R. hebd. Séances Acad. Sci. *261*, 759 (1965).

## The Electronic Effect of Phosphorus in para-Phosphorus-Substituted Dimethylanilines

By Dr. G. P. Schiemenz

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Phosphorus-containing substituents are held to have electron-acceptor properties in respect of an aromatic ring when there is 3d-orbital participation. We have found such an effect, of surprising strength[1], for dimethylanilines with phosphonium *(1)*, phosphinyl *(2)*, thiophosphinyl *(3)*, and phosphino groups *(4)* as *para*-substituents[2,3]; it is shown in the ultraviolet spectra by a bathochromic shift of the 1st primary dimethylaniline band; for the phosphorus compounds *(5)–(7)* with –M substituents it is reflected in the pK values of the acids *(5a)–(7a)*, in the infrared spectra by the frequency [and for *(6e)* also by the intensity] of the stretching vibrations of the –M substituents, and in the NMR spectra of *(6f)* and *(7f)* by the position of the formyl proton signal[5].

| Compound | HNP [mV] [6] | σ' [**] | Compound | HNP [mV] [6] | σ' [**] |
|---|---|---|---|---|---|
| ArBr [*] | −604 | 0.232 | $Ar_2(C_6H_5)PO$ | −505 | 0.80 |
| $Ar(C_6H_5)_2P$ | −574 | 0.43 | $Ar_2(C_6H_5)P$ | −492 | 0.87 |
| $Ar_3PS$ | −547 | 0.57 | $Ar(C_6H_5)_2PO$ | −490 | 0.88 |
| $ArCONH_2$ | −540 | 0.627 | $[Ar(CH_3)_3P]I$ | −474 | 0.95 |
| $Ar_3PO$ | −532 | 0.65 | ArCHO | −465 | 1.126 |
| $Ar_3P$ | −528 | 0.68 | ArCN | −458 | 1.000 |
| $Ar_2(C_6H_5)PS$ | −526 | 0.69 | $[Ar_3(C_2H_5)P]Br$ | −458 | 1.05 |
| $ArCOOCH_3$ | −520 | 0.636 | $[Ar(C_6H_5)_2(CH_3)P]I$ | −458 | 1.05 |
| $Ar(CH_3)_2PO$ | −516 | 0.74 | $[Ar_2(C_6H_5)(CH_3)P]I$ | −434 | 1.17 |
| $ArCOCH_3$ | −515 | 0.874 | $ArNO_2$ | −403 | 1.270 |
| $Ar(C_6H_5)_2PS$ | −512 | 0.76 | | | |

[*] Ar = $p$-$(CH_3)_2N-C_6H_4$.

[**] Values of σ' for phosphorus-free compounds are taken from [10].

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[1] Angew. Chem. *76*, 754 (1964).

[2] *G. P. Schiemenz*, Chem. Ber. *98*, 65 (1965).

[3] *G. P. Schiemenz*, IUPAC-Symposium Organo-Phosphorus Compounds, Heidelberg, May 22nd, 1964; Angew. Chem. *77*, 593 (1965); Angew. Chem. internat. Edit. *4*, 603 (1965); Tetrahedron Letters *1964*, 2729.

[4] *G. P. Schiemenz*, Chem. Ber., in press.

[5] *G. P. Schiemenz*, Angew. Chem. *77*, 1089 (1965); Angew. Chem: internat. Edit. *4*, 1093 (1965). – No electronic effect for *(5f)* (NMR spectroscopy), a small donor effect for *(5e)* and *(5g)* (IR spectroscopy).

[6] Relative to a glass electrode of unknown potential as arbitrary reference point; for the method, see, *e.g.*, *C. A. Streuli*, Analytic. Chem. *32*, 985 (1960). – The titrations were carried out in the Mikroanalytisches Laboratorium *M. Beller*, Göttingen.

[7] *H. Goetz* and *A. Sidhu*, Liebigs Ann. Chem. *682*, 71 (1965).

[8] *R. W. Bott*, *B. F. Dowden*, and *C. Eaborn*, J. chem. Soc. (London) *1965*, 4994.

[9] *L. D. Freedman* and *H. H. Jaffé*, J. Amer. chem. Soc. *77*, 920 (1955).

[10] *H. H. Jaffé*, Chem. Reviews *53*, 191 (1953).

## Structure of the Cyclooctatetraene Dimer of Melting Point 53 °C

By Priv.-Doz. Dr. G. Schröder and cand. chem. W. Martin

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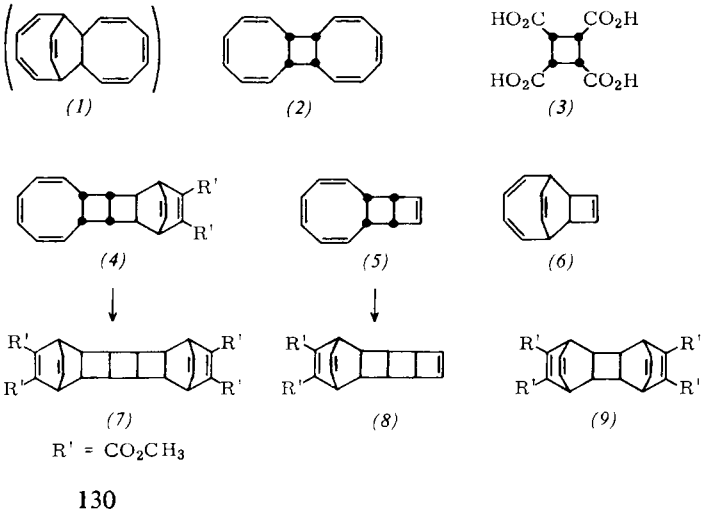
When cyclooctatetraene is heated at 100 °C two dimers $C_{16}H_{16}$ are formed, with melting points 53 and 76 °, respectively [1, 2]. After 68 h the yield of each isomer is about 40 % calculated on the cyclooctatetraene that has reacted (*ca.* 25 %). The structure *(1)* proposed by *Jones* for the dimer, m.p. 53 °C, is incorrect and must be replaced by *(2)*.

The dimer $C_{16}H_{16}$, m.p. 53 °C, absorbs 6 moles of hydrogen on catalytic hydrogenation. On ozonolysis in 90 % acetic acid and subsequent further oxidation with perhydrol, the dimer, m.p. 53 °C, affords the known [3] all-*cis*-cyclobutane-1,2,3,4-tetracarboxylic acid *(3)* [45 % yield, m.p. 215 °C (decomp.)]. The oxidative degradation proves the presence of an all-*cis*-cyclobutane ring as in *(2)*.




*(1)* *(2)* *(3)* *(4)* *(5)* *(6)* *(7)* *(8)* *(9)*

R' = $CO_2CH_3$

The dimer, m.p. 53 °C, reacts with one molecule of dimethyl acetylenedicarboxylate in boiling benzene to give a product $C_{22}H_{22}O_4$ (70 % yield), m.p. 140 °C [4]. The ultraviolet and NMR spectra of this compound are in agreement with the structure *(4)* [5]. When heated at about 150 °C this product decomposes [6] into dimethyl phthalate and a liquid hydrocarbon $C_{12}H_{12}$ (A), 70 % yield, m.p. 8–11 °, to which we allocate structure *(5)*, and which on catalytic hydrogenation absorbs 4 moles of hydrogen to form a hydrocarbon $C_{12}H_{20}$. The ultraviolet spectrum of compound A shows a maximum at 258 mμ (ε = 1300) in hexane; the NMR spectrum consists of a pseudo-singlet at τ = 3.66, a sharp singlet at τ = 4.39, and two multiplets centered at τ = 6.54 and τ = 6.73 with relative intensities 2:6:2:2. Degradation of compound $C_{12}H_{12}$ (A) with ozone and subsequent oxidation with perhydrol lead again to the acid *(3)* (34 %).

When the compound $C_{12}H_{12}$ (A) is warmed at *ca.* 120 °C (24 h) there are formed about equal amounts of benzene and an isomeric hydrocarbon $C_{12}H_{12}$ (B), for which we propose structure *(6)*. This compound absorbs 4 moles of hydrogen on catalytic hydrogenation and gives a product $C_{12}H_{20}$, m.p. 35–36 °C. The ultraviolet spectrum of $C_{12}H_{12}$ (B) in hexane shows maxima at 280 mμ (ε = 2700), 268.5 mμ (5000), and 258.5 mμ (4600). The NMR spectrum contains a multiplet centered at τ = 4.4, a singlet at τ = 6.80, and a pseudo-triplet at τ = 7.38 (8:2:2).

Compound *(4)* reacts with acetylenedicarboxylic ester at 80 °C, giving a diadduct $C_{28}H_{28}O_8$, m.p. 162–163 °C (46 % yield). This compound decomposes into dimethyl phthalate and cyclooctatetraene when heated at *ca.* 150 °C, and its ultraviolet and NMR spectra agree with structure *(7)* [7].

An adduct $C_{18}H_{18}O_4$ (17 %), m.p. 112–114 °C, is formed from compound *(5)* and acetylenedicarboxylic ester at *ca.* 70 °C. It decomposes into dimethyl phthalate and cyclooctatetraene when heated at 140–160 °C. Its ultraviolet and NMR spectra indicate structure *(8)* [7]. From compounds *(2)*, *(4)*, *(5)*, *(7)*, and *(8)*, each with an excess of dimethyl acetylenedicarboxylate at 100–120 °C, the same end product, $C_{24}H_{24}O_8$, m.p. 196–198 °C, is formed. When heated at 230 °C this compound decomposes into dimethyl phthalate and an unidentified gas. Ultraviolet and NMR spectra are in agreement with structure *(9)* for compound $C_{24}H_{24}O_8$ [*].

Received: November 6th, 1965 [Z 99/933 IE]
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[1] *W. O. Jones*, Chem. and Ind. *1955*, 16.

[2] a) *G. Schröder*, Chem. Ber. *97*, 3131 (1964). – b) *G. Schröder:* Cyclooctatetraen. Verlag Chemie, Weinheim 1965.

[3] a) *G. W. Griffin* and *D. F. Weber*, J. Amer. chem. Soc. *82*, 6417 (1960). – b) *R. Criegee* and *W. Funke*, Chem. Ber. *94*, 2358 (1961). – c) *M. Avram*, *I. G. Dinulescu*, *E. Marica*, *G. Matescu*, *E. Sliam*, and *C. D. Nenitzescu*, Chem. Ber. *97*, 382 (1964). – The all-*cis*-cyclobutane derivative *(3)* was identified by comparison with an authentic specimen, for which we thank Prof. *Criegee*.

[4] *B. Flügel*, Diploma Thesis, Technische Hochschule Karlsruhe, 1964.

[5] In this case the Diels-Alder reaction is preceded by valence isomerisation of the cyclooctatriene. Cyclooctatriene itself behaves analogously: *A. C. Cope*, *A. C. Haven*, *F. C. Ramp*, and *E. R. Trumbull*, J. Amer. chem. Soc. *74*, 4867 (1952).

[6] The decomposition follows the Alder-Rickert scheme.

[7] According to the Alder-Rickert scheme tricyclo[4.2.0.0$^{2,5}$]-octa-3,7-diene should be formed alongside dimethyl phthalate on pyrolysis of compounds *(7)* and *(8)*. This tricyclic compound is thermolabile and readily undergoes valence isomerism to yield cyclooctatetraene [3c].

[*] Note added in proof: The photolysis of *(2)* in ether gives in relatively good yield a deep-red, crystalline substance $C_{16}H_{16}$, m.p. 88-90 °C, the NMR spectrum of which comprises one sharp singlet centered at τ = 3.19.

## Cyclic Oxidation Products of Lysine

By Prof. Dr. B. Franck and Dipl.-Chem. D. Randau

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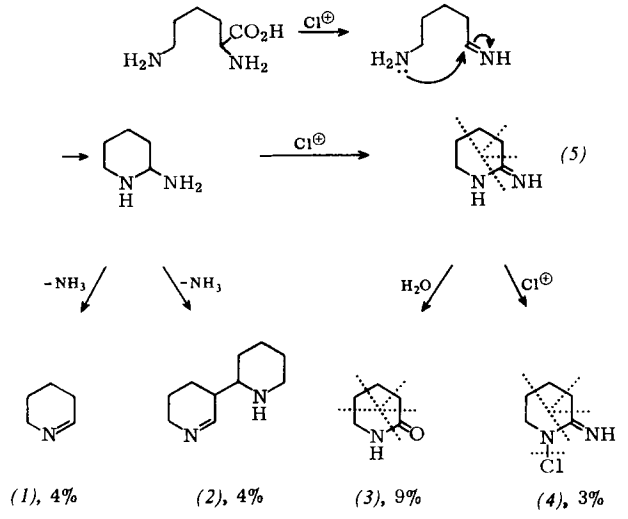
More than 150 alkaloids contain piperidine and quinolizidine groups that are formed in the plant by oxidative transformation of lysine[1]. We have now found that lysine can be converted also by oxidation with NaOCl into cyclic and, in some cases, alkaloid-like[2] products *(1)–(4)*.

Lysine was oxidized with 2 moles of alkaline NaOCl for 3 h at 20 °C. From a chloroform extract of the oxidation solution, piperideine *(1)* and tetrahydroanabasine *(2)* were isolated as picrates of their dihydroquinazolinium derivative with *o*-aminobenzaldehyde[4] (m.p. 172 °C and 181 °C, respectively). 2-Piperidone *(3)* (hydrochloride: m.p. 170 °C) was separated by sublimation, and *N*-chloro-2-iminopiperidine *(4)* by preparative layer chromatography. The yields under the formulae refer to the total amount of lysine, 35 % of which remained unchanged in the reaction mixture. The products *(1)–(3)* were identified by comparison with authentic specimens. In view of its benzidine reaction[5] and infrared spectrum (684 $cm^{-1}$) the previously unknown, non-basic product *(4)* contains an NCl group; its structure follows from elemental analysis, NMR spectrum, and the fragmentation in the mass spectrometer similar to that of *(3)* and *(5)*. Catalytic hydrogenation gave the known[6] hydrochloride (m.p. 157 °C) of compound *(5)*.




It may be assumed that the cyclic oxidation products arise from lysine by attack of one, two, or three $Cl^{\oplus}$ ions.

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[1] *K. Mothes* and *H. R. Schütte*, Angew. Chem. *75*, 265 (1963); *H. G. Boit*: Ergebnisse der Alkaloidchemie bis 1960. Akademie-Verlag, Berlin 1961.

[2] *N*-Acyl derivatives of tetrahydroanabasine are found as alkaloids in *Ammodendron* and *Adenocarpus* species, anabasine in tobacco [3].

[3] *N. F. Proskurnina* and *V. M. Merliss*, Zh. obshch. Khim. *19*, 1396 (1949); Chem. Abstr. *1950*, 1119. – *J. Ribas* and *M. Diago*, An. Real. Soc. espan. Fisica Quim., Ser. B, *55*, 83 (1959); Chem. Abstr. *1959*, 20106. – *E. Späth* and *F. Kesztler*, Ber. dtsch. chem. Ges. *70*, 704 (1937).

[4] *C. Schöpf* and *K. Otte*, Chem. Ber. *89*, 335 (1956).

[5] *F. Reindel* and *W. Hoppe*, Chem. Ber. *87*, 1103 (1954).

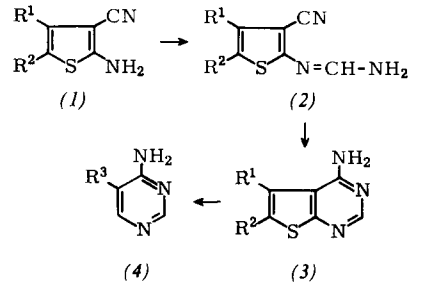
[6] *T. B. Grave*, J. Amer. chem. Soc. *46*, 1460 (1924).

## A New Synthesis of 5-Substituted Pyrimidines

By Prof. Dr. E. C. Taylor and Dr. J. G. Berger

Department of Chemistry, Princeton University, Princeton, New Jersey (U.S.A.)

Treatment of 2-amino-3-cyanothiophenes *(1)*[1] with excess ethyl orthoformate at reflux for 3–4 h, removal of excess reagent, and treatment of the residual ethoxymethylene compounds with excess anhydrous ethanolic ammonia gives in *ca.* 90 % yield the formamidines *(2)*, which precipitate from solution. These compounds can be cyclized to thieno[2,3-*d*]-pyrimidines *(3)* by brief heating in dimethylformamide solution at 80–100 °C with a trace of sodium methoxide. Compounds *(3)* are isolated by evaporation of the solvent and addition of water. Desulfurization of the thieno[2,3-*d*]pyrimidines *(3)* with a four- to tenfold excess of W-7 Raney nickel in refluxing ethanol or dimethylformamide at 80–120 °C leads to novel 5-substituted 4-aminopyrimidines *(4)*, which are isolated by evaporation of the solvent.




| | $R^1 + R^2$ | M.p. [°C] | Yield [%] [a] |
|---|---|---|---|
| *(3a)* | $-(CH_2)_4-$ | 148–149 | 77 |
| *(3b)* | $R^1=R^2=CH_3$ | 270–272 | 85 |
| *(3c)* | 3,4-Dihydronaphtho [1,2] | 257–258.5 | 74 |
| *(3d)* | Naphtho [1,2] | 312–313 | 81 |
| *(3e)* | 4-Aminopyrimido [5,6] | 324–325 (decomp.) | 33 |

| | $R^3$ | M.p. [°C] | Yield [%] [b] |
|---|---|---|---|
| *(4a)* | Cyclohexenyl | 156–158.5 | 40 |
| *(4b)* | Isopropyl | 140–141.5 | 51 |
| *(4d)* | 2-Naphthyl | 185.5–182.5 | 15 |
| *(4e)* | 4-Amino-5-pyrimidinyl | 356 (decomp.) | 17 |

[a] Based on *(1)*.
[b] Based on *(2)*.

The condensed pyrimidine derivative *(3c)* derived from 2-tetralone was aromatized to *(3d)* by diacetylation with acetic anhydride/pyridine, bromination with *N*-bromosuccinimide in $CCl_4$, and subsequent concomitant dehydrobromination and hydrolysis of the diacetyl grouping by refluxing with alcoholic sodium hydroxide.

Desulfurization of *(3b)* in ethanol gave a mixture of the 5-isopropyl and the 5-isopropenyl derivatives (65:35), which was converted by hydrogenation over W-2 Raney nickel to homogeneous *(4b)*.

4-Amino-5-(4-amino-5-pyrimidinyl)pyrimidine *(4e)* was prepared from 2,5-diamino-3,4-dicyanothiophene[2] by twofold cyclization to *(3e)* followed by desulfurization with W-7 Raney nickel in dimethylformamide.

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German version: Angew. Chem. *78*, 144 (1966)

[1] Prepared by condensation of malononitrile with an aliphatic or alicyclic ketone and sulfur, or with an α-mercaptoketone: *K. Gewald*, Z. Chem. *2*, 305 (1962); Angew. Chem. *73*, 114 (1961).

[2] *W. J. Middleton*, *V. A. Engelhardt*, and *B. S. Fisher*, J. Amer. chem. Soc. *80*, 2822 (1958).

## Synthesis and Reactions of Tris(dimethylamino)methane

By Prof. Dr. H. Bredereck, Dr. F. Effenberger, and Dipl.-Chem. Th. Brendle

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We have prepared the first member of the tris(dialkylamino)-methane series, namely tris(dimethylamino)methane *(1)*, in good yield, by treating tetramethylformamidinium salts[1] with alkali-metal dimethylamides.

$$[(CH_3)_2N\text{-}CH{=}N(CH_3)_2]^{\oplus}\ X^{\ominus} + M\text{-}N(CH_3)_2 \rightarrow$$

$$(CH_3)_2N\text{-}HC\begin{matrix}N(CH_3)_2\\N(CH_3)_2\end{matrix} + MX$$

*(1)*

X = Cl, $ClO_4$ M = Li, Na, K

The triamine *(1)* reacts smoothly with CH-acidic compounds to give dimethylaminomethylene compounds *(2)*[2]:

$$(1) + H_2C\begin{matrix}X\\Y\end{matrix} \rightarrow (CH_3)_2N\text{-}CH{=}C\begin{matrix}X\\Y\end{matrix} + 2\ (CH_3)_2NH$$

*(2)*

| X | CN | $COOCH_3$ | $C_6H_5CO$ |
|---|---|---|---|
| Y | CN | CN | H |

and with amines to give amidines *(3)*[3]:

$$(1) + RNH_2 \rightarrow (CH_3)_2N\text{-}CH{=}NR + 2\ (CH_3)_2NH$$

*(3)*

R = *p*-$NO_2$-$C_6H_4$, $NH_2CO$, *p*-$CH_3$-$C_6H_4$-$SO_3$

*Examples*:

Tris(dimethylamino)methane: Tetramethylformamidinium chloride (68 g) was added at −20 °C to a slurry of lithium dimethylamide (prepared according to [4] and [5] from 15.2 g of lithium, 137 g of n-butyl bromide, and 180 g of dimethylamine) in 600 ml of anhydrous ether. The mixture was stirred for 15 h at room temperature while nitrogen was led through the apparatus. The ether was distilled off and then the tris-(dimethylamino)methane in a vacuum (water-pump). Crude yield: 51.0 g, b.p. 40–43 °/12 mm. After redistillation through a Vigreux column: yield of pure product, 46.0 g (63 %), b.p. 42–43 °C/12 mm.

Methyl 2-cyano-3-dimethylaminoacrylate: A solution of 3.63 g of tris(dimethylamino)methane in 50 ml of anhydrous ether was dropped into a solution of 2.48 g methyl cyanoacetate in 50 ml of anhydrous ether at room temperature with stirring, moisture being excluded. The mixture was refluxed for 15 min and the solid filtered off. Crude yield: 3.8 g, m.p. 97–100 °C; after recrystallization from 30 ml of acetone/light petroleum (1:1), yield of pure product: 3.2 g (83 %), m.p. 101–102 °C.

*N,N*-Dimethyl-*N'*-*p*-nitrophenylformamidine: This was prepared from 3.45 g of *p*-nitroaniline in 50 ml of anhydrous ether and 3.63 g of tris(dimethylamino)methane in 50 ml of anhydrous ether as described above, but after the heating the ether was distilled off in a rotating evaporator and the yellowish-green crystals were recrystallized from 40 ml of anhydrous ethanol. Yield: 4.2 g (87 %), m.p. 82–83 °C.

Received: October 25th (1965) [Z 95/928 IE]
German version: Angew. Chem. *78*, 147 (1966)

[1] *Z. Arnold*, Coll. czechoslov. chem. Commun. *24*, 760 (1959).

[2] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[3] *H. Bredereck, F. Effenberger*, and *A. Hofmann*, Chem. Ber. *97*, 61 (1964).

[4] *C. Weygand* and *G. Hilgetag*: Organisch-chemische Experimentierkunst. Barth-Verlag, Leipzig 1964, p. 745.

[5] *Houben-Weyl*: Methoden der Organischen Chemie. Thieme-Verlag, Stuttgart 1958, Vol. 2/3, p. 184.

## "Thermolysis" of 3-Ethyl-2-tetrazobenzothiazoline

By Priv.-Doz. Dr. H. Balli

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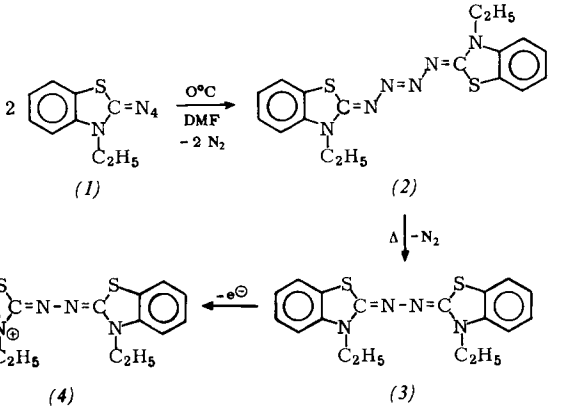
When 3-ethyl-2-tetrazobenzothiazoline *(1)*[1] is kept in dimethylformamide at 0 °C for 1 hr, *trans*(N),*trans*,*trans*(N)-1,4-bis(3-ethylbenzothiazolinylidene)tetrazene *(2)*[*] is formed in 35 % yield as a yellow compound, m.p. 297 °C (decomp.), that is very difficultly soluble in most organic solvents and fluoresces green only in the solid state.




*(1)* *(2)* *(3)* *(4)*

The constitution of the product *(2)* is proved by elemental and X-ray structure[2] analysis. Ultraviolet spectrum (in dimethylformamide, 275–500 mμ): $\lambda_{max}$ = 396 mμ (ε = 52500) [shoulders at 380 and 415 mμ], 304 mμ (4500). Formation of the tetrazene *(2)* from the tetrazo compound *(1)* corresponds formally to the formation of azines from diazoalkenes[3]. At the melting point *(2)* decomposes into nitrogen and bis(3-ethylbenzothiazolinylidene)hydrazine *(3)*[4], which can be oxidized by lead tetraacetate in dimethylformamide to the radical ion *(4)*[4].

Received: October 27th 1965 [Z 104/936 IE]
German version: Angew. Chem. *78*, 146 (1966)

[1] *H. Balli*, Angew. Chem. *76*, 995 (1964); Angew. Chem. internat. Edit. *3*, 803 (1964).

[*] *trans*(N) signifies *trans* to the ring nitrogen.

[2] *R. Allmann*, Angew. Chem. *78*, 147 (1966); Angew. Chem. internat. Edit. *5*, 133 (1966).

[3] *H. Staudinger* and *J. Meyer*, Helv. chim. Acta *2*, 608 (1919).

[4] *S. Hünig, H. Balli, H. Conrad*, and *A. Schott*, Liebigs Ann. Chem. *676*, 36 (1964).

## Crystal Structure of 1,4-Bis-(3-ethyl-1,2-dihydrobenzothiazol-2-ylidene)tetrazene

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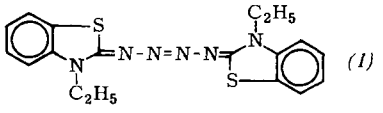
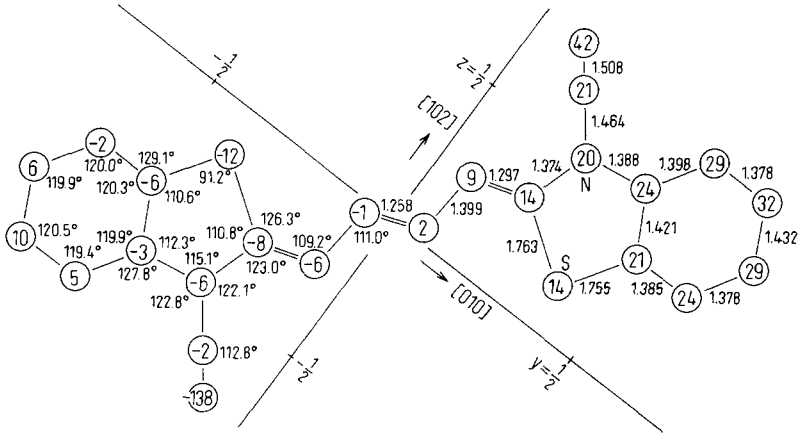
X-Ray structure analysis of 1,4-bis(3-ethyl-1,2-dihydrobenzothiazol-2-ylidene)tetrazene *(1)* [1] has shown that the tetrazene chain is present in the *trans*(N)-*trans-trans*(N)-form



*(1)*

(see figure). The substance crystallizes in space group $P\bar{1}$ with one molecule per unit cell, whence it follows that in the crystalline form the molecule has a center of symmetry. Except for the terminal methyl groups the molecule is almost planar, *i.e.*, the surroundings of the ring nitrogen are also planar. This atom is thus in the $sp^2$ state. The C–N single bonds of the ring are much shorter than usual; the N–N bonds are similarly shortened, whereas the C=N and N=N double bonds of the tetrazene chain are slightly longer than usual. The plane N–C–C of the 3-ethyl group is almost perpendicular (82°) to the plane of the rest of the molecule.




Projection of a tetrazene molecule on the plane ($\bar{2}01$). In the right-hand half of the figure, bond distances are given in Å and x-coordinates in a/100. In the left-hand half, angles are given, together with deviations from the best plane 7.02x–1.62y–1.84z = 0 in 1/100 Å.

Lattice constants are $a_0 = 7.307$ Å, $b_0 = 9.145$ Å, $c_0 = 7.252$Å, $\alpha = 94.95°$, $\beta = 111.06°$, $\gamma = 84.89°$; density measured 1.40, calculated 1.41 g cm$^{-3}$. 1888 X-ray intensities were estimated from Weissenberg photographs. In the Patterson synthesis calculated therefrom essentially only the S–S, S–N, and S–C Patterson peaks appeared, so that the coordinates of the S, N, and C atoms could be obtained at once. Subsequent Fourier synthesis showed also weak electron maxima for all the H atoms (not illustrated in the figure). After 5 cycles of refinement with 22 atoms and isotropic individual temperature factors the R index fell from 32 % to 12 %. The standard deviations of the bond lengths and angles given in the figure are less than 0.01 Å and 1°, respectively.

Received: November 19th, 1965 [Z 108/941 IE]
German version: Angew. Chem. *78*, 147 (1966)

[1] Synthesis: *H. Balli*, Angew. Chem. *78*, 146 (1966); Angew. Chem. internat. Edit. *5*, 132 (1966).

## Relation between Coulomb Potentials and Positions of Protons in Crystalline Hydroxo Compounds

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*Dedicated to Professor Wilhelm Klemm on the occasion of his 70th birthday*

Knowledge of the positions of the protons was needed for a study of the structure of complex hydroxides [1]. Direct determination of these positions cannot be carried out quickly or simply for crystalline compounds by neutron diffraction or nuclear resonance. We have now found that information on the proton positions in such compounds can be obtained by simple potential calculations [2].

Hypothesis: In crystalline hydroxo compounds, the lattice constituents, considered as point charges, produce minima of electrostatic potential at the proton sites. The potential minima and thus the positions of the protons should become apparent on calculation of the potential profile in the neighborhood of the atoms carrying the protons.

Restriction: It suffices always to calculate the potential profile for a spherical surface surrounding the proton carrier at a distance of $r_0$, where $r_0$ is taken as the probable separation d(O–H) [3]. The difficult calculation of the equilibrium distance d(O–H) is avoided in favor of determination of the bond vector $(\overrightarrow{O-H})$. The position of the proton is then determined approximately from $r_0$ and $(\overrightarrow{O-H})$.

The method of calculation was checked on compounds whose proton positions are known. There is surprisingly good agreement between experiment and the position of the potential minima at a distance $r_0$ from the proton carriers (cf. Table).

Calculations were then carried out for azurite $Cu_3(OH)_2(CO_3)_2$ [8] and for $\alpha$-$KNH_2$ [9]. According to measurements with polarized infrared radiation [10] the bond vector $(\overrightarrow{O-H})$ for azurite lies in the plane (010) and is

| Compound | $(xyz)_H$ exp. | $(xyz)_H$ calc. | |
|---|---|---|---|
| LiOH | z = 0.42 [4] | z = 0.42 | caused by |
| $Ca(OH)_2$ | z = 0.425 [5] | z = 0.42 | symmetry |
| AlO(OH) (Diaspore) | 0.909 [6]<br>0.412<br>0.750 | **0.91**<br>0.42<br>0.75 | Potential at $O_1$ less favorable |
| $KH_2PO_4$ (ferroel. form) | 0.1880 [7]<br>−0.0375<br>0.1355 | 0.20<br>−0.02<br>0.14 | |

inclined towards [100] at 138 ± 5°. The calculation shows a very small deviation from the plane (010) (about 5° in the direction [010]) and an inclination towards [100] of 140 ± 5°. With $r_0$ = 0.98 Å, $(xyz)_H$ = 0.75, 0.18, 0.61. Results for α-$KNH_2$ agree with the assumptions of *Juza* and collaborators [9].

It thus appears that a direct relation exists for crystalline hydroxo compounds between the course of the electrostatic equipotential lines near the proton-carrying particles and the positions of the protons, by means of which the latter can be estimated. Moreover the occurrence of bent hydrogen bonds can be traced to the interaction of the protons with their lattice neighbors, and the angle O–H···O can be calculated quite accurately.

Received: November 18th, 1965 [Z 110/943 IE]
German version: Angew. Chem. *78*, 113 (1966)

[1] *H. G. Schnering*, Angew. Chem. *77*, 1090 (1965); Angew. Chem. internat. Edit. *4*, 1094 (1965).

[2] *H. G. Schnering*, Habilitation Thesis, Universität Münster 1963.

[3] Cf. *G. E. Bacon*: Neutron Diffraction. Oxford University Press, 1962.

[4] *H. Dachs*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *112*, 60 (1959).

[5] *W. R. Busing* and *H. A. Levy*, J. chem. Physics *25*, 742 (1956).

[6] *W. R. Busing* and *H. A. Levy*, Acta crystallogr. *11*, 798 (1958).

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[8] *G. Gattow* and *J. Zemann*, Acta crystallogr. *11*, 866 (1958).

[9] *R. Juza, H. Jacobs*, and *W. Klose*, Z. anorg. allg. Chem. *338*, 171 (1965).

[10] *W. Gebert, E. Tillmanns*, and *J. Zemann*, Conference on Crystallography of the German Mineralogical Society, Marburg 1965.

## Potassium, Rubidium, and Cesium Thiomanganates(II)

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*Dedicated to Professor Wilhelm Klemm on the occasion of his 70th birthday*

When a mixture of manganese powder, sulfur, and potassium, rubidium, or cesium carbonate is heated at 750 to 850 °C in an atmosphere of nitrogen and the melt is then cooled and treated with water, the three ternary compounds $K_2Mn_3S_4$ [1], $Rb_2Mn_3S_4$, and $Cs_2Mn_3S_4$ can be isolated as garnet-red, platelike crystals. The preparation of analytically pure alkali thioamanganates, free from MnS, depends on temperature control during the experiment.

Evaluation of rotating-crystal and integrated Weissenberg diagrams for [010] and [001], as well as of Guinier photographs, showed an orthorhombic unit cell (space group: $C_{2v}^{21}$–Iba2) for $Cs_2Mn_3S_4$. Patterson, Fourier, and difference syntheses along [010] led to coordinates of the Mn, Cs, and S atoms with an R value of 0.16 for all the observed reflections. A statistical distribution of four Mn atoms at point positions 4a and 4b was obtained from the intensity distribution of the weak reflections (h 1 *l*) and (h 3 *l*). There was less satisfactory agreement between $F_0$ and $F_c$ values on inclusion of eight further Mn atoms at point positions 8c in a statistical distribution. Values of the parameters are:

4 Mn statisitically dstributed over 4a and 4b with z always 0.000.
8 Mn at 8c with x = 0.000, y = 0.250, z = 0.000;
8 Cs at 8c with x = 0.249, y = 0.125, z = 0.249;
8 S at 8c with x = 0.746, y = 0.126, z = 0.099;
8 S at 8c with x = 0.253, y = 0.124, z = 0.901.

Examination of Debye-Scherrer and Guinier powder photographs, and intensity calculations with the parameters found for $Cs_2Mn_3S_4$ led to a type of structure for $K_2Mn_3S_4$ and $Rb_2Mn_3S_4$ similar to that for the cesium compound.

| | Lattice parameters [Å] | Density | Z |
|---|---|---|---|
| $Cs_2Mn_3S_4$ | a = 5.92<br>b = 11.47<br>c = 14.16 | pyk. 3.83<br>X-ray 3.86 | 4 |
| $Rb_2Mn_3S_4$ | a = 5.86<br>b = 11.21<br>c = 13.68 | pyk. 3.37<br>X-ray 3.42 | 4 |
| $K_2Mn_3S_4$ | a = 5.83<br>b = 11.11<br>c = 13.49 | pyk. 2.85<br>X-ray 2.83 | 4 |

The alkali thiomanganates(II) have a layer structure. A series of manganese and cesium layers, each separated by a sulfur layer, is perpendicular to the plate axis c. The arrangement of the manganese layers is always the same, but the cesium layers are packed into gaps, *i.e.*, every third layer – or every fifth if the surrounding sulfur layers are counted – is identical with the first. In this structure the relatively short Mn–Mn distance is noteworthy; it is made possible because the sulfur tetrahedra surrounding the Mn atoms are joined along edges.

Magnetic measurements on $K_2Mn_3S_4$, $Rb_2Mn_3S_4$, and $Cs_2Mn_3S_4$ between 90 and 700 °K show paramagnetism that is substantially temperature-independent, indicating relatively strong Mn–Mn interactions within the Mn layers.

Received: November 19th, 1965 [Z 111/944 IE]
German version: Angew. Chem. *78*, 113 (1966)

[1] Cf. the results of *A. Völker*, Liebigs Ann. Chem. *59*, 35 (1846).

## Tri(cyclopentadienyl)americium(III)

By Prof. Dr. F. Baumgärtner, Prof. Dr. E. O. Fischer, Dr. B. Kanellakopulos, and Dipl.-Chem. P. Laubereau

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*Dedicated to Professor Wilhelm Klemm on the occasion of his 70th birthday*

We have prepared the first organometallic derivative of americium by treatment of $AmCl_3$ with molten $Be(C_5H_5)_2$ at 65 °C:

$$2\ AmCl_3 + 3\ Be(C_5H_5)_2 \rightarrow 2\ Am(C_5H_5)_3 + 3\ BeCl_2\ [*]$$

0.6 g of $^{241}AmO_2$ was converted, in 4 batches, into rose-colored $AmCl_3$ by passage of a $Cl_2/CCl_4$/argon stream over it at 650 °C for several hours. The chloride melted at 750 to 760 °C and traces began to sublime in the argon stream from 1000 °C. Quantitative sublimation, as for $PuCl_3$ [1] and $NpCl_4$ [2], could not be effected.

The yield of $Am(C_5H_5)_3$ from freshly prepared, powdered $AmCl_3$ amounted to 50 % (calculated on $AmCl_3$) after 12 h; it was materially less if a fused $AmCl_3$ cake or an older $AmCl_3$ powder was used.

$Am(C_5H_5)_3$ can be separated in an analytically pure state by fractional sublimation at $10^{-5}$ mm and 160–205 °C as a flesh-colored compound which glows in the dark with a pale light. It does not melt below 330 °C when heated in argon. At higher temperatures it darkens. It decomposes only slowly in air.

The compound is not pyrophoric, unlike $Pu(C_5H_5)_3$ [1], but discolors very quickly during C–H analysis in pure oxygen, with formation of a black decomposition product. For quantitative recovery of the americium as $AmO_2$, very careful ignition is necessary to avoid loss by volatilization. Solutions in benzene or tetrahydrofuran are very sensitive to moisture and oxygen.

The compound is decomposed by water or dilute acids, with gas evolution and deposition of white flocks, to give a rose-colored Am(III) solution.

Infrared spectra, taken for polycrystalline samples in Nujol or poly(tetrafluoroethylene), show the presence of symmetrical five-membered rings (intense, characteristic bands at 768/788 $cm^{-1}$ ($\gamma_{CH}$), 843 $cm^{-1}$ and 1010 $cm^{-1}$ ($\delta_{CH}$)]. The high specific radioactivity of the preparation requires measurement of the spectra by a special compensation technique; in poly(tetrafluoroethylene) only bands at *ca.* 3040 $cm^{-1}$ ($\nu_{CH}$) and *ca.* 1480 $cm^{-1}$ ($\omega_{CC}$) have so far been found.

It is concluded from the results that $Am(C_5H_5)_3$ and $Pu(C_5H_5)_3$ have analogous structures. The higher sublimation temperature, the greater thermal stability, the behavior in solution, and the absorption at 768/788 $cm^{-1}$ [*i.e.*, at lower wave numbers than for $Pu(C_5H_5)_3$] indicate that $Am(C_5H_5)_3$ resembles the cyclopentadienyl complexes of lanthanides [3] more closely than does $Pu(C_5H_5)_3$ [1].

Received: November 30th, 1965 [Z 107/940 IE]
German version: Angew. Chem. *78*, 112 (1966)

[*] Only a negligible neutron dose, due to the reaction $Be(\alpha,n)^{12}C$, was detected outside the shielded glove box.

[1] *F. Baumgärtner, E. O. Fischer, B. Kanellakopulos,* and *P. Laubereau,* Angew. Chem. *77*, 866 (1965); Angew. Chem. internat. Edit. *4*, 878 (1965).

[2] *E. O. Fischer, P. Laubereau, F. Baumgärtner,* and *B. Kanellakopulos,* J. organomet. Chemistry, in press.

[3] *E. O. Fischer* and *H. Fischer,* J. organomet. Chemistry *3*, 181 (1965).

# CONFERENCE REPORTS

## 7th Conference on Carbon

The 7th Conference on Carbon, which was organized by the American Carbon Committee and held at the Case Institute of Technology in Cleveland, Ohio, from June 21st to 25th, 1965, was concerned with the chemistry, physics, and technology of elementary carbon. 200 papers were presented to some 350 participants, about one fifth of whom came from abroad.

The parameters of the energy bands of graphite were accurately determined by *G. F. Dresselhaus* and *J. G. Mavroides* (Lexington, Mass., U.S.A.), by measurement of magneto-reflection and of the de Haas – van Alphen effect [1]. The authors referred to the important part played by spin-orbit interaction close to the Fermi level, which give rise to a band gap of 0.01 eV near point K.

*S. Sato, T. Oku,* and *T. Honda* (Tokyo) prepared thermocouples for very high temperatures (> 2000 °C) from polycrystalline graphite and vitreous carbon, a particularly impermeable and disordered microcrystalline from that does not graphitize even at 3000 °C.

*G. Montet* (Argonne, Ill., U.S.A.) irradiated single crystals of graphite with fast electrons and used an etching technique to determine the number of vacancies produced. An electron beam energy of at least 150 keV is required in order to knock carbon atoms out of the layer lattice. The displacement energy transferred to the C atoms [*] was found to be about 30 eV. *C. A. Coulson* (Oxford, England) found that in the neighborhood of C atoms situated between the layers, the C atoms in the layer can be displaced to a maximum extent of about 0.6 Å. The energy per interstitial atom was calculated to be 2.32 eV, while the migration energy is 0.14 eV.

Mass-spectrometric measurements by *P. D. Zavitsanos* (Philadelphia, Penn., U.S.A.) showed that carbon vapor in equilibrium with polycrystalline graphite contains $C_3$ and $C_1$ molecules as well as a relatively small number of $C_2$ molecules. Pyrolytically produced graphite evaporates predominantly in the direction of the carbon layers, and gives relatively large quantities of $C_2$ and $C_1$ together with relatively small quantities of $C_3$. When the vapor is produced by fast heating with a laser beam (no establishment of equilibrium), it contains no $C_3$. The vaporization coefficients [2] of $C_1$, $C_2$, and $C_3$ are 0.23, 0.34 to 0.46, and 0.023 to 0.046, respectively. The activity coefficient of boron dissolved in the graphite lattice was found to be about 0.3.

The electron spin resonance spectra of carbonization products that have been heated above 500 °C are affected by oxygen. *S. Mrozowski* (Buffalo, N.Y., U.S.A.) found that the resonance line is not broadened by $O_2$ if the carbonization products have been vapor-coated with alkali metals (Li toCs).

In connection with the determination of the crystallite dimensions, *F. A. Heckman* and *J. S. Clarke* (Cambridge, Mass., U.S.A.) and *W. Fritz* (Karlsruhe, Germany) referred to the importance of taking into account the broadening of the X-ray reflections in the X-ray diffractometer curves caused by the low absorption of carbon. – *C. Schiller, J. Mering,* and *M. Oberlin* (Paris, France) use the broadening of the X-ray reflections to determine the range of variation $\delta$ of the lattice dimensions in carbons and graphites. Only in graphitizable carbon is there any clear relationship between the values of $\delta$ in the a-direction and in the c-direction. As $\delta_c$ decreases, the diamagnetic susceptibility increases until it reaches a limiting value at very low values of $\delta_c$. In perfectly crystalline graphite, $\delta_c = 0$. In the course of the graphitization, the mean square $\overline{\delta_c^2}$ first passes through a minimum, then a maximum, and finally becomes zero. The coefficient of thermal expansion changes in the opposite direction to $\overline{\delta_c^2}$.

According to *A. Pacault* and *A. Marchand* (Bordeaux, France), the graphitization of cokes, pyrolytic carbon, and acetylene black takes place in several overlapping steps. The graphitization of acetylene black is so slow that it is possible to follow the kinetics of the individual steps; the paramagnetism, diamagnetism, and the Hall effect were measured. The first step leads to the formation of many localized unpaired electrons (free radicals), which rapidly become free electrons. In the second step, "aromatic" layers grow into crystallites with relatively large distances between the layers, little interaction between the layers, and strong diamagnetism. Unpaired electrons are trapped at lattice defects. The last

[1] For a description of the band model and its parameters for graphite, see *J. W. McClure,* Physic. Rev. *108*, 612 (1957).

[*] The displacement energy is the energy that must be transferred to a lattice atom by an incident particle in order that the former may be removed from its position in the lattice.

[2] In dynamic vapor-pressure measurements, the vaporization coefficient of a solid is a measure of the relative rate of vaporization or of the proportion of the surface that can contribute to the vaporization. See, *e.g., H. Cordes* and *H. Cammenga,* Z. physik. Chem. N.F. *45*, 186 (1965).

stage is the formation of a three-dimensional ordered graphite structure, with a slight decrease in the diamagnetic susceptibility; the valence band and the conductivity band overlap. Substantial changes take place in the first few minutes, or even seconds, of graphitization. – *D. B. Fischbach* (Pasadena, Calif., U.S.A.) used X-ray methods to study the kinetics of the graphitization of pyrolytic carbon at 2400 to 3000 °C. In this temperature range, many first-order reactions follow one another. In the first step the carbon layers become oriented parallel to one another; this is accompanied by a rapid decrease in the distance between the layers, but with no change in diameter. In the second step the layers grow rapidly in the layer direction, the distance between layers simultaneously decreasing, while the texture becomes more pronounced. The activation energy for these two processes is approximately 270 kcal/mole. An activation energy of 260 kcal/mole has also been found for the graphitization of petroleum cokes and coked coal tar pitch. *E. S. Bale* (London, England) and *A. Pacault* and *A. Marchand* (Bordeaux, France) found that the graphitization of cokes and carbon blacks is generally very fast and crystallite growth is usually complete after only 5 minutes.

*J. J. Kipling* and *P. V. Shooter* (Hull, England), using a polarizing microscope, observed optical anisotropy in graphitizable carbons prepared at about 700 °C, whereas non-graphitizable carbons are isotropic. Flow lines in the graphitizable carbons suggested that the first step, which takes place at about 425 to 550 °C, involves melting and parallel orientation of aromatic components.

According to *H. Honda* (Tokyo), many carbons, including some that normally do not graphitize at 3000 °C, or which do so only partially (*e.g.* carbon black) form well-crystallized graphite when electric arcs pass through the compressed sample. Examination with the aid of an electron microscope reveals the presence of flakes, which are very similar in appearance to those of a natural graphite with a small particle size. The lower the temperature at which the pretreatment of the carbon was carried out, the higher is the degree of graphitization (determined from the size of the crystallites and the distance between the layers).

*W. T. Eeles, M. S. Stagg,* and *J. A. Turnbull* (Berkeley, England) prepared single crystals of graphite containing about 1 % of boron by cooling a melt of boron and reactor graphite or by doping graphite crystals that had been irradiated with neutrons. The lattice constants of these crystals are initially greater than those of pure graphite. The a- and c-axes contract on annealing. At 1400 °C the c-axis becomes smaller than in pure graphite; at 2000 °C it begins to expand once more, to reach the ideal value at about 2500 °C. Examination with an electron microscope after heating at 1800 °C clearly shows the presence of loops exhibiting vacancy contrast.

Interesting growth spirals from 5 to 40 μ in diameter were observed by *E. Fitzer* and *H. Schlesinger* (Karlsruhe, Germany) in pyrographite deposited from methane at 1400 to 1700 °C.

Graphite is oxidized by $CO_2$ at 300 to 350 °C if atomic oxygen is released from the $CO_2$ by the action of ultraviolet light or β-radiation of more than 3 eV energy. In the course of this reaction, *I. M. Dawson* and *F. S. Feates* (Harwell, England) observed the formation of solid products, which were deposited from the gas phase, particularly at lattice defects, and which could be distinguished with the electron microscope. The oxidation of graphite by photolytically decomposed $CO_2$ is completely inhibited by free radicals, *e.g.* methylene from diazomethane. *P. G. Palmer* (Richland, Wash., U.S.A.) reported that the air oxidation of graphite is strongly retarded by small quantities of $CF_2Cl_2$ or $CF_3Cl$. The formation of etch pits in the basal surfaces was greatly reduced, whereas the specific surface area increased more rapidly than during oxidation in pure air.

*F. M. Lang* (Saclay, France) found that when graphite is oxidized in perfectly dry $O_2$, hexagonal etch pits are formed in the basal faces, whereas in the presence of small quantities of water, the boundaries of the pits become irregular. Penetrating into the graphite particles pores are formed, which have a larger radius when moist oxygen is used than with dry oxygen. Some of the water vapor is chemisorbed, *i.e.* bound in the form of functional groups.

When carbon blacks are oxidized with oxygen, ozone, or nitric acid, the external diameter of the particles decreases only slightly. In confirmation of an earlier report by *U. Hofmann*, it was found by *J.-B. Donnet* (Mulhouse, France) and *A. I. Medalia* (Cambridge, Mass., USA) that some of the particles are not oxidized, while others are hollowed out from the inside. According to *J.-B. Donnet*, the crystallites in the resistant outer shell have a shorter interlayer distance and a higher density than those in the center of the particles.

*J. M. Thomas* and *C. Roscoe* (Bangor, North Wales) produced oxidation etch pits on single crystals of graphite contaminated with boron. Examination under the microscope revealed dislocations, which are not parallel to the basal planes but are due to structural faults in the hexagonal honeycomb of the carbon layers. *J. M. Thomas*, together with *P. L. Walker* (University Park, Penn., U.S.A.) filmed the oxidation behavior of single crystals of graphite with the aid of a hot-stage microscope. The formation and growth of the etch pits could be clearly observed. The oxidation is fastest in the $<10\bar{1}0>$ direction, so that a boundary is formed parallel to $<11\bar{2}0>$. The oxidation is strongly accelerated by catalysts, such as small particles of Ag, Mo, Mn, Fe, Co, Mo, or Ti. The etch channels previously observed by *G. Hennig* are formed, their direction being fixed by the crystallographic a-axes; the etch pits start at defects. The "unwinding" of a screw dislocation could be clearly observed.

On the basis of kinetic measurements on the reaction of graphite with $CO_2$ between 900 and 1100 °C, *P. L. Walker* (University Park, Penn., U.S.A.) concluded that an unstable surface oxide is formed as an intermediate. This first-order reaction is inhibited by CO, and particularly strongly by $H_2$ or $CH_4$. The rate of reaction is reduced by more than one order of magnitude by $H_2$ at a pressure of $5\times10^{-4}$ mm Hg, hydrogen being simultaneously bound to the surface. Oxidation with labelled oxygen ($^{18}O_2$) at low pressures showed that both CO and $CO_2$ are formed as direct products. The two oxygen atoms of the $CO_2$ do not generally come from the same $O_2$ molecule. An equilibrium exists between gaseous $CO_2$ and chemisorbed $CO_2$. Some of the surface oxide formed on the oxidation of active charcoal yields $CO_2$ on thermal decomposition. According to *B. R. Puri* (Chandigarh, India), this "surface complex" (probably carboxyl groups) is responsible for the ion-exchange properties, adsorption of water or alcohols, wettability, *etc.* of charcoal. Thermal decomposition gives rise to unsaturated sites which are capable of binding one molecule of $Br_2$ or $O_2$ for every two molecules of $CO_2$ lost. After the oxidation of carbon black with $HNO_3$ or ozone, *A. Charlier* and *P. Taglang* (Mulhouse, France) observed an additional sharp peak in the relatively broad electron spin resonance signal of carbon black; this peak is associated with the presence of chemically bound oxygen, but is not affected by chemical reactions on the surface. *H. P. Boehm* and *R. Sappok* (Heidelberg, Germany) studied surface oxides on diamonds [3].

*P. L. Walker* (University Park, Penn., U.S.A.) replaced the hydrogen bound to anthracite by treatment with chlorine at 200 to 900 °C, the reaction being accompanied by evolution of HCl. The electrical conductivity increases more rapidly in this case than on heating in an inert gas. *D. Rivin* and *J. Aron* (Cambridge, Mass. U.S.A.) replaced part of the hydrogen at the edges of the carbon layers in carbon black by halogen at temperatures as low as 0 to 100 °C. The first step in this reaction was assumed to be the transfer of an electron from the carbon layer to physically adsorbed halogen molecules. Some of the bound halogen could be replaced by other functional groups, *e.g.* by treatment with alcohols, amines, water, or alkali metal hydroxides.

[3] Cf. Angew. Chem. *77*, 722 (1965); Angew. Chem. internat. Edit. *4*, 698 (1965).

*V. R. Deitz* (Washington, D.C., U.S.A.) studied the physical adsorption of $CO_2$ on a wide range of forms of carbon (*e.g.* natural graphite, pyrographite, graphitized carbon black, activated charcoal) at 0 °C, and found that the $CO_2$ was strongly absorbed on the edges of the carbon layer even at low pressures, while at higher pressures this is accompanied by relatively loose adsorption on the basal surfaces.

From density measurements with helium, *J. J. Kipling* (Hull, England) found that carbon samples prepared below 700 °C generally have a lower density at 300 °C than at 20 °C, while non-porous graphites prepared at 2700 to 3000 °C give identical values. On the other hand, many carbon samples prepared at an intermediate temperature were found by the helium displacement method to have higher densities at 300 °C than at 0 °C. This is attributed to the presence of very narrow pores, which permit the entry of the gas molecules only when the thermal vibration of the carbon atoms is sufficient. *T. G. Lamond, J. E. Metcalfe*, and *P. L. Walker* (University Park, Penn., U.S.A.) found that carbon samples obtained by the thermal decomposition of Saran [*] or polyvinylidene chloride at 1000 to 1500 °C act as molecular sieves. The adsorption behavior towards molecules with different shapes (isobutane, neopentane, benzene, and cyclohexane) indicates the presence of slot-shaped pores between 4.5 and 5.7 Å wide, which connect cavities having a diameter of at least 12 Å.

By the cleavage of large graphite crystals parallel to the basal planes, *G. Hennig* (Argonne, Ill., U.S.A.) obtained extremely thin single crystals from which it was possible to prepare intercalation compounds. The infrared spectra of these compounds could be measured directly between 0.2 and 25 μ. All intercalation compounds have a transmission band with a relatively low absorption coefficient and a half-width of about 0.2 μ. The wave number of this transparency maximum is proportional to the square root of the number of charge carriers in the carbon layer. Intercalation compounds of K, Rb, Cs, $AlCl_3$, and $FeCl_3$, and graphite hydrogen sulfate, were studied.

*W. Ostertag* and *W. E. Craven* (Wright-Patterson Air Force Base, Ohio, U.S.A.) prepared new intercalation compounds of graphite with Tb, Er, and Yb, containing one atom of a rare earth metal, two to three molecules of $NH_3$, and about 0.5 atom of I for every 18 to 24 carbon atoms.

*D. E. Nixon, G. S. Parry*, and *A. R. Ubbelohde* (London, England) determined the crystal structures of single crystals of graphite nitrates containing anion layers and acid layers in every space (1st stage), every second space (2nd stage), every third space (3rd stage), *etc.* between carbon layers. The layer sequence in graphite is ABABAB..., *i.e.* successive layers are mutually displaced by $^1/_3$ or $-^1/_3$ of the a-axis. In the first stage of graphite nitrate, the arrangement of the carbon layers is A/A/A/A..., *i.e.* the centers of the hexagons in one layer are directly above those in the next, as had been found earlier by *W. Rüdorff*. The arrangements in the higher stages are A/AB/BC/CA/A... (2nd stage), A/ABA/ACA/A... (3rd stage), and A/ABAB/BCBC/CACA/A... (4th stage). The oxidation proceeds through all the stages in turn. In the transition from the fourth stage to the third stage, for example additional layers of anions or acid are intercalated; at the same time, some of the spaces between layers must be emptied again, and when this happens, the former layer sequence is restored. Changes in the relative positions of two carbon layers occur only when an anion layer is inserted or removed. The structures of the graphite nitrates are evidently determined not by kinetic effects, but by the energies of the electron bands.

*J. G. Hooley, W. P. Garbey*, and *J. Valentin* (Vancouver, Canada) observed that the intercalation of $Br_2$ in pyrographite discs begins at the frontal surfaces and proceeds in stages towards the middle. The bromine diffuses only parallel to the basal planes, and cannot penetrate the frontal surfaces of sheets of well-graphitized pyrographite. Swelling in the middle layer of the sheet is probably hindered at first by the fact that, as the bromine penetrates, the distance between the layers increases from the edge inwards, and bending of the layers is possible only near the frontal surfaces. The replacement of carbon by boron in graphite leads to a considerable lowering of the Fermi level. *R. Tremion, J. Maire, F. Tombrel*, and *J. Mering* (Paris, France) accordingly observed marked hindrance of the intercalation of bromine in pyrographite doped with boron.

*F. J. Salzano* and *S. Aronson* (Brookhaven, N.Y., U.S.A.) have studied the kinetics of the thermal decomposition of the intercalation compound $C_8Cs$, and found a distinct discontinuity at the composition $C_{10}Cs$. The heat of formation of $C_8Cs$ is 33.8 kcal/mole. Between $C_{72}Cs \rightarrow C_{60}Cs$ and $C_{24}Cs \rightarrow C_{10}Cs$, $\Delta H$ steadily decreases from one stage to the next; in the stage $C_{10}Cs \rightarrow C_8Cs$, on the other hand, $\Delta H$ shows a pronounced increase. The entropy of formation for the first stage of cesium graphite ($C_8Cs$) is 40 cal/°K, while the values for all the other stages are between 16 and 19 cal/°K. An energy of 1.4 kcal/g-atom of carbon is required in order to separate the graphite layers.

When petroleum coke is heated rapidly during graphitization, the presence of sulfur leads to "puffing" and to destruction of the molding. *H. F. Volk* and *M. Janes* (Parma, Ohio, U.S.A.) found an analogy between the behavior of petroleum coke containing sulfur and that of petroleum coke containing small quantities of $Br_2$ between the layers (residue compounds). Destruction of the molding is avoided by the addition of Fe or Ca. At 1200 to 1500 °C, a compound containing carbon is formed, in which Fe or Ca and S are present in equal atomic proportions. The corresponding Br compound contains two Br atoms instead of one S atom. Excess Fe or Ca can be readily leached out, whereas the ternary compounds $FeSC_x$ and $CaSC_x$ are completely insoluble. The Hall coefficient indicates that the Fe in these compounds is not ionic. The quantity of Fe or Ca required in order to prevent puffing depends not only on the sulfur content, but also on the crystallite structure of the coke.

[VB 957/264 IE]

German version: Angew. Chem. 78, 148 (1966)
Translated by Express Translation Service, London

[*] A copolymer of 1,1-dichloroethylene and vinyl chloride.

# Physical Chemistry of Protactinium

A colloqium at which 39 papers were read concerning the present state of the chemistry of protactinium was organized by the Centre National de la Recherche Scientifique in the Institut du Radium at Orsay near Paris for July 2nd–8th, 1965.

The preparation of metallic protactinium on the milligram scale by reduction of $PaF_4$ by metallic barium or calcium was described by *J. A. C. Marples* (Harwell, U.K.) and *B. B. Cunningham* (Berkeley, U.S.A.). The tetragonal body-centered structure ($a = 3{\cdot}925$ Å and $c = 3{\cdot}238$ Å at 25 °C, $Z = 2$, $\rho = 15.37$ g·cm$^{-3}$) found by *Zachariasen* [1] was confirmed, but two further modifications appear to exist at higher temperatures. The melting point of metallic protactinium was determined as 1570 °C; the molar magnetic susceptibility at 25 °C is $270 \times 10^{-6}$ CGS units and is substantially independent of temperature, as is that of tantalum.

[1] *P. A. Sellers, S. M. Fried, R. E. Elson*, and *W. H. Zachariasen*, J. Amer. chem. Soc. 76, 5935 (1954).

According to *L. E. J. Roberts* (Harwell) there exist in the system Pa–O, besides $PaO_{2.00}$ (fluorite structure, a = 5·509 Å) and $Pa_2O_5$ (3 modifications: at 700–900 °C tetragonal, a = 5·429 Å, c = 5·503 Å; at 1050 °C hexagonal, a = 3·817 Å; c = 13·32 Å; and above 1240 °C rhombohedral, a = 5·424 Å, a = 89·76 °), four further phases, namely: $PaO_{2.17}$–$PaO_{2.20}$ (cubic face-centered, a = 5·473 Å), $PaO_{2.33}$ (tetragonal, a = 5·425 Å, c = 5·568 Å), $PaO_{2.40}$–$PaO_{2.42}$ (tetragonal, a = 5·480 Å and c = 5·416 Å), and $PaO_{2.42}$–$PaO_{2.44}$ (rhombohedral, a = 5·449 Å, α = 89·65 °). $PaO_{2+x}$ thus shows great structural similarity to $UO_{2+x}$. $PaO_2$ forms a continuous series of mixed crystals with $ThO_2$. The mixed crystals are oxidized without alteration of structure to a fluorite phase $Pa_2O_5$–$ThO_2$, in which the additional oxygen ions are accomodated at intermediate lattice positions. Protactinium peroxide, $Pa_2O_9 \cdot 3H_2O$, is formed as an amorphous, easily decomposable precipitate, according to *T. Stchouzkoy* (Paris), when $H_2O_2$ is added to a protactinium(V) solution; above 200 °C it can be degraded to a hydrate of protactinium pentoxide, $Pa_2O_5 \cdot H_2O$.

As *C. Keller* (Karlsruhe), Germany was able to show, $PaO_2$ and $Pa_2O_5$ behave in their solid-state reactions as typical actinide oxides. Compounds such as $PaGeO_4$, $PaSiO_4$, $Pa_{0.25}TaO_3$, and $PaNb_3O_{10}$ correspond largely to the analogous oxides of quadrivalent thorium, uranium, and transuranium elements. $Pa_2O_5$ reacts with sesquioxides of actinides and lanthanides, giving double oxides $(M_{0.5}, Pa_{0.5})O_2$ with fluorite structure and statistical distribution of the heavy-metal atoms. These double oxides, like the actinide oxides themselves, take up any excess of $M_2O_3$ or $Pa_2O_5$ into solid solution. In the system alkali oxide/$PaO_5$, *C. Keller* and *A. J. Smith* (Sheffield, U.K.) obtained compounds of the type $MPaO_3$ (M = Li–Cs), $M_3PaO_4$ (M = Li or Na), and $Li_7PaO_6$; fluorite phases of unknown extent, with Pa:Na(Li) = 2:1 to 4:1, occur in the $Pa_2O_5$-rich region. A crystallochemical relation of protactinium(V) to the elements niobium and tantalum is recognizable only among the ternary oxides such as $Ba(Ba_{0.5}, Pa_{0.5})O_{2.75}$ (a = 8·932 Å) and $Ba(M^{III}_{0.5}, Pa_{0.5})O_3$ (a = 8·885 Å for M = La).

Several authors reported on protactinium fluorides. *L. Stein* (Argonne, U.S.A.) obtained $Pa_4F_{17}$, isostructural with $U_2O_9$, besides the known fluorides $PaF_4$, $PaF_5$, $PaF_5 \cdot 2H_2O$, and $Pa_2OF_8$, by reaction of $Pa_2O_5$ with a $HF/H_2$ stream at 500 °C; it is cubic face-centered, with a = 8·507 Å. Interest attaches to the preparation of $PaF_2SO_4 \cdot 2H_2O$ and particularly the analogous uranium compound from aqueous solution, since the ion $UF_2^{2+}$ appears to be a uranium(IV) analogue of the stable uranyl ion $UO_2^{2+}$. From solutions of protactinium(V) in hydrofluoric acid, *L. B. Asprey* (Los Alamos, U.S.A.), *O. L. Keller* (Oak Ridge, U.S.A.), *A. G. Maddock* (Cambridge, U.K.), and *C. Ferreira de Miranda* (Paris) prepared double fluorides of the type $M^IPaF_6$ ($NH_4$, K, Rb), $M^I_2PaF_7$ ($NH_4$, K, Rb), and $M_3PaF_8$ (Li, Na), in which the anions $PaF_6^-$, $PaF_7^{2-}$, and $PaF_8^{3-}$ were detected by electrochemical and spectroscopic methods even in aqueous solution and their stability constants were determined. NMR investigations showed that the mean residence time of a $F^-$ ion in the Pa-F complexes in hydrofluoric acid solution lies between $1{\cdot}6 \times 10^{-5}$ sec ($PaF_6^-$) and $3{\cdot}6 \times 10^{-4}$ sec ($PaF_7^{2-}$). The fluoro-complexes of protactinium(V) are adsorbed by anion-exchangers with high distribution coefficients, a fact that can be used for many analytical separations. Double fluorides of the type $(NH_4)_4PaF_8$ and $7MF \cdot 6PaF_4$ (tetragonal for M = Li, rhombohedral for M = Na, K, Rb), derived from protactinium(IV) by reaction in the solid state were described. These are isotypic with the corresponding compounds of thorium and uranium(IV). According to *J. Flegenheimer* (Buenos Aires) $PaCl_5$ is obtained by chlorination of $Pa_2O_5$ with $Cl_2/CCl_4$ at 300–400 °C. The ready volatility of $PaCl_5$ can, according to *J. Merinis* (Paris) be utilized for separation of protactinium – even in tracer amounts – from thorium, *e.g.* for the preparation of pure $^{233}Pa$ from irradiated $ThCl_4$, by which method high yields can be achieved. By reduction of $PaCl_5$ with hydrogen at 400 °C one obtains pure $PaCl_4$. $PaCl_5$ dissolves readily in organic solvents; with thionyl chloride it forms a double chloride $SO(PaCl_6)_2$ and on addition of CsCl, $[(CH_3)_4N]Cl$, or $[(C_6H_5)_4As]Cl$ to a solution of $PaCl_5$ in $SOCl_2$ the corresponding sparingly soluble double chlorides, *e.g.* $CsPaCl_6$, are precipitated [*D. Brown* and *K. W. Bagnall* (Harwell)]. With phosphine oxides, *e.g.* $(C_6H_5)_3PO$, $PaCl_5$ forms addition compounds of the type $PaCl_5 \cdot (C_6H_5)_3PO$. The hexabromoprotactinates(V) can be obtained, like the analogous double chlorides, only from non-aqueous solutions, since extensive hydrolysis of the $Pa^{5+}$ ion occurs immediately even in concentrated acids. In contrast to the bromo-complexes, but in analogy to uranium, octachloroprotactinates(V) such as $[(CH_3)_4N]PaCl_8$ can also be obtained in pure form. The oxide bromides $PaO_2Br$ and $PaOBr_3$ were prepared by reaction of $Pa_2O_5$ with bromine at elevated temperatures. According to *P. J. Jones* (Harwell) the action of $N_2O_5$ on Pa hydroxide, $PaCl_5$, or $SO(PaCl_6)_2$ affords hydrogen hexanitratoprotactinate(V), $HPa(NO_3)_6$, salts of which can be prepared by interaction of $N_2O_5$ and the corresponding double halides, *e.g.*:

$$CsPaCl_6 + N_2O_5 \rightarrow CsPa(NO_3)_6.$$

The analogous reaction with niobium or tantalum leads only to oxide nitrates, *e.g.* $CsNbO(NO_3)_4$.

In contrast to the unambiguous results of the investigations into the solid-state chemistry and the chemistry of its non-aqueous solutions, the chemistry of protactinium in aqueous solution is often difficult to interpret. The formation of oxo and hydroxy species of protactinium cannot be suppressed even in concentrated acids, except in hydrofluoric acid. The results may however be due more to condensation of protactinium species than to hydrolysis of a species with one protactinium atom:

$$\text{Pa–OH} + X^- \rightleftharpoons \text{Pa–X} + OH^-$$

$$\downarrow$$

$$(\gtrless\text{Pa–O–Pa}\lessgtr)_n \text{ irreversibly with } n \approx 4\text{–}5$$

Up to the present no $PaO_2^+$ ion analogous to $UO_2^+$ or $NpO_2^+$ has been found. Thus the behavior of protactinium(V) in aqueous solution is rather unclear, like that of niobium(V) or tantalum(V).

The results of investigations of sulfuric acid solutions are the easiest to interpret, because of the formation of strong Pa(V)–$SO_4^{2-}$ complexes; but according to *D. O. Campbell* (Oak Ridge, U.S.A.), the distribution coefficient for extraction of protactinium(V) by 0.03 M trilaurylamine (in diethylbenzene) decreases greatly if the protactinium concentration is greater than 4 μg/ml. This indicates condensation reactions of protactinium(V) species. With protactinium concentrations of 0.01 mg/ml distribution equilibrium is not attained even after very long extraction times; the reproducibility of the results is poor. By evaporating a solution of protactinium(V) containing $H_2SO_4$–HF with sulfuric acid, *K. W. Bagnall* (Harwell) obtained hydrogen oxotrisulfatoprotactinate(V) $H_3PaO(SO_4)_3$ (hexagonal, a = 9·743 Å, c = 5·506 Å), which above 300 °C is transformed into $HPaO(SO_4)_2$. Analogous seleno acids were also obtained. From extraction experiments with thionyltrifluoroacetone (TTA) *R. Guillaumont* (Paris) concluded that the ion $Pa(OH)_3^{2+}$ [or $PAO(OH)^{2+}$] occurs in acid solutions of protactinium(V) and that this is hydrolysed at low acid concentrations to $Pa(OH)_4^+$ [or $PaO(OH)_2^+$] (hydrolysis constant $K_1 = 0.09$ at 25 °C). A synergistic effect was observed on extraction of protactinium(V) with TTA + tributyl phosphate (TBP) and was ascribed to extraction of a mixed species $Pa(OH)_3(TTA)_2 \cdot 2 \updownarrow$ TBP. Extraction of protactinium(V) with 8-quinolinol (*C. Keller*, Karlsruhe) or acetylacetone (*J. Rydberg*, Göteborg, Sweden) is, however, hardly to be explained by postulating species $Pa(OH)_3^{2+}$ and $Pa(OH)_4^+$. Protactinium is partly extracted even from 8 M $H^+$ solutions, specifically and with high distribution coefficents, by secondary or tertiary amines (*R. Muxart* and *P. Guillot*, Paris), by phenylarsonic acid (*B. Mjassoedov*, Moscow), or by derivatives of hydroxylamine such as *N*-benzoylphenylhydroxylamine or *N*-nitrosonaphthylhydroxylamine (*A. V. La-*

*pickij*, Moscow); these reagents can be used for analytical separations. From systematic study of the extraction of protactinium(V) with dialkylphosphinic acids, *e.g.* di-n-octylphosphinic acid (HY) [*], *G. W. Mason* (Argonne) postulates extraction of the species:

$(Cl)(O)(HY_2)PaY_2Pa(HY_2)(O)(Cl)$

Experiments with the extraction of protactinium(IV) by a benzene solution of TTA lead to the conclusion that protactinium(IV) behaves like other quadrivalent actinides in aqueous solution. Hydrolysis of the $Pa^{4+}$ occurs stepwise over $Pa(OH)^{3+}$ (hydrolysis constant $K_{0,1} = 0.725$) and $Pa(OH)_2^{2+}$ ($K_{0,2} = 0.302$) to $Pa(OH)_3^{+}$ ($K_{0,3} = 0.017$) before $Pa(OH)_4$ is precipitated (*R. Guillaumont*, Paris). $Pa^{4+}$ shows a stronger tendency than $Pa(OH)_3^{2+}$ to complex-formation.

*H. W. Kirby* (Miamisburg, Ohio, U.S.A.) reported on the hydrolysis of protactinium(V). By utilizing the approximately 100-times greater stability of the niobium oxalate complex than of the analogous protactinium(V) complex a highly specific precipitation of protactinium(V) can be achieved from Nb–Pa solutions (enrichment factor for Nb up to 10). With pure $^{231}Pa$ solutions, hydrolytic precipitation from 1 N to 6 N HCl or 1 N $HNO_3$ can be used for separation from the decay products $^{227}Ac$, $^{227}Th$, and $^{223}Ra$. Specific adsorption of traces of protactinium on glass or silica gel is possible from solutions in 1–6 M HCl or 1–10 M $HNO_3$, and desorption occurs with over 90% yield by use of complexing agents (oxalic or tartaric acid).

*W. H. Burgus* (Idaho Falls, U.S.A.) described a process for separating 1 g of $^{233}Pa$ (20000 C) from 200 g of irradiated metallic thorium. The enrichment steps for $^{233}Pa$ comprised three $MnO_2$ precipitations, and the final purification a protactinium iodate precipitation. The heat evolution of the dried product (50 watts/g) sufficed for partial decomposition of the iodate. The neutron-capture cross-section for $^{233}Pa_2O_5$ was measured, the value found being only about half that previously assumed. [VB 950/257 IE]

German version: Angew. Chem. *78*, 118 (1966)

[*] Present as imer ($H_2Y_2$) in xylene.

# Symposium on Molecular Relaxation Processes

The Symposium on Molecular Relaxation Prozesses, organized by the Chemical Society and held in Aberystwyth, Wales, on July 7th–9th, 1965 was attended by some 180 scientists. In the 38 lectures delivered, the speakers discussed problems of molecular relaxation arising in electric polarization, nuclear magnetic resonance, electron spin resonance, excitation of molecular vibrational states, and ultrasonic propagation. These lectures and the subsequent discussions are to be published soon in book form.

From the lectures:

## Dielectric Relaxation

*C. P. Smyth* (Princeton, U.S.A.) pointed out that dielectric relaxation times supply valuable information on molecular and intramolecular motion, enabling inferences to be drawn concerning molecular structure, the shape and size of particles, the intermolecular forces responsible for internal friction, and even concerning the structure of liquids. When the molecular dimensions of a solvent and solute are about the same, the simple Debye model treating a molecular dipole as a spherical rotator in a viscous medium leads to appreciably longer relaxation times than the observed values. In such cases, Stokes' law is clearly not applicable. Good agreement with observed values is obtained only when the volume of a solute molecule is about three or more times larger than that of a solvent molecule.

The particularly interesting appearance of two relaxation processes has been ascertained on numerous systems, such as solutions of substituted benzenes containing the $CH_2Cl$, $CH_2CN$, $CH_3O$, $CH_3CO$, or OH group. The longer relaxation time is ascribed to rotation of the whole molecule, and the second, generally shorter relaxation time (of the order of $10^{-12}$ sec) to free rotation of the substituent. In some cases, however, the short relaxation time is absent, indicating a suppression of the free rotation by steric hindrance. The extraordinarily short intramolecular relaxation time of various arylamines is probably due to inversion such as that known to take place in the ammonia molecule.

Measurements carried out on ten straight-chain alcohols at 16 wavelengths between 0.22 cm and 300 m revealed three different relaxation times in each case. The longest of these is explained by the rupture of hydrogen bonds in molecular aggregates, resulting in molecular rotation. The other two relaxation times are again attributed to the rotation of a monomeric molecule and of an OH group, respectively. Relaxation observed in water-dioxane mixtures is also to be attributed to the rupture (and re-formation) of hydrogen bonds and to the rotation of the water molecules as a whole. Dielectric dispersion measurements carried out on binary mixtures of some polar liquids indicate the presence of relaxation processes of molecules, but not of larger aggregates. *G. Williams* (Teddington, England) discussed the complex dielectric constants of polar compounds (*e.g.* polymethyl acrylate and polyethyl methacrylate) as a function of the frequency, temperature, and pressure, and pointed out that the effect of pressure had previously been neglected in most cases. Increasing pressure at constant temperature leads to restriction of molecular motion, as shown by an increase in the relaxation time. Quantitatively, however, this effect varies greatly, depending on the relaxation mechanism. The effect of pressure (up to 3000 atm) on the dielectric relaxation of polar linear polymers (*e.g.* polymethyl acrylate) was mainly disussed. These molecules usually exhibit two relaxation processes -- a medium-frequency $\alpha$-dispersion due to the motion of the whole chain, and a high-frequency $\beta$-dispersion due to rotation of small sub-units of the molecule. It is interesting that the broad relaxation band observed for polyethyl methacrylate at 1 atm is split into two relaxation bands ($\alpha$ and $\beta$) when the pressure is increased to about $10^3$ atm, because one of the two mechanisms is much more greatly affected than the other by the change in the pressure.

*D. W. Davidson* (Ottawa, Canada) summarized the results of recent investigations on the dielectric relaxation of six ice structures (I–VI) formed at high pressures. The static dielectric constant and the relaxation frequency increase with increasing density. In the case of structures III, V, and VI, the relaxation frequency is about 10 kc/s, which is much higher than that of common ice (structure I), 150 c/s. The rotation in structure II is independent of the temperature. These results support the general Bjerrum model of relaxation based on defect diffusion in the ice crystal.

*J. D. Hoffman* (Washington, D.C., U.S.A.) developed a theory for the interpretation of the relaxation spectra of systems in which polar molecules form a molecular lattice, as in the case of long-chain ketones in urea addition compounds. This theory treats the polar molecule as a rigid

rotator and represents the crystal field, where the rotation takes place, by a system of potential barriers. The orientation of the dipole then corresponds to a site displacement process, and the elementary process is represented by a transition between two adjacent sites (lowest-energy orientations), taking place over the intermediate potential barrier. The periodic change in the occupancy of the individual sites is expressed by a set of n linear differential equations, where n is the number of sites. We thus obtain (n−1) non-vanishing relaxation times for the description of the dielectric relaxation of the system. The theory has already been confirmed experimentally on long-chain ketones and secondary bromides in urea addition complexes.

*M. Davies* (Aberystwyth, Wales, Great Britain) discussed some dielectric studies on molecular motion in solids, selecting systems whose dielectric properties indicate that the transition from the liquid to the solid state is not accompanied by the disappearance of dipole orientation. The degree of rotation varies greatly in systems of this group, as shown by variation of the relaxation time from about $5\times10^{-12}$ sec [for $(CH_2)_2O$ in ice and for $SO_2$ in hydroquinone] to over 1 sec (for zeolites, according to their water content).

*E. H. Grant, M. W. Aaron,* and *S. E. Young* (London, England) investigated the dielectric properties of some amino acids, peptides, and proteins in solution, the wavelength region used being of the order of 10 cm. The observed dipole moments of glycine, and α- and β-alanine obtained by using *Kirkwood*'s method of calculation are in good agreement with the values expected on the basis of structural data. The results show that peptides are not fully extended in solution. The activation energies for the relaxation process of the dissolved substances are about 3 to 4 kcal/mole, indicating deformation or rupture of a hydrogen bond. Measurements on ovalbumin and bovine serum albumin carried out in the region 15 to 160 cm revealed an additional, weak dispersion between the β-dispersion (due to orientation of the protein molecules) and the γ-dispersion (due to relaxation of the water dipole). This effect is attributed to the relaxation of bound water molecules. The enthalpy of the relaxation process is given approximately as 13 kcal/mole, the weight fraction of bound water being 0.30 for ovalbumin and 0.35 for bovine serum albumin.

*G. Schwarz* (Göttingen, Germany) pointed out that – under the usual conditions of measurement – molecular dielectric relaxation can also result from chemical relaxation, *i.e.* the process of readjustment of an equilibrium which has been disturbed, provided that the dielectric polarization of the system is altered by the chemical reaction (*e.g.* by changing the dipole moment of the partners), and provided that the relaxation of the dipole orientation is slower than the chemical relaxation. While the second condition is usually not fulfilled in the reactions of simple molecules, the prospects are more promising in macromolecular systems. The change in the configuration of polypeptides in solution (helix-coil transformation) is thus expected to result in a measurable dielectric relaxation effect. – Results of preliminary measurements on poly(benzyl-L-glutamate) in dichloroethylene/dichloroacetic acid mixtures support the theoretical predictions.

## Relaxation of Nuclear Magnetic Resonance and Electron Spin Resonance

*J. S. Waugh* (Cambridge, U.S.A.) emphasized the versatility of nuclear magnetic resonance in its applications to the study of molecular phenomena ranging from fast chemical reactions to lattice vibrations. More specifically, the statistical treatment of molecular motion in gases and liquids was discussed.

*J. G. Powles* (Canterbury, England) dealt with the correlation time $\tau_c$ [*] obtained from NMR measurements of molecular orientation in molecular liquids along the liquid-vapor coexistence line. The correlation frequencies $\nu_C$ [$= 1/2\,\pi\tau_c$)] between the glass transition temperature and the critical temperature have been collated for a great number of liquids. For practically all substances, $\nu_C$ at high temperatures (*i.e.* in the vicinity of the critical temperature) reaches approximately the same upper limiting value of somewhat over $10^{12}$ c/s. In the case of certain substances however, the value of $\nu_C$ is significantly lower. At low temperatures, the values of $\nu_C$ may become very small. Comparison between $\tau_C$ and the dielectric relaxation times $\tau_D$ shows the frequent failure of the relationship $\tau_D/\tau_C = 3$, which has been derived by assuming a continuous rotational diffusion. According to a recent theory of *Ivanov*, $\tau_D/\tau_C$ assumes a smaller value whenever the change in the molecular orientation is not continuous but stepwise.

[*] The correlation time is the time needed for orientated molecules to re-establish statistical distribution.

*H. S. Resing* (Washington, D.C., U.S.A.) showed that a wide spectrum of correlation times causes an apparent phase shift in the spin-spin relaxation time. A sensitive test of this theory is provided by measurements of the spin-spin relaxation time for liquid water adsorbed in the pores of a charcoal adsorbent. This effect allows an estimation of the range of the activation energies for surface diffusion, and therefore provides a new technique for studying surface heterogeneities.

*K. Bergman* and *K. Nawotki* (Ludwigshafen, Germany) discussed a new method of determining molecular motion in high polymers. The method consists in representing the observed NMR lines as a superimposed pattern of known unit spectra and calculating the statistical weights of the components. This method offers certain advantages over the usual second moment technique. Measurements on amorphous, solid high polymers, such as polymethyl methacrylate, show that rotation of the methyl groups in the chain increases as the temperature increases from −180 to −100 °C, and that rotation of the methyl groups in the side chain begins at about −100 °C.

*A. Carrington* (Cambridge, England) spoke on the effect of molecular relaxation on electron spin resonance, as shown in electronic transition, rupture and re-formation of hydrogen bonds, proton transition equilibria, the equilibrium of ligand exchange in metal chelates, and processes occurring in crystals.

## Ultrasonic Relaxation

*T. A. Litovitz* (Washington, D.C., U.S.A.) surveyed molecular relaxation processes causing the absorption and dispersion of ultrasound in liquids, mentioning structural relaxation, transitions between vibrational and translational energy, and rotational isomerism. *Litovitz* discussed structural relaxation, *i.e.* the temporary establishment of the equilibrium structure in water and fused salts. It is of great interest that the relation associated with the lattice structure generally exhibits a scatter of relaxation times. This is apparently connected with the fact that the shear viscosity does not obey the Arrhenius law. He also discussed the relationship between structural relaxation and the relaxation processes of NMR and of dielectric polarization. According to his theory concerning the appearance of relaxation spectra, a wide scatter of relaxation times is expected if the dielectric relaxation time $\tau_D$ is of the same order of magnitude as the structural relaxation time $\tau_S$, while on the other hand a single relaxation time arises when $\tau_D$ is large compared to $\tau_S$.

*G. Atkinson* (College Park, Maryland, U.S.A.) reported on measurements of ultrasonic absorption for the determination of fast reactions in solutions, such as the dissociation of manganese sulfate in aqueous organic solvents. The results indicate a preferential solvation of the ions by water molecules, which must be removed in two steps in the recombination of the ions. Furthermore, the water molecules and the organic solvent are believed to form a complex which is stabilized by hydrogen bonding and is associated with desolvation. At about 30 to 40 Mc/s, an ultrasonic absorption

band is observed which is so sharp that it cannot be attributed to a relaxation effect; its nature has not yet been elucidated.

*E. W. Jones* and *W. J. Orville-Thomas* (Aberystwyth, Wales, Great Britain) have carried out measurements of ultrasonic absorption to determine the difference between enthalpies ($\Delta H \sim 0.9$ to 2.1 kcal/mole) of rotational isomers in the liquid state. These values differ appreciably from those obtained from infrared measurements ($\Delta H \sim 0$ to 0.83 kcal/mole). The data on sound absorption apparently lead to incorrect values of $\Delta H$. It can be shown that, in the case of rotation around a C—C bond, the basic assumptions used for calculating the enthalpies are incorrect. On the other hand, the values obtained for the activation energies are acceptable.

### Relaxation of Excited Molecular Vibrational States

*R. C. Millikan* (Schenectady, N.Y., U.S.A.) surveyed the processes of energy transfer in the gas phase. In favorable cases, the vibrational relaxation times can be found with an accuracy of ± 20 %. *Millikan* also discussed the effect of rotation on the vibrational relaxation, the exchange of vibrational energy on collision, and the energy transfer between molecular vibrational states and excited electronic states of atoms and free electrons.

*H. J. Bauer* and *H. Roesler* (Stuttgart, Germany) dealt with the relaxation of the vibrational degrees of freedom in binary mixtures of diatomic gases. An exchange reaction between the excited and the non-excited molecules of different components of mixtures ensures a coupling between the relaxation processes of the two components. The two relaxation times for the sound absorption of the entire system depend in a complicated manner on the composition. The reciprocal relaxation times give a conic curve when plotted against the mole fraction. They were determined experimentally by measuring the sound absorption in $O_2/N_2$ and in $O_2/CO$ mixtures. With the aid of these values, the transition probability for the return to the ground state at 300 and 365 °K was found, *e.g.* for $O_2/O_2$ collision at 300 °K, to be $8.3\times10^{-9}$.

[VB 956/263 IE]

German version: Angew. Chem. *78*, 120 (1966)
Translated by Express Translation Service, London

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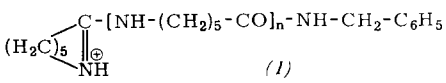
## Oligoamides and their Role in Lactam Polymerization

*M. Rothe*, Mainz (Germany) [1]

Higher linear oligomers or pleionomers of ε-aminocaproic acid containing up to 14 monomer units per chain and their derivatives with protected amino and carboxyl functions were synthesized *via* the carbobenzoxyoligoamide benzyl esters using the phosphite method conventionally [2] or occasionally on a polymeric support [3]. Cyclic oligomers containing up to 8 monomer units per ring were obtained by cyclizing the chain compound by the phosphite method [2]. Separation of the linear oligomers with up to 7 monomer units was achieved by thin-layer electrophoresis and the separation of cyclic oligomers containing up to 8 monomer residues by thin-layer chromatography with n-butanol/acetic acid/ammonia (1:4)/water (6:1:1:2) or with ethyl acetate/acetone/water (10:10:2).

In the absence of water, oligomers with *N*-terminal amidinium groups *(1)* do not initiate cationic lactam polymerization



*(1)*

even on heating them with the monomer at 250 °C for several hours. Hence the formation of terminal amidinium groups during lactam polymerization [4] does not contribute to normal chain propagation [5], but causes chain termination. Higher lactams, *e.g.* caprylolactam or laurolactam do not form amidine rings in appreciable amounts, since these would have to have 9 or 13 ring members.

[Lecture at Marl (Germany), June 16th, 1965] [VB 945/252 IE]

German version: Angew. Chem. *78*, 151 (1966)


[1] In collaboration with *D. Essig*, *I. Rothe*, and *H. Schneider*.

[2] *M. Rothe* et al., Makromolekulare Chem. *75*, 122 (1964).

[3] *R. B. Merrifield*, J. Amer. chem. Soc. *85*, 2149 (1963).

[4] *P. Schlack*, Z. ges. Textilind. *1963*, 1052; reported in a lecture at the Synthetic Fibre Symposium, Berlin, March 30th, 1965.

[5] *M. Rothe et al.*, Makromolekulare Chem. *54*, 183 (1962).


## The Influence of Neutral Salts on the Hydrogen Ion Activity

*K. Schwabe*, Dresden (Germany)

It was shown by comparison of potentiometric, polarographic, and spectrophotometric measurements of pH in dilute solutions of strong acids and bases that the addition of large amounts of neutral salts produces a genuine, occasionally large change in the pH. The conventional pH value was determined using glass and hydrogen electrodes. Simultaneous measurements of the pwH and ptH values [1] revealed that shifts sometimes as large as 2 pH units were caused by a change in the activity coefficient of the hydrogen ion at constant hydrogen ion concentration. In salts with a common anion, the pH shift to lower values increases as the radius of the cation decreases; with very large cations, *e.g.* quaternary ammonium ions, an increase in pH may be observed. With a common cation, the shift to higher pH values becomes greater, the smaller the radius of the anion. Salts with large, non-hydrated ions *e.g.* $NH_4CNS$, cause only small changes in pH, even at very high concentrations (> 20 moles/kg). The decrease in the pH of acids usually is proportional to the molality m of the salt. The same applies for some cations, *e.g.* $Li^{\oplus}$, for the reduction in the pH of alkali metal hydroxide solutions; in other cases, *e.g.* with sodium salts, the pH of sodium hydroxide solution passes through a minimum as the amount of salt added increases.

The results can be interpreted by assuming that the change in the activity coefficients of $H^{\oplus}$ (or $OH^{\ominus}$) is caused by the electrostatic interaction of the charge of the $H^{\oplus}$ (or $OH^{\ominus}$) ions, which is "smeared out" uniformly over the whole solvent on account of the rapid exchange with water molecules, and the cations and anions of the salt. With the additional assumption that this interaction increases with the number of water molecules held in the hydration sphere of the salt ions, an equation can be set up for the excess Gibbs free energy of the $H^{\oplus}$ ions which fits at least the experimental values for the decreases in the pH of acids $\Delta pH/\Delta m_{salt}$.

The binding of water molecules by hydration of the salt and the resultant increase in the $H^{\oplus}$ concentration in the "quasi-eutectic" system and the observed decrease in the product $m_{H^{\oplus}} \cdot m_{OH^{\ominus}}$ at high salt concentrations may also contribute to the change in pH. It was shown that the kinetics of decomposition of acetoacetic ester and of the anodic dissolution of Fe and Co depend on the $H^{\oplus}$ activity, but that cathodic discharge of $H^{\oplus}$ depends upon the $H^{\oplus}$ concentration.

[Lecture at Saarbrücken (Germany), July 16th, 1965]

[VB 953/254 IE]

German version: Angew. Chem. *78*, 151 (1966)

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[1] $pwH = -\log m_{H^+} \cdot f_{H^+} \cdot f_{Cl^-}$, $ptH = -\log m_{H^+} \cdot f_{\pm}$.

## Formation of Coordination Complexes in Anhydrous Acetonitrile

*V. Gutmann*, Vienna (Austria)

Chloride or azide ions were added gradually to solutions of anhydrous perchlorates, tetrafluoroborates, hexafluoroantimonates, and hexachloroantimonates of $Ti^{3\oplus}$, $V^{3\oplus}$, $VO^{2\oplus}$, $Cr^{3\oplus}$, $Mn^{2\oplus}$, and $Fe^{3\oplus}$ in anhydrous acetonitrile. The formation of coordination complexes was followed by spectrophotometric, potentiometric (silver/silver azide electrode), and conductometric methods. With the azides, the following complex species were identified:

$Ti(N_3)_3$, $[Ti(N_3)_4]^{\ominus}$, and $[Ti(N_3)_6]^{3\ominus}$

$V(N_3)_3$ and $[V(N_3)_6]^{3\ominus}$

$VO(N_3)_2$ and $[VO(N_3)_5]^{3\ominus}$

$[Cr(N_3)_6]^{3\ominus}$

$Mn(N_3)_2$ and $[Mn(N_3)_4]^{2\ominus}$

$Fe(N_3)_3$ and $[Fe(N_3)_6]^{3\ominus}$

With chloride ions, on the other hand, the tetrachloro complexes were the highest formed:

$TiCl_3$ and $[TiCl_4]^{\ominus}$

$VCl_3$ and $[VCl_4]^{\ominus}$

$[CrCl_2]^{\oplus}$, $CrCl_3$, and $[CrCl_4]^{\ominus}$

The formation of complexes of $SbCl_5$, $SnCl_4$, $TiCl_4$, $BCl_3$, $AlCl_3$, $GaCl_3$, $InCl_3$, $BBr_3$, $AlBr_3$, $GaBr_3$, and $BF_3$ with *trans*-azobenzene, *p*-dimethylaminoazobenzene, and *p*-methoxyazobenzene was examined spectrophotometrically in anhydrous acetonitrile. The equilibrium constants were determined and the validity of the Hammett equation established. A few of the complexes could be isolated. The results of infrared spectrographic studies made it possible to fix the position of the –N=N- vibration in azobenzene derivatives.

[Lecture at Bonn (Germany), July 20th, 1965]

[VB 954/255 IE]
German version: Angew. Chem. *78*, 151 (1966)

## Structural Investigations on New Mercury Compounds

*K. Brodersen*, Erlangen (Germany)

Addition of methylamine to ethereal or benzene solutions of mercury(II) chloride or bromide leads to precipitation of the compounds $HgX_2 \cdot 2\ NH_2CH_3$ and $HgX_2 \cdot NH_2CH_3$ (X = Cl or Br). The former are converted into stable, pure compounds $HgX_2 \cdot NH_2CH_3$ on treatment with the pure solvent or with a solution of the mercury(II) salt. The 1:2 adducts also lose amine on thermal degradation, whereas the monoadducts sublime unchanged. The compound $HgCl_2 \cdot NH_2CH_3$ contains four molecules per unit cell, and the following lattice constants were found for single crystals: a = 15.05 Å; b = 5.81 Å; c = 5.72 Å; $\beta = 97°$.

Dimethylamine gives 1:2 adducts from benzene solution, but only the 1:1 adducts from ether. Under the same conditions trimethylamine gives only the adducts 3 $HgX_2 \cdot 2\ N(CH_3)_3$, which can occlude $HgX_2$. Daylight or ultraviolet irradiation decomposes these adducts with production of mercury(I) compounds.

Primary aliphatic amines (ethyl-, n-propyl, n-butyl-, and n-pentyl-amine) give the substitution products $Hg_3(RN)_2X_2$ alongside the 1:1 and 1:2 adducts, the relative amounts depending on the solvent used.

[Lecture at Marl (Germany), October 13th, 1965]

[VB 959/266 IE]
German version: Angew. Chem. *78*, 151 (1966)

# SELECTED ABSTRACTS

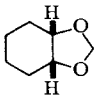
**The chemisorption of nitrogen on various surfaces of tungsten single crystals** at room temperature and below was investigated by *T. A. Delcher* and *G. Ehrlich* by measurement of the contact potentials against platinum (platinum does not adsorb nitrogen at room temperature). The work function for electron emission from tungsten is reduced by chemisorption of nitrogen on the (100) surface by 0.4 eV, for the nitrogen is present in the atomic state. The work function is increased by 0.15 eV on the (111) surface; here some of the nitrogen is adsorbed as atoms, some as molecules. At low pressures (ca. $10^{-7}$ mm) and room temperature the (110) surface does not adsorb nitrogen; adsorption occurs only at lower temperatures (ca. 130 °K) or at relatively high pressures ($10^{-3}$ mm). Here too the adsorbed nitrogen is atomic but is attached differently from that on the (100) surface; the work function is lower than that of the pure surface. / J. chem. Physics *42*, 2686 (1965) / –Hz. [Rd 364/573 IE]

**Benzene is synthesized from acetylene in Avocado pears.** *E. F. Jansen* and *J. M. Wallace* kept the unripe fruit for 4 h in an atmosphere of [$^{14}$C]acetylene. Four-fifths of the absorbed radiocarbon recurred in the respired carbon dioxide, the remainder was incorporated into several compounds in the fruit. Of these, 25% were non-volatile and 30% was benzene with a specific activity of 0.5% of that of the acetylene. Another radioactive product identified was toluene. The benzene was identified by converting it into β-benzoylpropionic acid, benzoic acid, and *p*-phenyl phenacylbenzoate, the toluene analogously. / J. biol. Chemistry *240*, 1042 (1965) / –Hö. [Rd 374/583 IE]

**The oxidation of tungsten** at 1400 to 3150 °K has been followed mass-spectrometrically by *P. O. Schissel* and *O. C. Trulson*. The principal oxidation products are $W_3O_9$, $W_2O_6$, $WO_3$, and $WO_2$, the ratio depending on the oxygen pressure and on the temperature of the metal surface. The observations can be explained by a reaction scheme involving two oxygen species bound firmly to the surface. / J. chem. Physics *43*, 737 (1965) / –Hz. [Rd 397/606 IE]

**The reactivity and function of the thiol groups of alcohol dehydrogenase** from horse-liver have been studied by *T. L. Li* and *B. L. Vallee*. The alcohol dehydrogenase (ADH) can be inhibited by iodoacetate, two of the 24 thiol groups being carboxymethylated. The other 22 groups react much less readily; after denaturation, however, the reactivities of all the thiol groups are the same. DPNH protects the ADH against inhibition and carboxymethylation. The inhibited and dicarboxymethylated ADH still interacts with DPNH and alcohol, as can be seen from the rotatory dispersion and the spectrum. Thus the two most reactive thiol groups are not required for the binding of the coenzyme and the substrate. However, the dissociation constant (at pH 7.5) of the complex of carboxymethylated ADH with DPNH is increased to $4 \times 10^{-5}$ (native enzyme with DPNH: $4 \times 10^{-7}$). The exchange of enzyme-bound $^{65}Zn^{2+}$ with $Zn^{2+}$ is faster, the "half-life" under the conditions used being 20 hours for the native enzyme and 14 hours for the carboxymethylated enzyme. / Biochemistry *4*, 1195 (1965) / –Hö. [Rd 402/611 IE]

**The reaction of *cis*- and *trans*-1,2-cyclohexanediols with dihalogenomethanes** has been studied by *J. S. Brimacombe, A. B. Foster, B. D. Jones*, and *J. J. Willard*. At room temperature, the *cis*-compound reacts with dibromo- or dichloromethane and a suspension of NaH in dimethylformamide to give *cis*-cyclohexa-1,3-dioxolane *(1)* as major product together with about 2% 1,3,6,8-biscyclohexa[*d,i*]tetraoxacyclodecane *(2a)*, m.p. 142–143 °C. This new ring system occurs



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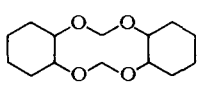

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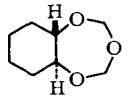

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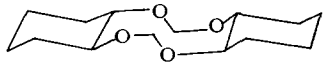
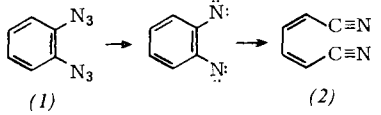


*(2b)*

in the *cis,syn,cis*- or *cis,anti,cis*-forms. Similarly, the *trans*-diol gives mainly *trans*-cyclohexa-1,3-dioxolane, b.p. 50 to 51 °C/15 mm, plus a little *trans*-cyclohexa-1,3,5-trioxepane *(3)* and a tetraoxacyclodecane *(2b)*, m.p. 166–167.5 °C, which has probably the stable *trans,syn,trans*-configuration. / Chem. Commun. *1965*, 174 / –Ma. [Rd 345/554 IE]

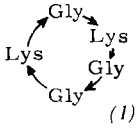
**The thermolysis of derivatives of *o*-azidoaniline** has been studied by *J. H. Hall* and *D. R. Kamm*. *o*-Azidoaniline readily condenses with aromatic aldehydes containing strongly electron-attracting groups in the *o*- or *p*-positions to form Schiff bases. Thermolysis of the latter affords high yields of 2-substituted benzimidazoles. When *o*-azidoaniline is diazotized and coupled with phenol, *p*-cresol, α-naphthol, or β-naphthol it gives rise to *o*-azidoazo compounds, while with *N,N*-dimethylaniline and *N*-methylaniline it gives the *o*-azidoazo and *o*-azidoazoamino derivatives which on heating decompose to 2-substituted benzotriazoles. Diazotization of



*(1)* *(2)*

*o*-azidoaniline and subsequent treatment with $NaN_3$ gives *o*-diazidobenzene *(1)*, which on refluxing in decalin undergoes cleavage of the benzene ring to yield 79% 1,4-dicyano-1,3-butadiene. / Abstracts 149th Meeting Amer. Chem. Soc. *1965*, 55P / –Ma. [Rd 335/544 IE]

**The cyclic pentapeptide *(1)* is not hydrolysed by trypsin.** *G. W. Kenner* and *A. H. Laird* have found that *(1)* is completely resistant to trypsin for a period of 24 hours, whereas the open-chain peptide Gly–Lys–Gly–Lys–Gly is completely broken down within 3 hours. *(1)* was prepared from the *p*-nitrophenyl thiol-ester of the pentapeptide *(2)*, which had previously been provided with protective groups, (X = t-butoxycarbonyl, Y = benzyloxycarbonyl). The protected peptide *(2)* was cyclized with the ion-exchanger Amberlite



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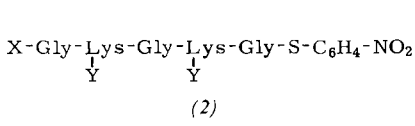


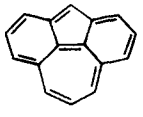
*(2)*

IRA 410 (OH form) in dimethylformamide (yield 52%). No other cyclic peptides were formed. The protective groups were removed with HBr in glacial acetic acid, and the cyclic product was separated from open-chain material by chromatography on Amberlite IRA 410. / Chem. Commun. (London) *1965*, 305 / –Hö. [Rd 399/608 IE]

**The transport of acetyl-CoA from the mitochondria** (site of formation from pyruvate) into the cytoplasm space (site of fatty-acid synthesis) has been studied by *J. Bartley, S. Abraham*, and *I. L. Chaikoff*. Four possibilities are discussed: 1. diffusion as acetyl-CoA; 2. hydrolysis and diffusion of the acetate, followed by regeneration of acetyl-CoA; 3. conversion into acetylcarnitine and transport of the latter; 4. incorporation into citrate and transport of the citrate or of one of its reaction products, followed by liberation of acetyl-CoA. When methyl-tritiated acetyl-CoA is used, tritium should be lost only in case 4. The starting materials used were [1-$^3$H, 1-$^{14}$C]-glucose, [6-$^3$H, 6-$^{14}$C]-glucose, 1-[3-$^3$H, 3-$^{14}$C]-lactate, and [2-$^3$H, 2-$^{14}$C]-acetate. The ratio $^3H/^{14}C$ was then compared with that in the terminal methyl groups of the fatty acids synthesized from the four substrates. Assuming the ratio in the starting material to be equal to 1, the ratios in the fatty acids were 0.54, 0.54, 0.61, and 0.90. Thus the conversion of acetate into acetyl-CoA involves very little tritium exchange. The results obtained with glucose and lactate, on the other hand, can only be explained by possibility 4 above. / Biochem. biophysic. Res. Commun. *19*, 770 (1965) / –Hö. [Rd 401/610 IE]

**There is only a single cysteine residue in the active center of streptococcal proteins** and its precursor cymogen according to observations of *W. H. Stein, S. Moore, et al.* Nevertheless, no mercapto group can be detected in cymogen. A volatile, hitherto unidentified thiol is split off on reaction with sodium borohydride or cysteine. The SH group in reduced cymogen and in the proteinase can be blocked with [$^{14}$C]iodoacetic acid; the enzymatic activity of the proteinase is lost during this process. Hydrolysis of the labelled enzyme with trypsin yields a single radioactive polypeptide containing 27 amino acids whose sequence was established. The cysteine is next to a histidine. / J. biol. Chemistry *240*, 1143, 1150 (1965) / –Hö. [Rd 375/584 IE]

**Cyclohepta[*def*]fluorene** *(1)*, according to MO calculations by *P. Baumgartner, E. Weltin, G. Wagnière*, and *E. Heilbronner*, must have an unusually low lying triplet state, which is either lower than, or at most 0.25 eV higher than, the



*(1)*

lowest singlet state. The molecule should therefore exist as a biradical in a triplet ground state, or else the triplet form should exist in measurable concentration in equilibrium with the singlet state. Preparation of compound *(1)* is being attempted. / Helv. chim. Acta *48*, 751 (1965) / –Hz. [Rd 398/607 IE]

**Reversible denaturation of a univalent antibody fragment** was observed by *P. L. Whitney* and *C. Tanford*. The antibody fragment against the haptene group dinitrophenyl from rabbit contains two polypeptide chains A and B and both inter- and intramolecular disulfide bridges. Reduction with 2-mercaptoethanol in 6 M guanidine hydrochloride denatures the antibody with complete loss of activity. Dialysis and reoxidation restores up to 80% of the activity according to assays by titration with dinitrophenyllysine followed by fluorescence spectroscopy. Thus the specificity in antibodies too appears to be determined solely by the amino acid sequence. The identity of the renatured and the native antibody was demonstrated by the similarity in reaction of the two with an antibody obtained by immunizing goats with the natural antibody fragment (now used as antigen). / Proc. nat. Acad. Sci. U.S.A. *53*, 524 (1965) / –Hö. [Rd 373/582 IE]

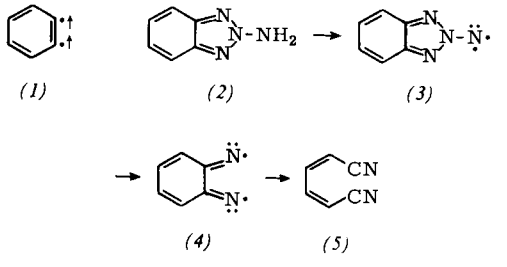
**Indole compounds were isolated from bovine pineal glands** by *W. M. McIsaac, G. Farrell, R. G. Taborsky*, and *A. N. Taylor*. Compounds identified were 5-methoxytryptophol (tryptophol = 3-indolylethanol), *N*-acetyl-5-methoxytryptamine (melatonin), 5-hydroxytryptophol, 5-methoxy-3-indolylacetic acid, and 5-hydroxy-3-indolylacetic acid. Comparisons were made with the melting points (sometimes of picrates), electrophoretic mobilities, color reactions, and $R_f$ values in 5 solvent systems of authentic samples. These serotonin derivatives are of physiological importance, *e.g.* *N*-acetyl-5-methoxytryptamine affects thyroid functions, the onset of estrus, and the ovary weight, while 5-methoxytryptophol inhibits the onset of estrus and suppresses ovary growth. / Science (Washington) *148*, 102 (1965) / –De.

[Rd 377/586 IE]

**A serotonin synergist was found in the blood of schizophrenics** by *D. W. Woolley* and *B. W. Gommi*. In combination with this substance, small amounts of serotonin which are otherwise insufficient to cause contraction of isolated rat uterus effect a strong muscular contraction. The synergist is possibly a ganglioside and cannot produce a muscular contraction alone. It augments the tissue sensitivity to acetylcholine and bradykinine. The substance cannot be dialysed, is thermostable, and dissolves in chloroform/methanol; it does not occur in the blood of normal persons. It seems possible that there is a causal connection between this substance and schizophrenia. / Science (Washington) *148*, 670 (1965) / –De.

[Rd 378/587 IE]

**The oxidation of 1- and 2-aminobenzotriazoles** with lead tetraacetate in benzene was studied by *C. D. Campbell* and *C. W. Rees*. Dehydrobenzene is produced rapidly and quantitatively from 1-aminobenzotriazole, which in the absence of a trapping agent yields nitrogen and 83% biphenylene plus about 0.5% triphenylene as by-product. Analogously, 1-amino-5-methylbenzotriazole yields 67% 2,6-dimethylbi-



*(1)* *(2)* *(3)* *(4)* *(5)*

phenylene. This tendency to dimerize is not so marked in dehydrobenzene that has been prepared in other ways. It is possible that the dehydrobenzene made from 1-aminobenzotriazole occurs more in a triplet state *(1)* than in a singlet state. Oxidation of 2-aminobenzotriazole *(2)* causes evolution of nitrogen and formation of *cis,cis*-muconitrile *(5)*, m.p. 127 °C, in 64% yield. The latter is probably formed *via* the nitrenes *(3)* and *(4)*. / Chem. Commun. *1965*, 192 / –Ma.

[Rd 356/565 IE]

**A new synthesis of ketones** involves treatment of acid chlorides or anhydrides with hexaalkyldisilanes *(2)*. *E. Frainnet, R. Calas, P. Gerval*, and *J. Bonastre* found that acyl chlorides *(1)* react rapidly with *(2)* in the presence of equimolar amounts of $AlCl_3$ to give ketones *(3)*, in yields of 60–85%.

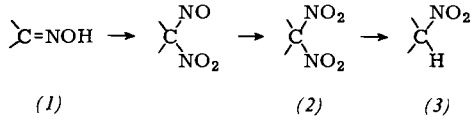
$$RCOCl + R'_3Si{-}SiR'_3 \rightarrow R{-}CO{-}R' + R'_3Si{-}SiR'_2Cl$$

*(1)* *(2)* *(3)*

$R = C_2H_5$, $C_3H_7$, or $C_6H_5$; $R' = CH_3$ or $C_2H_5$

If dimethyltetraethyldisilane is used, a mixture of methyl and ethyl ketones is formed. Acid anhydrides react analogously./ Bull. Soc. chim. France *1965*, 1259 / –Ma. [Rd 352/561 IE]

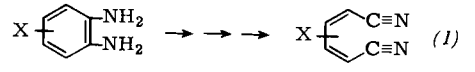
**A new preparation of nitrosteroids** is described by *J. R. Bull, E. R. H. Jones*, and *G. D. Meakins*. Nitration of steroid oximes *(1)* with fuming nitric acid and subsequent oxidation of the pseudo-nitrols with $H_2O_2/HNO_3$ gives the *gem*-dinitro compounds *(2)*, which are converted by careful hydrogenation into the mononitro compounds *(3)*. The α-nitro group is removed selectively from 4,4-, 6,6-, and 17,17-dinitro steroids. The 3,3-dinitro compound yields a mixture of α- and



*(1)* *(2)* *(3)*

β-mononitrosteroid. Reduction of the 7,7-dinitro derivative gave the 7α-mononitro compound. The equatorial conformer is the more stable epimer in mononitro compounds. The relative stabilities of the equatorial and axial conformers depend on the position substituted. / J. chem. Soc. (London) *1965*, 2601 / –Ma. [Rd 354/563 IE]

**The formation of *cis,cis*-1,4-dicyano-1,3-butadienes** *(1)* was observed by *K. Nakagawa* and *H. Onoue* on oxidation of *o*-phenylenediamines with nickel peroxide in benzene or ether at room temperature. The *cis,cis*-configuration was concluded from the melting points and infrared, ultraviolet, and NMR spectra. The dienophilic character of *cis,cis*-1,4-dicyano-1,3-butadiene is demonstrated by its formation of a Diels-Alder adduct with cyclopentadiene. For example, *o*-phenylenediamine → 14.2% 1,4-dicyano-1,3-butadiene *(1)*, X = H, m.p. 128–129 °C; *(1)*, X = 3-methyl, m.p. 70.5–71 °C, 8.2%; *(1)*,

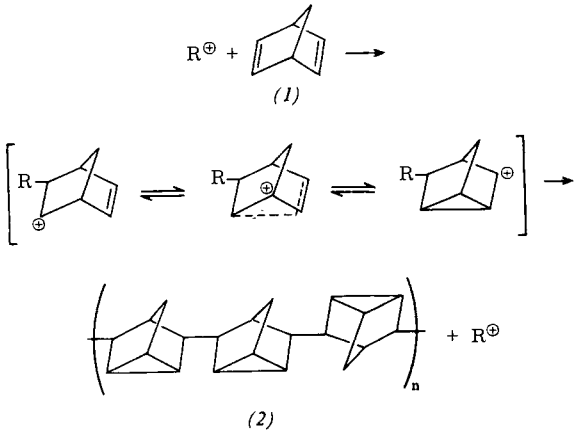


*(1)*

X = 4-methoxy, m.p. 116–117 °C, 11.6%; and 1,2-diaminonaphthalene → 25.8% 1-cyano-2-(β-cyanovinyl)benzene, m.p. 70–70.5 °C. / Tetrahedron Letters *1965*, 1433 / –Ma.

[Rd 355/564 IE]

**Cationic transannular polymerization of norbornadiene** is described by *J. P. Kennedy* and *J. A. Hinlicky*. Norbornadiene, *i.e.* bicyclo[2.2.1]hepta-2,5-diene *(1)*, can be polymerized in chloroethane at –123 °C with $AlCl_3$ as initiator. The amorphous polymer obtained in 17.2% yield after 37 min has a molecular weight of 5500 and is completely soluble in benzene, ether, and carbon tetrachloride. The yield of poly-



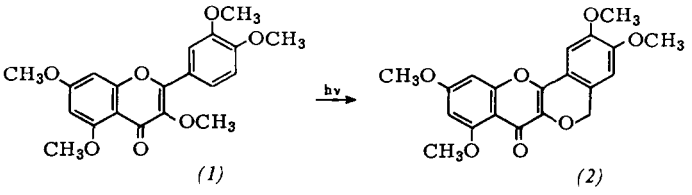
*(1)* *(2)*

mer increases at higher temperatures (–78, 0, or +40 °C) but the products are then partially cross-linked. It is assumed that the norbornadiene behaves like butadiene under these conditions. The structures of the polymers were shown by infrared and NMR spectroscopy to involve 2,6-disubstituted nortricyclene units *(2)*. / Polymer *6*, 133 (1965) / –Hl.

[Rd 379/388 IE]

**The photochemical decarboxylation of acyl hypoiodites** was found by *D. H. R. Barton, H. P. Faro, E. P. Serebryakov*, and *N. F. Wooley* to be useful for preparing iodides. A solution of the acid plus lead tetraacetate in an inert solvent, *e.g.* carbon tetrachloride or benzene, is boiled and irradiated, and iodine is added until its color persits. The reaction probably proceeds via an acyl hypoiodite, which on photolysis liberates acyloxy radicals. On decarboxylation, these leave carbon radicals which add iodine (Method a). The formation of acyl hypoiodites can also be effected by an exchange reaction with t-butyl hypoiodite (Method b). For example, n-hexanoic acid gives 100% iodide (a), 12-acetoxystearic acid, 82% (a), 12-oxostearic acid, 87% (a), cyclohexanecarboxylic acid, 91% (a), 70% (b), and apocamphanecarboxylic acid, 62% (b). / J. chem. Soc. (London) *1965*, 2438 / –Ma. [Rd 351/560 IE]

**A photo-oxidative cyclization of quercetin pentamethyl ether** *(1)* was observed by *A. C. Waiss* and *J. Corse*. Irradiation of an oxygen-free solution of *(1)* in methanol under nitrogen with light of 350 mμ wavelength for 40 h produced a 31% yield of a yellow compound, m.p. 209–210 °C, whose NMR spectrum and chemical properties indicate it to be 2,3,8,10-tetramethoxy-7-oxo[2]benzopyrano[4,3-*b*] [1]benzopyran *(2)*.




*(1)* *(2)*

This reaction is the first example of a photo-oxidative cyclization of an alkoxyl group with an aromatic ring. A similar type of cyclization may be involved in the formation of some unusual flavonoid compounds. / J. Amer. chem. Soc. *87*, 2068 (1965) / –Ma. [Rd 353/562 IE]

# BOOK REVIEWS

**Handbuch der Spurenanalyse.** (Handbook of Trace Element Analysis). By *O. G. Koch* and *Gertrud Koch-Dedic*. Bestimmung von Spurenelementen unter Anwendung extraktiver, photochemischer, spektrochemischer, mikrobiologischer und anderer Verfahren (Determination of trace elements using extractive, photometric, spectrochemical, microbiological, and other methods). Springer-Verlag, Berlin-Göttingen-Heidelberg-New York 1964. 1st edit., XVI + 1232 pp., 273 figs., linen DM 226.– (about $ 56.90).

This manual deals in its general section with units, detection and estimation methods, and methods of separating and enriching trace elements, with experimental techniques, and the sensitivity and accuracy of these processes. The specialized section contains chapters on sample preparation, extraction techniques, scope of application of extracting agents, and then an alphabetically arranged description of the assays of the elements Ag, Al, As, Au, B, Be, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ga, Ge, Hf, Hg, In, Ir, Mg, Mn, Mo, Nb, Ni, Os, P, Pb, Pd, Pt, Re, Rh, Ru, Sb, Sc, Se, rare earths (seltene Erden), Si, Sn, Ta, Tc, Te, Th, Ti, Tl, U, transuranics, V, W, Y, Zn, and Zr. Further sections are to be found on the determination of the element groups in water, biological materials, metals and alloys, soils, and rock samples, and on microbiological methods for assaying Cu, Fe, Mg Mn, Mo, Zn, K, and P. Detailed practical procedures are given mainly for separations and photometric determinations, less often for spectrographic and polarographic estimations and microbiological assays. The author index contains about 4800 names covering around 3800 publications; there is a 23-page subject index.

The book is intended for the use of the practical worker. It is the first anthology of the methods of trace analysis arranged according to elements and groups of materials. The text is easy to read, and the numerous survey tables contain an abundance of experimental material. Scrutiny of selected German publications revealed that the literature has been well covered. The numerous practical methods described often make recourse to the original publications unnecessary. The quality of the print and binding – and unfortunately the high price – are in keeping with the high standards of the publishers.

Without wishing to decry the magnificent achievement of the authors, who both work in the laboratories of a large foundry works, a few minor wishes for future editions might be voiced. The alkali metals and the halogens should also be included and – in contrast to the monograph by *Sandell* – greater attention should be paid to non-photometric methods.

It is a little disturbing that the literature references are given at the end of each of the many individual sections and then in the sequence in which they appear in the text. A list at the end of the book arranged alphabetically according to author names would save one the tedious task of searching at the ends of the chapters, would eliminate repetitions, and would facilitate further searches in the literature by giving leading authors' names.

The make-up of the book calls for an indication of the future development of trace analysis. Trace analysis means the detection of less than 0.01 % of a substance in a large excess of foreign matter – the matrix – which determines the method of analysis applicable. High sensitivities and selectivities usually can be achieved only by making preliminary chemical separations; this often calls for initial samples of 10–1000 g. It must be emphasized that any chemical separation is always undesirable because of the danger of introducing impurities, the dificulties sometimes involved, and the amount of time required. However, only a few physical methods can forego prior chemical separations; for example, apart from spectrography and X-ray fluorescence analysis, both of which are not extremely sensitive, there are differential cathode-ray and pulse polarography, modifications of double-focussing mass spectrometry, and gamma-ray spectrometry. Analyses in the nanogram and picogram range are beyond the potentialities of normal methods and can be achieved only by activation analysis, mass spectrometry, and occasionally electron microscopy, but then sometimes only after previous chemical separations.

It is clear that this handbook of chemical trace analysis naturally cannot follow these developments. As a supplement, it would be desirable to have a corresponding handbook of instrumental trace analysis, which could of course be written only by a group of specialists. The present volume is an indispensible aid to the analyst. As the sole comprehensive treatise of its kind, it should be present in every general chemical library. *B. Sansoni* [NB 388/264 IE]

**Les nucleases. Application à l'étude des acides nucleiques** (Nucleases. Their Application to the Study of Nucleic Acids). By *M. P. de Garilhe*. Chimie des substances naturelles (Chemistry of natural products). Edited by *E. Lederer*. Edition Hermann, Paris 1964. 1st edit., 284 pp., 22 figs., 26 tables, linen NF 36.– (about $ 7.50).

Here introductory chapters deal with the (French) nomenclature, properties, syntheses, and isolation of nucleic acids.

Numerous methods of isolation are carefully described. The beginner is also introduced to all the relevant analytical methods.

Thus there remain only about 100 pages for the discussion of nucleases. For the more important of the 50 nuclease preparations mentioned, details are given of their preparation and properties. Among the endonucleases, the enzymes from *Staphylococcus pyogenes* and *Azotobacter agilis* which attack DNA and RNA to yield nucleoside-3′-phosphates or oligonucleotides with 5′-phosphate receive such attention. Ribonuclease from beef pancreas hydrolyses specifically at positions adjacent to pyrimidines and affords 3′-phosphates; the crystallization and amino-acid sequence of this enzyme are described, and data on its mode of action are given. The T1-RNase which splits the chains next to guanosine to give 3′-guanylic acid derivatives is discussed very briefly. DNase I from beef pancreas and DNase II from calf thymus yield 5′- and 3′-phosphates respectively. The most important exonucleases which attack DNA and RNA lead to either 3′- or 5′-nucleoside monophosphates. An exo-DNase from *Escherichia coli* splits off 5 nucleotides. Most monoesterases produce an alcohol or phenol plus orthophosphate. There are some specific 5-nucleotidases, whereas an alkali phosphatase from *E. coli* hydrolyses even polyphosphates. A table is given at the end of the book in which the ion requirements, pH optima, substrate specificity, *etc.* of the enzymes discussed are given together with references. A bibliography with 665 titles, table of contents and author and subject indices close the book, which is intended as an introduction to practical experimentation in this field, but which offers indications of new methods for the expert as well.

*J. H. Matthaei* [NB 357/215 IE]

**Molecular Orbitals in Chemistry, Physics, and Biology. A Tribute to R. S. Mulliken.** Edited by *P.-O. Löwdin* and *B. Pullman*. Academic Press, New York-London 1964. 1st edit., VIII + 578 pp., numerous illustrs. and tables, clothbound $ 22.–.

"In addition to the Schrödinger equation, there is a second fundamental law in quantum chemistry which states:

M. O. = Molecular orbital = Mulliken orbital."

With these words the editors describe the extraordinary contribution that *R. S. Mulliken* has made to the development of theoretical chemistry. This volume has appeared in his honour on the occasion of his retirement and contains 33 contributions on the subject of quantum theory and molecular structure research which impressively document the influence of the ideas and work of *R. S. Mulliken* on this subject. The articles range from biographical notes (by *C. A. Coulson* and *J. C. Slater*) to short communications; they deal with the development of the SCF theory and calculations on small molecules (*R. G. Parr*; *P.-O. Löwdin*; *G. Berthier*; *M. Simonetta*, and *E. Gianinetti*; *W. A. Bingel*; *L. Pauling*; *K. Reudenberg*; *B. G. Anex* and *H. Shull*; *E. Scrocco* and *J. Tomasi*; *S. J. Strickler* and *K. S. Pitzer*; and *T. L. Gilbert*), with the theory and analysis of molecular spectra (*F. A. Matsen* and *J. C. Browne*; *A. C. Hurley*; *S. J. Strickler* and *M. Kasha*; *G. Amat* and *H. H. Nielsen*; *G. J. Hoijtink*; and *M. Kotani*), with π-electron theory (*R. McWeeny*; *E. Heilbronner*; *I. Fischer-Hjalmars*; *W. T. Simpson*; *A. L. H. Chung*, *M. J. S. Dewar* and *N. L. Sabelli*; *T. Nakamura*, *S. Kwun* and *H. Eyring*; *R. Pauncz*; and *T. Nakajima*), with chemical reactivity (*O. Chalvet*, *R. Daudel* and *F. Peradejordi*; *R. D. Brown*; and *K. Fukui*), with group theory (*H. C. Longuet-Higgins*; and *J. Serre*), and with the applications of the MO theory to biological problems (*A. Pullman* and *B. Pullman*).

The book gives a very good survey of the current status of knowledge in the field of theoretical chemistry. Since most of the contributions contain not only new results but also summaries of the field they deal with, the book will be of value not only to the specialist but also to those with only a secondary interest in the theoretical side of molecular structure research. Of major interest for chemists are the justification and generalization of the Hückel theory on the basis of the SCF theory by *McWeeny*, the derivation of the rules of resonance theory for excited states from the Hückel theory by *E. Heilbronner*, the detailed discussion by *I. Fischer-Hjalmars* of the semiempirical determination of parameters in the Pariser-Parr-Pople theory, and the review by *R. D. Brown* on MO calculations and electrophilic substitution. However, it may be a despondent experience for many to read here the "Elementary Introduction to the SCF Theory" given by *M. Simonetta* and *E. Gianinetti*, which is explicitly for the use of chemists, for it shows that much more importance is attached to the mathematical and theoretical training of chemists abroad than in Germany.

*M. Klessinger* [NB 374/232 IE]

**Analytical Methods for Pesticides, Plant Growth Regulators, and Food Additives** (in 4 volumes). Edited by *G. Zweig*. Academic Press. New York-London 1964. 1st edit., Vol. II: Insecticides. XVII + 619 pp., numerous figs. and tables, linen $ 23.00; Vol. III: Fungicides, Nematicides and Soil Fumigants, Rodenticides, and Food and Feed Additives. XII + 237 pp., numerous figs. and tables, linen $ 12.00; Vol. IV: Herbicides. XIII + 269 pp., numerous figs. and tables, linen $ 12.00.

Volumes II, III, and IV of this series have appeared in a most welcome rapid sequence soon after Vol. I [1] and deal with 47 insecticides, including acaricides (Vol. II), 14 fungicides, 5 nematicides and soil fumigants, 2 rodenticides, 3 food or feedstuff additives (Vol. III), and 27 herbicides (Vol. IV), *i.e.* 98 exit ingredients in all.

In the individual chapters, brief details are given on the composition, designations, history, properties, synthesis, toxicology, and applications of each preparation discussed, followed by a critical review supported by literature references of the methods known for quantitative estimation of its components and of residues which remain in harvested products of foodstuffs. One or more recommended analytical methods are then given for most of the preparations with detailed practical instructions.

These foolproof analytical procedures, worked out by acknowledged experts, make the volumes – which are also of tasteful outward appearance – a reliable laboratory aid for the analyst. It is to be hoped that the editor will soon complete his valuable work with supplementary volumes and then keep it up to date. The widespread development of chemical crop protection and the increasing demand for routine control of foodstuffs for toxic residues necessitate the development of fast and reliable methods of analysis of every poison used in agriculture. In addition, there is often a need to check analytical results by other methods. In the present volumes, methods are given neither for the most recent products (perhaps because suitable analytical procedures have not yet been worked out well enough) nor for some well-established biocides; *e.g.* the important insecticide Lindane should have been included in Vol. II. In view of the widespread distribution that the work will probably attain, it seems advisable to designate the active ingredients of pesticides in future by the "common names" proposed by the technical committee TC 81 of the International Standardization Organization (ISO) instead of trade names of the formulations in which they are contained, for these are often not generally known, *e.g.* Dylox® for trichlorophon.

*H. Maier-Bode* [NB 392/250 IE]

[1] Cf. Angew. Chem. 77, 358 (1965); Angew. Chem. internat. Edit. 4, 377 (1965).

**Mammalian Protein Metabolism.** Edited by *H. N. Munro* and *J. B. Allison*. Vol. 1. Academic Press, New York-London 1964. 1st edit., XV + 566 pp., numerous figs. and tables, linen $ 18.50.

It is the intention of the editors to present in this two-volume work all aspects of protein metabolism in higher animals and humans. This first volume is devoted to physiological-

chemical and biochemical aspects. The second volume is to contain the contributions from nutritionalists and clinicians. After a short historical introduction (*H. N. Munro*), protein digestion and the absorption of nitrogenous compounds (*C. Gitler* and *A. T. Phillipson*) are discussed. Next come articles on the free amino acids and peptides in tissues (*H. N. Christensen*), on amino acid metabolism (*H. A. Krebs*) and plasma protein metabolism (*A. S. McFarlane*), on the mechanism of protein synthesis (*A. Korner*), and on turnover studies in the whole animal (*A. Neuberger* and *F. F. Richards*). The last three chapters deal with the relationships between hormones and protein metabolism (*J. H. Leatham*), the regulation of protein metabolism (*H. N. Munro*)) and nitrogen elimination from the body (*J. B. Allison* and *J. W. C. Bird*).

The editors stress the didactic aims of the book: scientists with some knowledge of physiological chemistry who want to initiate studies in this field can read the book from cover to cover. However, most readers will probably be satisfied to read only one or a few chapters in order to obtain insight into special problems. Extensive indexing makes the book useful as a work of reference, although it must be realized that, as is usual for works of this nature, the latest literature is seldom included. For example, in the chapter on protein synthesis, most 1962 publications, a few 1963 publications, but no 1964 publications have been included. Older literature, particularly the classical work in this field, has been well reviewed, so that the book can assume and hold a justified position in chemical libraries alongside books of a more chemical and biochemical nature such as "The Proteins" and "Advances in Protein Chemistry".

*H. G. Zachau* [NB 372/230 IE]

**Structure Elucidation of Natural Products by Mass Spectrometry.** Vol. II: Steroids, Terpenoids, Sugars, and Miscellaneous Classes. By *H. Budzikiewicz, C. Djerassi*, and *D. H. Williams*. Holden-Day Series in Physical Techniques in Chemistry. Holden-Day Inc., San Francisco-London-Amsterdam 1964. 1st edit., X + 306 pp., numerous figs. and tables, linen $ 10.50.

This book is an exhaustive review covering even the latest literature reports of the results of mass spectrometric investigations of steroids, steroid alkaloids, terpenes, amino acid derivatives, carbohydrates, long-chain aliphatic compounds, microbiological metabolites, and oxygen heterocycles. This is particularly welcome because numerous publications have recently appeared in these fields and it is therefore becoming more and more difficult to get a clear overall picture of the spectral data published. The book is therefore a valuable help for natural-products chemists who want to obtain information on the possibilities of applying mass spectrometric methods to their special problems.

As in earlier books by the same authors, the mechanistic interpretation of the pertinent fragmentation reactions is placed in the forefront Since such interpretations are extremely difficult, particularly in the analysis of the spectra of complex steroids and terpenes, many of the conclusions are highly speculative. Such speculations are not always justified, as witnessed by the discussion of the mechanism of formation of the ion of mass number 149 on p. 96: in effect it is concluded that the fragment either must add on a hydrogen atom in some inexplicable manner (when, however, it would attain the mass number 150) or must contain a carbon atom with an electron sextet (an impossibility).

Since the book is intended for the use of students as well, it would have been better to lay less emphasis on mechanistic considerations which cannot be proved, and to concentrate more on the facts, even though not every fragmentation step can be explained. However, the book is indispensable to the expert in the interpretation of the spectra of natural products, alone on account of its ordered presentation and comprehensive evaluation of the literature.

*G. Spiteller* [NB 367/225 IE]

**Applications of NMR Spectroscopy in Organic Chemistry.** Illustrations from the Steroid Field. By *N. S. Bhacca* and *D. H. Williams*. Holden-Day, Inc., San Francisco-London-Amsterdam 1964. 1st edit., X + 198 pp., 74 figs., 24 tables, linen $ 7.95.

The aim of this book is to furnish "an up-to-date account of the basic knowledge required to obtain structural information from an NMR spectrum". The practical examples used to achieve this aim are nearly all taken from the steroid field, hence it might have been better to point out this restriction even more precisely in the title, for not all the important applications of nuclear magnetic resonance in organic chemistry can be illustrated with these compounds. Thus there are no data given of effects of intramolecular mobility or intermolecular exchange reactions on the NMR spectra. Moreover, not all of the coupling types frequently encountered in practice are discussed, because $A_2B_2$ and $A_2X_2$ systems, for example, occur only rarely in steroids.

On the other hand, many aspects of proton magnetic resonance can in fact be demonstrated particularly well with the rigid steroid skeleton. The absorptions of the individual CH proton types are discussed in detail (72 pp.), even slight differences in the chemical shifts due to steric effects being considered in order to solve structural problems. The factors affecting vicinal and geminal coupling constants are described very clearly on 13 pages; the same applies for long-range coupling (26 pp.). It is a great credit to the authors that in the section on configuration and conformation (23 pp.), they demonstrate in detail why analysis of ABX spectra whose AB portion is concealed often gives rise to erroneous results; some methods are given which can nevertheless be applied successfully here.

The book is illustrated with numerous very clear structural formulae and spectra. Two hundred references, some of them from 1964, make the book a good work of reference. It is absolutely up to date – not only on account of the discussion of double resonance and of 100 Mc spectra, but especially because it has appeared only three to four months after completion of the manuscript! The book is not intended as an introduction to proton magnetic resonance. It can, however, be recommended to every chemist who wants to devote himself to the measurement and interpretation of spectra to the full extent at present possible with the available equipment and knowledge, whether he is interested in steroids or not.

*A. Mannschreck* [NB 398/256 IE]

**Molecular Complexes in Organic Chemistry.** By *L. J. Andrews* and *R. M. Keefer*. Holden-Day, Inc., San Francisco-London-Amsterdam 1964. 1st edit., VIII + 196 pp., numerous illustrs. and tables, linen $ 8.75.

The size of this book and the organization of the material are sufficient to indicate that the authors have not intended to produce a comprehensive and detailed presentation of this field. Their aim has apparently been to give some insight into the most important results of research on molecular compounds of the type of electron donor/electron acceptor complexes and thus to provide a book, particularly for the use of students, supplying an introduction to this interesting, many-sided field of physical and organic chemistry. The six chapters of the book deal with the following topics:

I. General considerations of donors, acceptors, inclusion compounds, and the formation of complexes. II. The spectra of molecular complexes. III. The geometry of molecular complexes, particularly crystal structures. IV. The stability of molecular complexes in solution. V. Electrical and magnetic phenomena such as dipole moments, conductivity, and paramagnetism. VI. The function of complexes in organic chemistry.

Despite the brevity of the presentation, which disregards any theoretical derivations, the book gives a very good introduction to the problems of this line of research and clearly brings

to the view of the reader just how many physico-chemical aspects are encountered in organic chemistry here. The book can therefore be recommended to all students to aquaint themselves with this field of research.

*H.-H. Perkampus* [NB 386/244 IE]

**Encyclopedia of Polymer Science and Technology. Plastics, Resins, Rubbers, Fibers.** Edited by *H. F. Mark*, *N. G. Gaylord*, and *N. M. Bikales*. Vol. 1: A to Amino Acids. Interscience Publishers, a Division of John Wiley & Sons, New York-London-Sydney 1964. 1st edit., XVIII + 893 pp., numerous illustrs. and tables, price of single volume £ 18.15.0 (about $ 51.50), subscription price £ 15.0.0 (about $ 41.50).

In view of the rapid development of polymer science and plastics production within the past decades and of the accompanying divergence of individual aspects of the subject, a complete survey of the field is highly welcome. The present series will comprise about twelve volumes appearing at a rate of at least two per year. About one thousand individual contributions written by acknowledged authorities are planned.

The editors' aims are clear from the following comments. The production and the physical, chemical, and toxic properties of all monomers will described together with their polymerization behavior. The production, properties, processing, and fields of application of polymers will be discussed. Finished articles, *e.g.* rubber goods, and economic questions will also be dealt with. Wherever appropriate, theoretical considerations are also to be interspersed.

This first volume contains 31 contributions. Each contribution contains a detailed bibliography (including patents); particularly many references are given under the keywords Abrasion Resistance (187 citations, not including general references), Acids and Derivatives, Aliphatic (198), Acrylic Ester Polymers (447), Acrylonitrile Polymers (333), Adhesion and Bonding (156), Amines (176). The literature is covered to 1962 (inclusive), in some places to 1964. Several tables and figures contain previously unpublished results, mostly made available by chemical companies.

A table ($5^1/_2$ pp.) gives a detailed list of the symbols and abbreviations used in the work. However, the list is not consistent. For example, the symbols for kinetic and thermodynamic quantities are missing and there is no mention that x can mean "conversion" as well as "degree of polymerization" (DP) or that the DP can also be denoted by n or y or that c indicates the concentration. The average degree of polymerization is denoted by DP, but the number and weight averages of the DP are designated $x_n$ and $x_w$.

Some space could have been saved here and there, *e.g.* by reduction of the size of some figures or by omission of simple formulas in tables; moreover, in the reviewer's opinion, descriptions of methods for producing saturated compounds of low molecular weight (*e.g.* alcohols, acids, and esters) or for preparing alkali metals need not have been included in this encyclopedia.

Since the r-values of copolymerization depend on the temperature and on the reaction medium, indications of these should have been given in all the tables or in the text, but these are often omitted. On p. 512, the boiling point given for methanol is 0.3 °C too high.

Temperatures are sometimes given in Centigrade and sometimes in Fahrenheit degrees, so that conversions have to be made for comparison. To simplify this matter, a centigrade-Fahrenheit conversion table should be included as a loose insert in a future volume. Conversion tables for area, volume, and mechanical units might also be added.

A few proposals might be made of features for inclusion in the last volume in order to simplify use of the book.

1. In the contributions on individual polymers and monomers, the same concepts and properties are often given in more than one place. Comparison of the data for various products is made difficult by the fact that one does not know where to look for numerical data. It is therefore suggested that the last volume contain an index of key words including such headings as r-values for copolymerization, conversion temperatures, Θ-temperatures, solubilities, solubility parameters, types of polymerization, graft and block polymers (subheadings: production, properties), transfer constants, statistics, methods for characterizing polymers (subheadings: structure, molecular-weight distribution), *etc.* 2. Many substances (monomers, polymers, auxiliaries, *etc.*) are mentioned in many contributions, but then mostly in different connections. Consequently, many searches for specific information of certain substances will remain futile. Hence, in order to find data on substances throughout the whole work, a substance index would be very useful. 3. A list of important technical terms in several languages would be most helpful. Some readers will frequently encounter translation difficulties, especially in the field of rheology, or relative to mechanical properties and plastics processing. Numerous clear structural formulas are given (in Equation 24 on p. 60 and at the foot of p. 735 there are errors in the equations which do not however change the sense); the reproduction of the figures is good.

After perusal of the first volume, the reviewer feels that he can recommend the work to those engaged in the field of polymers.

*O. Fuchs* [NB 390/248 IE]

**Phospholipids. Chemistry, Metabolism and Function.** By *G. B. Ansell* and *H. M. Hawthorne*. B. B. A. Library. Vol. 3. Elsevier Publishing Co., Amsterdam-London-New York 1964. 1st edit., XIII + 439 pp., 56 figs., 39 tables, linen DM 61.50 (about $ 15.50).

In 14 chapters the authors give a really comprehensive survey of the current status of our knowledge in the field of phosphatides. It was only the development of new synthetic and analytical methods within about the past 15 years that made it possible to achieve a more intimate knowledge of this class of compounds, whose importance still cannot be fully appreciated at present. This realization is expressed primarily in the chapter on the theory of the functions of phosphatides, which is relatively short, probably for this reason. However, the authors give a detailed discussion of the structures of phosphatides and of analytical and preparative methods for their identification and isolation. Finally, after all the known facts about the biosynthesis and degradation of phosphatides are presented, a description of the phospholipids from individual organs and tissues or subcellular components is given. It is a moot point whether the father brief treatment given to the interesting and characteristic fatty acids, especially those of glycerophosphatides, is justified or not. Here the authors were undoubtedly led by the consideration that much has already been written on this topic elsewhere.

Since both authors work on the experimental biochemistry of phosphatides in animal organisms, they have restricted their presentation to this field and have not included vegetable lipids. This necessarily reduces the readership of the book. However, since any such book was not hitherto available, this new publication is particularly welcome and will therefore be gratefully greeted by many biochemists, clinicians, and other scientists.

*Hildegard Debuch* [NB 369/227 IE]

**The Biosynthesis of Steroids, Terpenes, and Acetogenins.** By *J. H. Richards* and *J. B. Hendrickson*. Frontiers in Chemistry. Edited by *R. Breslow* and *M. Karplus*. W. A. Benjamin Inc., New York-Amsterdam 1964. 1st edit., X + 416 pp., a few figures and tables, linen $ 20.35.

In this book, possible and established routes for the biosynthesis of two classes of natural products are described. The first class comprises the acetogenins, which can, in principle at least, be formed by head-to-tail condensation of acetate units, with or without subsequent rearrangement or

substitution; this category includes fatty acids, flavonoids, quinones, coumarins, xanthones, depsides, macrolides, *etc.* The second class comprises the terpenes, which are acetate derivatives arising *via* isopentenyl pyrophosphate.

There are twelve chapters dealing with the principles of biogenetic theory, the construction of the acetate hypothesis, a statistical survey of important natural products, the experimental verification of the acetate theory, the isoprene unit, mono-, di-, sesqui-, and triterpenes, higher terpenoids. the biosynthesis of cholesterol, and further transformations of cholesterol. An impressive number of compounds are treated (about 1000 acetogenins are listed in one appendix) and many references are given; the list of references is not always complete but mostly covers the literature up to 1963.

The best features of the book are the large amount of material it contains and the purely chemical approach adopted in considering many of the biosynthetic steps postulated; its weaknesses become apparent when the discussion turns to enzymological data or hypotheses. Probably any enzymologist consulted would have recommended deletion of the whole second chapter, for here much is encountered to which objection must be taken. One can read there, for example, that many natural products have no or only secondary importance in metabolism and it is therefore reasonable to assume that for economic reasons the cell uses as few reactions as possible for their production. It is not always indicated clearly enough in the text and in formula schemes what is speculation, hypothesis, or fact, *e.g.* in the scheme for the synthesis of fatty acids on p. 130, which has since been revised. This weakness applies especially to the writing of biochemical reactions; when the stoichiometry of a reaction is known, it is desirable to include all the participating species in writing the reaction, *e.g.* on p. 178:

$$CO_2 + (CH_3)_2C{=}CH{-}COSCoA \rightarrow$$

$$HOOC{-}CH_2{-}C(CH_3){=}CH{-}COSCoA$$

By elimination of a few errors (*e.g.* that the enzymes of the fatty acid cycle do not react with *S*-acylcysteamines on p.128) or inaccuracies (*e.g.* in the scheme for the biosynthesis of shikimic acid and its derivatives on pp. 20–21, steric formulae are only occasionally used, and the formation of *p*-hydroxybenzoic acid without 5-phosphoshikimic acid as an intermediate is highly improbable), the extraordinary value of this book as a work of reference for the expert in this field will be increased further. The quality of the volume is de luxe and printing errors are few.

*U. Henning* [NB 391/249 IE]

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# Allyl-Transition Metal Systems

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*Dedicated to Prof. K. Freudenberg on the occasion of his 80th birthday*

*As a continuation of a report published in 1963, recent results in the field of allyl-transition metal complexes are described*[*]. *Syntheses and reactions of these compounds, as well as the bonding between metal and allyl group, are discussed. Allyl-transition metal complexes form the basis of extremely selective catalysts for homogeneous reactions of 1,3-diolefins and of olefins; the metal atoms in these "matrix" catalysts are either "bare"* [**] *or are bound to only a few ligands.*

Introduction
1. Synthesis of Pure Allyl Compounds of Transition Metals
2. Properties and Reactions of the New Compounds
3. Structure and Bonding
4. Particular Allyl Compounds of Nickel
5. Allyl-Nickel Halides
6. Catalytic Processes Induced by Allylmetal Complexes
7. Comparison of Cyclopentadienylmetal and Allylmetal Systems

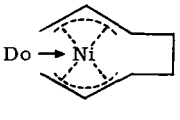
## Introduction

In 1963 we gave an outlook [1] on allyl-transition metal complexes, which we believed would offer new and interesting possibilities for preparative chemistry, and especially for homogeneous catalysis. This belief has been fully justified, though many difficulties have had to be overcome on the preparative side.

Our interest was first drawn to allyl-transition metal systems when a study of the cyclotrimerization of butadiene to cyclododeca-1,5,9-triene led us to the intermediate *(1)* which is crystalline below 0 °C [2].

The ends of the $C_{12}$ chain in this compound are bonded to the central metal atom *via* $\pi$-allyl groups. We subsequently found a similar system [1] in the (also crystalline) intermediate *(2)* in the cyclodimerization of butadiene to cycloocta-1,5-diene (Do denotes donor).

*(1)*



*(2)*

These results led to the recognition of two basic facts:

1. Allyl-metal systems evidently play an essential part in the reactions of butadiene (and probably of 1,3-diolefins in general) on transition metal catalysts.

2. A "bare" transition metal atom, either as such or combined with a ligand system, forms the matrix for

[*] The term "allyl compounds" in the present paper refers not only to compounds containing the simple allyl group ($CH_2$=CH–$CH_2$–), but also to those that contain substituted allyl groups or allyl groups forming part of a ring system.

[**] The description "bare" is applied to complexed metal atoms from which the ligands can be quantitatively displaced by the substances taking part in catalytic reactions.

[1] *G. Wilke et al.*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 105 (1963).

[2] *G. Wilke, M. Kröner*, and *B. Bogdanović*, Angew. Chem. *73*, 755 (1961).

[3] *G. Wilke* and *B. Bogdanović*, Angew. Chem. *73*, 756 (1961).

extremely stereospecific and selective homogeneous catalytic processes.

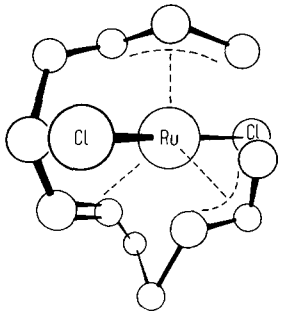
These two principles could at first not be deduced from the results obtained with catalysts containing nickel. However, the investigations of the latter led to a general method for the synthesis of allyl-metal compounds [1,3], so that we were then able to carry out similar experiments with catalysts based on other metals.

Our assumption that *(1)* contains two allyl systems bonded to one metal atom was supported by the synthesis of bis-(π-allyl)nickel *(3)* [3], the properties of which are analogous to those of *(1)*.

$$NiBr_2 + 2\ CH_2{=}CH{-}CH_2{-}MgBr \longrightarrow \text{Ni} + 2\ MgBr_2$$

*(3)*

Meanwhile, *Shaw et al.* [4] treated butadiene with ruthenium(IV) chloride at 100 °C, and obtained a crystalline complex $C_{12}H_{18}RuCl_2$ *(4)*, on which X-ray studies were carried out by *Truter* [4].




*(4)*

As in our nickel complex *(1)*, the $C_{12}$ chain is joined to the metal atom by two terminal π-allyl groups and a double bond.

## 1. Synthesis of Pure Allyl Compounds of Transition Metals [5][*]

The method first used for nickel was subsequently improved somewhat for more critical cases, and can now be used in the following form for the preparation of pure allylic compounds of a wide range of transition metals.

A Grignard compound is prepared from the desired allyl halide (preferably the chloride) at the lowest possible temperature (−15 to +20 °C) It is advisable in some cases to distil off the solvent (usually ether) and any dimers that may have been formed, and to use a suspension or solution of the residue in *e.g.* ether for the actual reaction. The Grignard compound, which is generally used in excess, is treated with halides of transition metals at temperatures of −78 to +20 °C, depending on the stability of the product expected. The reaction generally gives rise to colored solutions.

The isolation of bis-(π-allyl)nickel [3] from the reaction mixture is a special case, since this compound is so volatile that the best method is distillation or sublimation. In nearly all other instances, as much of the solvent as possible is distilled off at low temperatures (−78 °C in some cases), and the residue is extracted with a hydrocarbon such as pentane or toluene. Only the pure allylmetal compounds dissolve; metal salts and excess of Grignard compound are insoluble. The color of the solutions and their freedom from halide can generally be taken as a good indication of a successful synthesis. The compounds are separated from the filtered solutions by crystallization at low temperatures. All operations must naturally be carried out in the strict absence of air and moisture.

Table 1. Pure allyl compounds of transition metals.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $(MgA_2)$ [a] [6] colorless | | | | | | | |
| | $(TiA?)$ [7] brown (−80 °C) [b] | $VA_3$ [7] brown (−30 °C, deflagrates) | $CrA_3$ [8] red m.p. 70–80 °C (20 °C) | $FeA_3$ [10] golden orange (−40 °C) | $CoA_3$ [11] golden red (−40 °C) | $NiA_2$ [3, 12] yellow m.p. 1 °C (20 °C) | $ZnA_2$ [6, 14] colorless m.p. 84 °C |
| | | | $(CrA_2)_2$ [9] red-brown (70–80 °C) | | | | |
| | $ZrA_4$ [7] red (0 °C) | $(NbA_4)$ [7] green (0 °C) | $MoA_4$ [8] green (125–130 °C, spontan.) | | | $PdA_2$ [13] light yellow m.p. 30 °C (20 °C) | |
| | | | $(MoA_2)_2$ [8] deep green (110–115 °C, spontan.) | | | | |
| | | $(TaA_4)$ [7] green (0 °C) | $WA_4$ [8] light brown (95 °C) | | | $PtA_2$ [13] colorless m.p. 44 °C (20 °C) | |
| | $ThA_4$ [7] light yellow (0 °C) | | | | | | |

[a] A = $CH_2{\cdots}CH{\cdots}CH_2$. The compounds in parentheses have not yet been definitely characterized. All the other compounds exist in the crystalline form.

[b] The compounds decompose at the temperatures indicated, though sometimes very slowly. Diallylmagnesium [6] and diallylzinc [6, 14] were synthesized for comparison.

The above method was used for the synthesis of the allylmetal compounds listed in Table 1.

[4] *J. E. Lydon, J. K. Nicholson, B. L. Shaw,* and *M. R. Truter,* Proc. chem. Soc. (London) *1964*, 421.

[5] π-Allyl compounds of Group IIIb–VIIIb metals: German Published Patent Application 1190939 (April 18th, 1962), Studiengesellschaft Kohle.

[*] "Pure" allylmetal compounds in this context are those in which no ligands other than allyl groups are bonded to the metal.

During these syntheses it was found, at least as an approximation, that in a given group of the periodic system the stabilities of the allylmetal compounds increase with the atomic number of the transition metal. This is particularly noticeable in the sequences Ni < Pd < Pt, Cr < Mo < W, and Ti ≪ Zr < Th. Surprisingly, however, the yields decrease within each triad in the order of increasing stability. Another rule appears to be that the allylmetal compounds of elements with even numbers of electrons are much easier to prepare and to handle than those of elements with odd numbers of electrons. Another observation is that within the above three groups, the color intensity of a compound decreases as the atomic number of the metal increases. Some of our attempts to synthesize compounds of this type have so far been unsuccessful, *e.g.* in the case of manganese and to some extent that of titanium.

The situation with manganese is still obscure. The difficulties in the preparation of allyltitanium compounds may be due to the high reactivity of intermediates such as allyltitanium halides. Even in the case of titanium, however, we were able to prepare halide-free orange-yellow solutions (in pentane), containing extremely reactive titanium compounds, by the above general method of synthesis (at −78 °C). The low-temperature infrared spectra of these solutions seem to indicate that at least some of the allyl groups are σ-bonded. Similar remarks apply to the allyl compounds of niobium and tantalum; although green solutions (in pentane) have been obtained, the compounds present have not yet been identified.

Though a number of gaps still remain, one can regard as confirmed our guess expressed in 1963, *i.e.* that the allyl group can combine with most transition metals to form complexes in which the transition metal need not be bonded to other groups such as anions (particularly halide ions) or to donor molecules such as carbon monoxide.

## 2. Properties and Reactions of the New Compounds

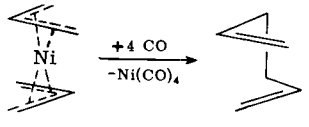
The allyl compounds of the transition metals are true organometallic compounds in which pure hydrocarbon residues are attached to the metal atoms through C atoms. However, they appear to be compounds of a special kind, since with few exceptions transition metals do not form stable metal-carbon bonds unless these bonds are stabilized by other ligands attached to the metal.

The most typical property common to all allyl-transition metal compounds, which they share with the organometallic compounds of the elements of the main groups, is their reactivity towards oxygen, which is so great that most of the compounds ignite in air. However, the position with regard to protolysis is different. Thus most allyl-transition metal compounds behave towards H-acids in the same way as the organometallic compounds of the main group elements, *i.e.* in the presence of water, alcohol, or even organic acids, at least some of the allyl groups are split off as propylene. The allyl compounds of nickel, palladium, and platinum, on the other hand, are characterized by excellent stability under these conditions; solutions of these complexes in ether are essentially stable towards water or alcohol.

All the allyl-transition metal compounds prepared so far are at least slightly volatile, and in many cases readily volatile, in a high vacuum. The mass spectra of some of the compounds can therefore be recorded. Those molecular weights that have been determined cryoscopically in benzene show that the compounds are monomeric, with the exception of diallylchromium[9] and diallylmolybdenum[8], both of which are dimeric, evidently because of metal-metal bonding.

Thus the allyl-transition metal compounds are best compared to the organoboron or organoaluminum compounds, but not to the strongly associated organometallic derivatives of the elements of groups 1 and 2. The allylmetal compounds apparently do not form electron-deficient bonds such as are typical of trialkylaluminum compounds. However, exchange experiments (see Section 6c) indicate that allyl groups attached to one metal atom can interact with another metal atom in solution, this interaction presenting a certain analogy with the alkyl exchange in trialkylaluminum compounds. The relationships between the allyl-transition metal compounds and the cyclopentadienyl-transition metal compounds will be discussed in Section 7.

Carbon monoxide was excluded as far as possible from our experiments, particularly those involving catalytic processes, since this compound often exerts an inhibiting action; on the other hand, it was frequently used to displace ligands from metal atoms. The reaction of carbon monoxide with some allylmetal compounds is particularly informative in this respect. Bis-(π-allyl)nickel *(3)* takes up one equivalent of CO at −78 °C and atmospheric pressure. The quantity of CO consumed increases above −40 °C to a total of four equivalents at +20 °C[3]. The two allyl groups combine to form hexa-1,5-diene (diallyl) with concurrent formation of $Ni(CO)_4$.




*(3)*

The product of the reaction between triallylcobalt *(5)*[11] and CO at −35 °C, on the other hand, is π-allylcobalt tricarbonyl *(6)*, which was first shown to be a π-allyl compound by *Heck* and *Breslow*[5] on the basis of its $^1$H-NMR spectrum.

$$(C_3H_5)_3Co \xrightarrow{+3\ CO} C_6H_{10} + \text{}$$

*(5)* *(6)*

The processes occurring in the cases of nickel and cobalt are comparable in that two allyl groups are detached from the metal; in the cobalt compound, however, one

[6] *G. Wilke* and *P. Heimbach*, unpublished work.

[7] *E. Steinrücke*, Dissertation, Technische Hochschule Aachen, planned for 1966.

[8] *W. Oberkirch*, Dissertation, Technische Hochschule Aachen 1963.

[9] *E. Kurras* and *P. Klimsch*, Mber. dtsch. Akad. Wiss. Berlin *6*, 735 (1964).

[10] *P. Hardt*, Dissertation, Technische Hochschule Aachen 1964.

[11] *G. Wilke* and *K. Tanaka*, unpublished work.

[12] *B. Bogdanović*, Dissertation, Technische Hochschule Aachen 1962.

[13] *W. Keim*, Dissertation, Technische Hochschule Aachen 1963,

[14] *K. H. Thiele* and *P. Zdunneck*, J. organometal. Chemistry *4*. 10 (1965).

allyl group remains attached to the metal. Possibly the third allyl group cannot be removed by simple displacement, since it has no partner with which to form hexa-1,5-diene, and since the CO ligands evidently give rise to further stabilization. This third allyl group could then only come off as a free radical.

A process of this type seems to take place with triallyliron *(7)* [10]. The reaction with CO in pentane does not begin below +15 °C, a temperature at which *(7)* already decomposes. It is possible, however, to isolate a complex that appears to be π-allyl-σ-1-propenyliron tricarbonyl *(8)*; thus one allyl group has been removed, another has isomerized, and three molecules of CO have been bound.

$$(C_3H_5)_3Fe \xrightarrow{+3\ CO} \underset{\displaystyle Fe(CO)_3}{\overset{\displaystyle CH{=}CH{-}CH_3}{\text{⟨allyl⟩}}} + \cdot C_3H_5$$

*(7)* *(8)*

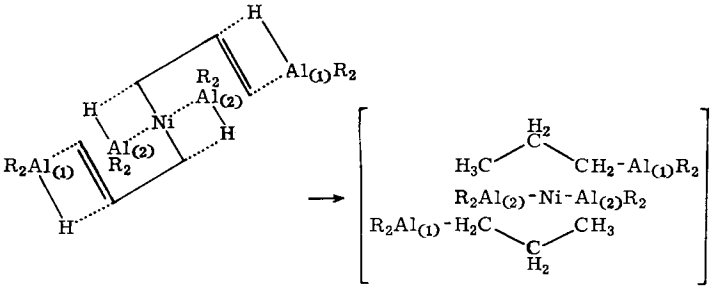
Triallylchromium *(8)* in solution takes up CO at atmospheric pressure even at −60 °C, but the reaction does not proceed completely to the $Cr(CO)_6$ stage, since the product also appears to contain a diallylchromium monocarbonyl, although this has not been definitely identified. Under pressure, on the other hand, only $Cr(CO)_6$ is formed.

$$(C_3H_5)_3Cr + 6\ CO \rightarrow Cr(CO)_6 + {}^3/_2\ C_6H_{10}$$

*(9)*

The allyl groups usually can also be removed by hydrogenation. This reaction proceeds particularly readily with the allyl compounds of nickel, palladium, and platinum, which react when simply shaken with hydrogen at normal pressure; the compounds of the group 6 elements, on the other hand, require the addition of a catalyst or the use of elevated pressures for hydrogenation. The products are the free metals and propane.

In this connection we may mention a reaction that has so far been studied in two cases, and which leads to a remarkable result for which no satisfactory explanation has yet been found. If diethylaluminum hydride is allowed to act on bis-(π-allyl)nickel or triallylchromium, the Al-H bond adds to the allylmetal system in such a way that subsequent deuterolysis yields 1-deuteriopropane as the principal reaction product of the allyl group.



$$\xrightarrow{4\ D_2O} 4\ R_2AlOD + 2\ CH_3{-}CH_2{-}CH_2D + D_2 + Ni$$

The addition of $R_2Al_{(1)}$-H (see formula) is the usual reaction of $R_2Al$–H with terminal CC double bonds. $R_2Al_{(2)}$–H, on the other hand, must formally react with the Ni-C bond in such a way as to form a $CH_3$ group and an Al-Ni bond. This interpretation is supported by the fact that the deuterolysis gas contains $D_2$. On the basis of our experiences with similar reactions, it seems necessary in all cases to consider intermediate bonding between aluminum and the transition metal, as indicated above [*].

An important part in catalytic reactions is played by another reaction of pure allyl-transition metal compounds. These compounds react even at low temperatures with anhydrous hydrogen halides in ether to form well-defined allylmetal halides, with loss of some of the allyl groups. The compounds listed in Table 2 (some of which had already been obtained by other methods) have been synthesized in almost quantitative yields by this method.

Table 2. Allyl-transition metal halides

| Complex | Preparation [a] | Color | Ref |
|---|---|---|---|
| π-Allylnickel chloride | A | brown | [32c] |
| π-Allylnickel bromide [b] | A, B | red | [32a] |
| π-Allylnickel iodide | A, B | deep red | [32b] |
| π-Methallylnickel chloride [c] | A | red-brown | [32c] |
| π-Crotylnickel chloride [d] | A | red-brown | [32c] |
| π-Cinnamylnickel chloride | B | red | |
| Benzyl-π-allylnickel chloride | B | red | |
| Triphenyl-π-cyclopropenylnickel bromide | B | red | [34] |
| 1,3-Dimethyl-π-cyclobutenylnickel bromide | B | red | |
| π-Cyclopentenylnickel chloride | B | red | |
| π-Cyclohexenylnickel chloride | B | red | |
| π-Cycloheptenylnickel bromide | B | red | |
| π-Cyclooctenylnickel chloride | A, B | red | |
| Bis-(π-allyl)chromium chloride | A | red-brown | |
| Bis-(π-allyl)cobalt chloride | A | dark-red | |
| π-Allylpalladium chloride | A | yellow | [17,b,d] |
| π-Allylplatinum chloride | A | quince yellow | |
| Tris-(π-allyl)zirconium chloride | A | red-brown | |

[a] Method A: prepared from allyl-transition metal compounds with anhydrous hydrogen halides in *e.g.* ether (see Section 2).
Method B: prepared from bis(cycloocta-1,5-diene)nickel and allyl halides in *e.g.* ether (see Section 5).
[b] This compound was also obtained from allyl bromide and cyclooctatetraenenickel(0).
[c] Methallyl = $CH_2{=}C(CH_3){-}CH_2{-}$
[d] Crotyl = $CH_3{-}CH{=}CH{-}CH_2{-}$

Partial elimination of allyl groups and formation of defined allylmetal derivatives generally occurs [16] with H-acids, *e.g.* phenol, hydrogen cyanide, and acetylacetone.

### 3. Structure and Bonding

Allylmetal compounds in which other ligands in addition to allyl groups are bonded to the transition metal were known in the pure form as early as 1958 [17]. How-

[*] *G. Wilke, G. House,* and *T. Arakawa,* Angew. Chem., in press.

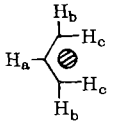
[15] *R. F. Heck* and *D. S. Breslow,* J. Amer. chem. Soc. *82,* 750 (1960).
[16] Organometallic compounds: German Published Patent Application 1 197453 (Aug. 10th, 1963), Studiengesellschaft Kohle.

ever, it was not until 1960 that *Heck* and *Breslow*[15] showed that the allyl group in allylcobalt tricarbonyl is bonded as a symmetrized system to the metal atom. The final proof was supplied by the $^1$H-NMR spectrum. According to *McClellan et al.*[18] and *Nordlander* and *Roberts*[19], it is possible to distinguish three types of allylmetal compounds on the basis of their $^1$H-NMR spectra. Both π- and σ-allylmetal compounds have so far been reported for transition metals, whereas the "dynamic" type is observed for main-group elements, such as magnesium.

The simplest $^1$H-NMR spectrum is given by the allyl system of the allylmagnesium halides *(10)*[19]. This spectrum contains a quintet and a doublet in the ratio 1:4, *i.e.* the protons of the $CH_2$ groups are indistinguishable. This result is formally explained as resulting from a rapid interchange between the following forms:

$$XMg-CH_2-CH=CH_2 \rightleftarrows CH_2=CH-CH_2-MgX$$

When the allyl group is bonded as a symmetrized system to a transition metal[15], the $^1$H-NMR spectrum contains three signals with intensity ratio 1:2:2; one of these signals, corresponding to $H_a$ in formula *(11)*, is split into at least seven components. It is accompanied



*(11)*

by two doublets due to $H_b$ and $H_c$. Thus the protons of the $CH_2$ groups can be distinguished in pairs, the $H_b$ protons (which are *syn* with respect to $H_a$) being less shielded than the $H_c$ protons (which occupy the *anti* position), which are more strongly influenced by the transition metal.

Finally, the NMR spectra of σ-allylmetal compounds, *e.g.* σ-allylmanganese pentacarbonyl[20], contain four signals, and their infrared spectra contain the C=C stretching band at 1620 $cm^{-1}$ characteristic of an unperturbed vinyl group. π-allyl and dynamic allyl systems cannot be distinguished simply by their infrared spectra, even though the C=C stretching bands of π-allyl systems generally occur at longer wavelengths (*ca.* 1500 $cm^{-1}$) than those of dynamic allyl systems. The position of the band in dynamic systems depends on the electropositivity of the metal attached to the allyl group, its wavelength increasing with the ease with which the metal can give up an electron to the allyl group [$C_3H_5Na$: 1535 $cm^{-1}$, $(C_3H_5)_2Mg$: 1575 $cm^{-1}$, $(C_3H_5)_2Zn$: 1605 $cm^{-1}$].

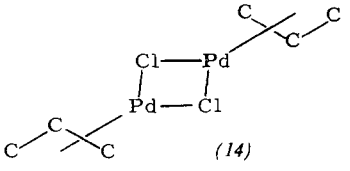
Transitions[18,20] between the types σ-allyl- ⇌ π-allylmetal compounds [*e.g.* between *(12)* and *(13)*] and π-allyl- → dynamic allylmetal compounds[21] have been

$$CH_2=CH-CH_2-Mn(CO)_5 \rightleftharpoons \text{(13)} Mn(CO)_4 + CO$$

*(12)*

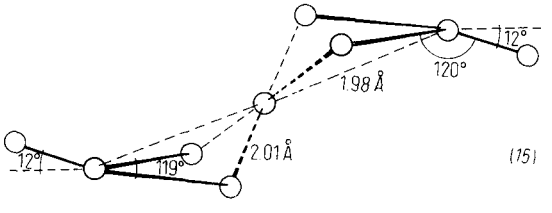
reported. The latter transition was only recently observed with the addition products of triphenylphosphine to π-methallylpalladium chloride[22] and to π-allylnickel bromide[23]. For zinc we also found a transition from the dynamic to the σ-allyl system (see page 156).

The clearest evidence for the symmetrical bonding of the allyl groups to the metal is provided by X-ray structure analysis. The dimer of π-allylpalladium chloride is a typical example[24]. The formula *(14)* shows the positions of all the atoms except hydrogen. The C atoms of each allyl group lie in a plane perpendicular to that containing the Pd and Cl atoms.



*(14)*

The results of our studies on pure allylmetal compounds have been corroborated by X-ray analysis[25] of bis-(π-methallyl)nickel *(15)*[13]. This compound, which is prepared by the general method described above, crystallizes very readily (m.p. 31 °C) and is much more stable than bis-(π-allyl)nickel. It has a sandwich structure in




*(15)*

which the methyl groups are *trans* to each other. Three C atoms in each methallyl group are situated at about the same distance from the central nickel atom. It should be noted that the methyl groups are inclined towards the metal at an angle of about 12 ° to the planes of the allyl groups. The latter are symmetrized, so that each formally occupies two coordination positions of the nickel atom, which is presumably $dsp^2$-hybridized.

X-ray structure analyses of the compounds $M(C_3H_5)_4$ (M = Zr, Th, Mo, W) are in progress. In these complexes, the metal

[17] a) *H. B. Jonassen*, J. Amer. chem. Soc. *80*, 2586 (1958); b) *J. Smidt* and *W. Hafner*, Angew. Chem. *71*, 284 (1959); c) *R. Hüttel* and *J. Kratzer*, *ibid.* *71*, 456 (1959); d) *I. I. Moiseev*, *E. A. Fedorowskaya*, and *Y. K. Syrkin*, Zh. neorg. Khim. *4*, 2641 (1959).

[18] *W. R. McClellan*, *H. H. Hoehn*, *H. N. Cripps*, *E. L. Muetterties*, and *B. L. Howk*, J. Amer. chem. Soc. *83*, 1601 (1961).

[19] *J. E. Nordlander* and *J. D. Roberts*, J. Amer. chem. Soc. *81*, 1769 (1959).

[20] *H. D. Kaesz*, *R. B. King*, and *F. G. A. Stone*, Z. Naturforsch. *15b*, 682 (1960).

[21] *J. C. W. Chien* and *H. C. Dehm*, Chem. and Ind. (London) *1961*, 745.

[22] *J. Powell*, *S. D. Robinson*, and *B. L. Shaw*, Chem. Commun. *1965*, 78.

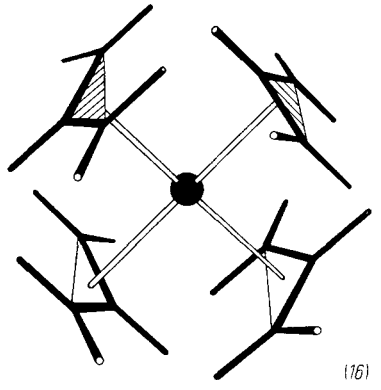
[23] *D. Walter*, Dissertation, Technische Hochschule Aachen 1965.

[24] a) *J. M. Rowe*, Proc. chem. Soc. (London) *1962*, 66; b) *W. E. Oberhansli* and *L. F. Dahl*, J. organometal. Chemistry *3*, 43 (1965); c) *A. E. Smith*, Acta crystallogr. *18*, 331 (1965).

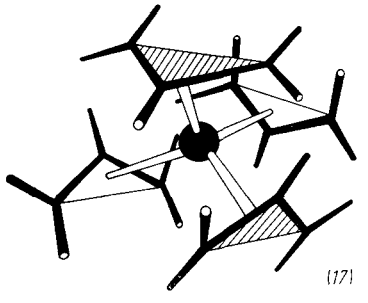
[25] *H. Dietrich* and *R. Uttech*, Naturwissenschaften *50*, 613 (1963); Z. Kristallogr. *122*, 60 (1965).

atom has a coordination number of 8 if each of the allyl groups occupies two coordination positions. Since $Zr(C_3H_5)_4$[7] and $Th(C_3H_5)_4$[7] in particular have typical π-allyl $^1$H-NMR spectra, it can be assumed that they have a very regular structure, since all four allyl groups could not otherwise give the same spectrum.

Two particular arrangements of the four allyl groups about the central atom would ensure that all the groups were perfectly equivalent. In the first of these, the centroids of the allyl groups occupy the corners of a square with the metal atom at the center, and the eight coordination positions lie at the corners of a square prism: *(16)*. In the second case the basic framework is tetrahedral, and the eight coordination positions are situated at the eight corners of a solid bounded by two rectangles and four trapezia, *i.e.* a tetrahedron truncated at two non-intersecting edges: *(17)*. The tetraallyl systems cannot be represented by the usual arrangements found with eight-fold coordination ($d^5p^3$ – square antiprism: $d^4sp^3$ – dodecahedron), since the separation in each pair of coordination positions, determined by the structure of the allyl group, is disproportionately small.



(16)



(17)

It can be seen from the model that the distance between allyl groups, and particularly between $CH_2$ groups, is greater in the arrangement *(17)*, so that this structure should be the more likely. Complications seem to arise in the analogous complexes of molybdenum[8] and tungsten[8], where $^1$H-NMR spectra indicate that either two of the allyl groups are bonded differently to the other two, or that the two terminal C atoms of each allyl group do not interact with the metal in the same way.

The $^1$H-NMR spectra of only a few allylmetal compounds can be discussed here (detailed discussion will be reserved for another publication). It should first be pointed out that the $^1$H-NMR spectra of some complexes could not be recorded, either because the substances decompose too readily or are not sufficiently soluble at low temperatures (V, Co), or because of interference due to paramagnetism (Cr, Fe, Nb, Ta).

$Zr(C_3H_5)_4$ and $Th(C_3H_5)_4$, both of which crystallize very well, were found to be particularly interesting. Both of these compounds have temperature-dependent $^1$H-NMR spectra. The classic π-allyl spectrum given by *e.g.* $Th(C_3H_5)_4$ in $C_6D_6$ at 10 °C ($H_a$: $\tau = 3.97$; $H_b$: $\tau = 6.46$; $H_c$: $\tau = 7.61$ with tetramethylsilane as internal standard) slowly changes with rising temperature, and ultimately (at 80 °C) exhibits the characteristics of a dynamic allylmetal system ($H_a$: $\tau = 3.95$; $H_{bc}$: $\tau = 7.09$). Similar results were obtained with $Zr(C_3H_5)_4$, for which the transition temperatures, however, are about 80 to 100 °C lower. This was the first demonstration of a thermal transition from a π-allyl to a dynamic allyl system. A particularly remarkable feature of this transition is that the infrared spectra of the two compounds show no comparable effect of temperature on the position of the typical C=C stretching band.

For comparison purposes, we also prepared $(C_3H_5)_2Mg$[6] and $(C_3H_5)_2Zn$[6] and recorded their infrared and $^1$H-NMR spectra. At 20 °C, both of these compounds give the typical $^1$H-NMR spectrum of a dynamic allyl system, and the C=C stretching bands in the IR spectra are situated at 1575 $cm^{-1}$ and 1605 $cm^{-1}$. *Thiele* and *Zdunnack*[14] independently described the preparation and properties of diallylzinc. The reported $^1$H-NMR spectrum agrees well with that obtained in our own work at 20 °C in tetrahydrofuran. We observed another peculiarity at −100 °C, namely the conversion of the dynamic system into a σ-allyl system[*]. All the transitions π-allyl → dynamic allyl → σ-allyl have thus been observed for allylnickel halides.

A final explanation for the transition from the π-allyl to the dynamic allyl system cannot yet be given. The hypothesis agreeing best with all results is that in the initially symmetrized allyl groups, the CC bonds, which are already weakened by the interaction with the transition metal (C=C stretching band at *ca.* 1500 $cm^{-1}$) become further loosened at higher temperatures. The $CH_2$ groups can thus be relatively easily rotated around the CC-axis. The frequency of this rotation should be roughly 150–200 $sec^{-1}$ at the coalescence temperature; *i.e.* above this temperature the signals of the *syn* and the *anti* protons coalesce as a result of rapid exchange of their positions.

The activation energy of the π-allyl → dynamic allyl transition was estimated very roughly by *Gutowsky*'s method[26] from the $^1$H-NMR spectra of $Zr(C_3H_5)_4$ and $Th(C_3H_5)_4$ at various temperatures. The values obtained are about 10 and 15 kcal/mole, respectively.

It is particularly noteworthy that the above temperature-dependent transition occurs for $Zr(C_3H_5)_4$ and $Th(C_3H_5)_4$. If it is assumed that four allyl anions are bonded to the central metal in these two compounds, the metal cations can have no filled d-orbitals available for normal back-donation to the ligand. Formally, therefore, the bonding of the allyl groups to the metal must depend entirely on the donor function of the allyl anion, any additional charge transfer from the metal to the ligand as described in the *Chatt-Duncanson* picture[27] of olefinmetal complexes being at most of minor importance. The easy transition from the π-allyl to the dynamic

[*] It is not impossible that THF acts as a ligand on the Zn at low temperatures.

[26] *H. S. Gutowsky* and *A. Saika*, J. chem. Physics *21*, 1688 (1953).

[27] *J. Chatt* and *L. A. Duncanson*, J. chem. Soc. (London) *1953* 2939.

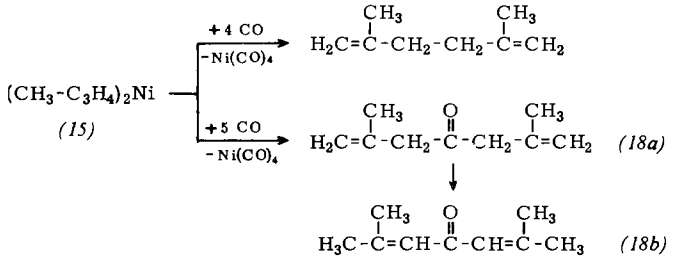
allyl system could therefore be due to the absence of sufficiently strong back-donation.

According to this rather primitive picture, the allyl compounds of zirconium and thorium occupy a position between the π-allyl compounds of metals with pronounced acceptor and donor properties, such as nickel, and those of the main-group elements, which form only dynamic allyl systems. Zinc, which has a filled d-shell, also forms the dynamic type.

## 4. Particular Allyl Compounds of Nickel

### a) Bis-(π-methallyl)nickel and Bis-(π-crotyl)nickel [13]

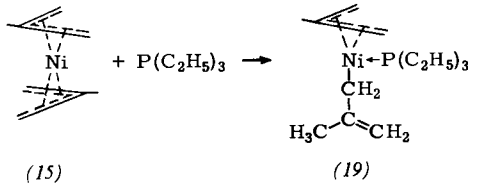
The most convenient complexes to work with are those of nickel. Variations of the allyl system were therefore studied with nickel as the central atom. That bis-(π-methallyl)nickel is more stable than bis-(π-allyl)nickel is shown by the fact that butadiene does not react directly with the methallyl complex at 20 °C, as it does with π-$(C_3H_5)_2Ni$. Cyclododeca-1,5,9-triene is formed only at elevated temperature. Displacement experiments with CO showed that a very unstable 1:1 adduct is first formed at −80 °C; this takes up further CO at higher temperatures, and is finally converted into $Ni(CO)_4$, with displacement of 2,5-dimethylhexa-1,5-diene. A minor side reaction is the insertion of CO, leading first to the formation of the ketone *(18a)*, which isomerizes to phorone *(18b)*.




*(18a)*

*(18b)*

A 1:1 adduct of bis-(-methallyl)nickel with triethylphosphine has been isolated in the crystalline form. This complex formation should lead to an increase in the number of outer electrons on the nickel from 16 to 18, and so stabilize the complex. This is not so, however, since firstly the triethylphosphine can be easily removed at $10^{-4}$ mm Hg, and secondly the infrared spectrum of the adduct shows that complex formation apparently occurs at the expense of one π-allyl group, which appears to be σ-bonded as in *(19)* (band at 1605 $cm^{-1}$).



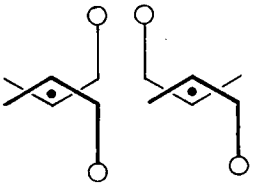

*(15)* *(19)*

It must therefore be concluded that the sandwich arrangement is a particularly preferred system, even when the nickel atom formally has at its disposal only 16 outer electrons.

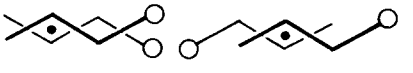
Bis-(π-crotyl)nickel, which also has been obtained in the crystalline form, should exhibit stereoisomerism, since the crotyl group can be bonded to the metal in either the *syn* or the *anti* form [*], as had already been observed for π-crotylcobalt tricarbonyl *[(20), (21)]* [28].

*(20)*, anti *(21)*, syn

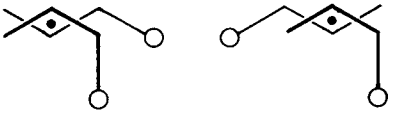
Bis-(π-crotyl)nickel probably also has a sandwich structure. If we look along an axis perpendicular to the planes of the allyl groups and passing through the central atom, the structures of the isomers will be as shown in *(22)* to *(24)* (the circles denote methyl groups).



*(22)*, anti-anti



*(23)*, syn-syn



*(24)*, syn-anti

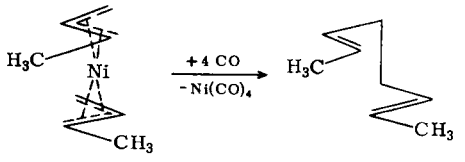
Assuming that the crotyl groups cannot rotate freely around this axis and that the mutual arrangement of the crotyl groups corresponds to the *trans* arrangement in bis-(π-methallyl)-nickel *(15)*, six isomers are possible (not counting optical isomers). Six isomers are also expected for free rotation around the axis. The number of isomers increases to twelve if two positions differing by an angle of 180 °C (*cis* and *trans*) are possible.

Dissimilar bonding of the C atoms in the allyl systems to the nickel atom must also be considered.

In view of these relatively complex structural relationships, the results obtained in the reaction of bis-(π-crotyl)nickel with CO appear even more surprising. When the reaction is carried out with the crystalline product or in solution at −40 °C and normal pressure, the products are $Ni(CO)_4$ and a mixture of *trans,trans*-octa-2,6-diene *(23a)* (98 %) and 3-methylhepta-1,5-diene *(23b)* (2 %) in a total yield of 96 to 98 %. The displacement reaction is stereospecific under these conditions, and proceeds as if the bis-(π-crotyl)nickel consisted only of the *syn,syn* forms.

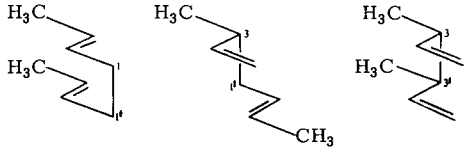
[*] Here the terms *syn* and *anti* refer to the position of the central H atom of the allyl group with respect to the methyl group.

[28] *J. A. Bertrand, H. B. Jonassen*, and *D. W. Moore*, Inorg. Chem. *2*, 601 (1963).



(23) (23a)

Thus the linkage occurs almost exclusively through the unsubstituted ends of the allyl systems. At higher temperatures, this reaction leads to the formation of three dienes in a total yield of 88 %, consisting of 58 % of octa-2,6-diene *(23a)*, 38 % of 3-methylhepta-1,5-diene *(23b)*, and 4 % of 3,4-dimethylhexa-1,5-diene *(23c)*, *i.e.* all three possible products are formed. No ketone was found among the products.



(23a) (23b) (23c)

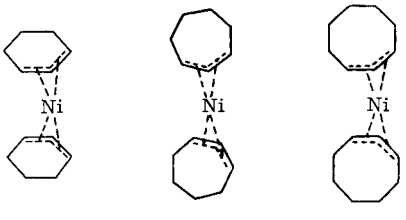
The reasons for the highly specific course taken by the bond formation at low temperatures presumably are as follows:

1. A definite spatial arrangement of the crotyl groups in the starting material.

2. The activation energies for the formation of the 1-1′, 3-1′, and 3-3′ linkages are not equal, but increase in this order.

b) Cyclic Bis-(π-allyl)nickel Compounds [13]

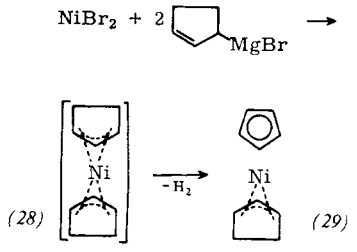
In order to find whether cyclic allyl systems can be bonded to nickel, we synthesized the compounds *(25)* to *(27)*, which exist in the *anti,anti* form.



(25) (26) (27)

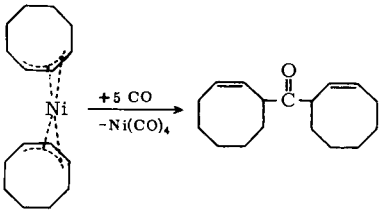
Though all three compounds were ultimately obtained in the crystalline form, considerable difficulty was encountered in the synthesis of those containing 6- and 7-membered rings. Bis-(π-cyclohexenyl)nickel *(25)* decomposes already between −40 °C and −30 °C, whereas bis-(π-cycloheptenyl)nickel *(26)* is stable for short periods at room temperature. Bis-(π-cyclooctenyl)nickel *(27)* is very stable, and nickel separates from crystals kept in a sealed tube only after a number of days.

Examination of Dreiding models shows that all three compounds should be stable if it were simply a question of finding a strain-free arrangement of three adjacent C atoms as $sp^2$ hybrids. The same applies to *(28)*, but instead of this compound, we obtained cyclopentadienyl-π-cyclopentenylnickel *(29)*, first prepared by *E. O. Fischer* and *H. Werner* [29], which is very stable, probably because of the electron-attracting action of the cyclopentadienyl group. A similar stabilizing effect is shown by halogen atoms (see Section 5).



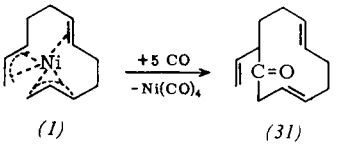
(28) (29)

Bis-(π-allyl)nickel and bis-(π-crotyl)nickel undergo exclusively displacement with CO. With bis-(π-methallyl)-nickel, insertion of CO to form a ketone was observed as a side reaction (see Section 4a), and this insertion becomes the principal reaction (92 % yield) in the case of bis-(π-cyclooctenyl)nickel, the product being the ketone *(30)*.



(27) (30)

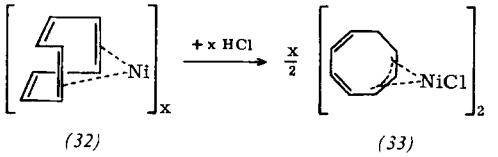
The insertion observed in the case of *(1)*, with formation of *(31)* [1, 12] also belongs to this group of reactions.



(1) (31)

It is not yet known what factors determine whether the reaction of a given system will lead to displacement or insertion, but steric effects could be of some importance, *i.e.* insertion may always occur when linkage to form a diallyl system is sterically opposed.

A special type of cyclic allylnickel compound was obtained by another method. Cyclooctatetraenenickel *(32)* [30] reacts with HCl gas at −80 °C in toluene to form red crystals of π-cyclooctatrienylnickel chloride *(33)*.

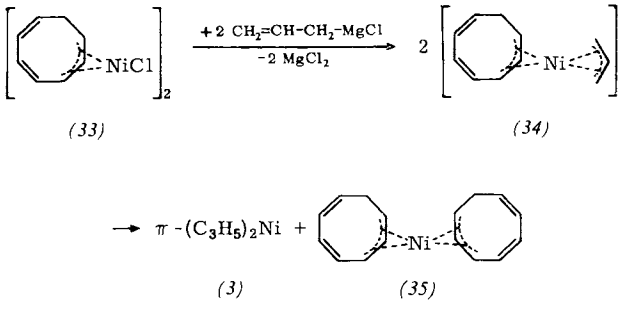


(32) (33)

[29] *E. O. Fischer* and *H. Werner*, Chem. Ber. *92*, 1423 (1959); Tetrahedron Letters *1961*, 17.

[30] *G. Wilke* and *M. Kröner*, unpublished work.

In the course of attempts to obtain π-cyclooctatrienyl-π-allynickel *(34)* by the reaction of *(33)* with allyl Grignard compounds, we obtained a product that decomposed immediately into volatile bis-(π-allyl)nickel and the red crystalline bis-(π-cyclooctatrienyl)nickel *(35)*.

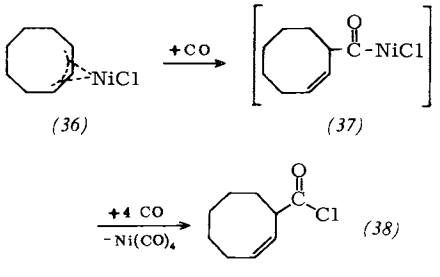



## 5. Allylnickel Halides [31]

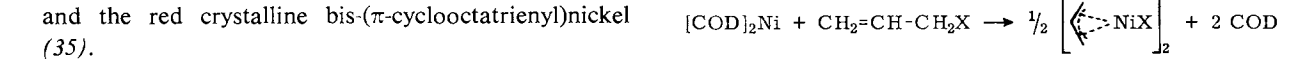
In connection with the formation of cyclopentadienyl-π-cyclopentenylnickel *(29)* it has already been pointed out that strongly electron-attracting ligands, such as halogen atoms, can often stabilize an allyl system bonded to the same nickel atom. We have frequently observed that the bis-(π-allyl)nickel complexes have poor or no stability, whereas the corresponding allylnickel halides can be prepared without difficulty.

We shall first describe a simple, general method for the synthesis of allylnickel halides. *E. O. Fischer* and *G. Bürger* [32] were the first to show that $Ni(CO)_4$ reacts with allyl halides, *e.g.* with allyl bromide to form π-allylnickel bromide. The yields leave much to be desired (10 %), evidently because the displaced CO reacts with the π-allylnickel halide by insertion, at least to a great extent [33].

Insertion of this type has been observed particularly with π-cyclooctenylnickel chloride *(36)*, which initially forms an insertion product *(37)*. The nickel reacts with excess of CO to form $Ni(CO)_4$, or else separates as the metal, and the acid chloride *(38)* is formed at the same time.




For this reason, $Ni(CO_4)$ is not the ideal starting material for the synthesis of π-allylnickel halides. On the other hand, bis-(cycloocta-1,5-diene)nickel, which can readily be prepared in good yields and in a very pure state, reacts with allyl halides in ether to give almost quantitatively any desired allylnickel halide [31] (COD = cycloocta-1,5-diene).

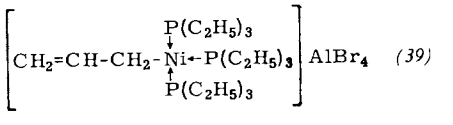



Equally good results are obtained with cyclododeca-1,5,9-trienenickel, but this complex of nickel(0) is much more difficult to handle. Owing to its greater reactivity, the reaction can be carried out at very low temperatures.

Bis(cyclo-octa-1,5-diene)nickel was used to synthesize a number of π-allylnickel halides (see Table 2). All these complexes are very stable, including those of which the allyllic components do not form stable diallylnickel compounds. The complexes containing 3-, 4-, and 6-membered rings are particularly worthy of mention. Bis-(π-allyl)nickel compounds with cyclopropenyl or cyclobutenyl systems have not so far been obtained, and all attempts to prepare them have yielded elementary nickel and the dimeric hydrocarbons.

The π-allylnickel halides can be used as components for the preparation of highly active catalysts (see Section 6). According to *E. O. Fischer* and *G. Bürger* [32], these compounds ($C_3H_5NiX$ with X = Cl, Br, or I) are dimeric; they behave in the same way as π-allylpalladium chloride. The $^1$H-NMR spectra agree with the π-allyl structure. With phosphines various adducts are formed, in which the perturbation of the allyl group is strong, weak, or absent, depending on the nature and number of phosphine molecules introduced. A general characteristic of these additions is the conversion of the original, readily ether-soluble complexes into sparingly soluble products, and the breaking of the halogen μ-bridges so that the adducts are monomeric in solution. It can be seen from the $^1$H-NMR spectra that the ligands exert an important and interesting effect on the allyl groups. Increasing donation of electrons to the nickel atom causes the π-allyl group to change into a dynamic allyl system, and in the extreme case into a σ-allyl system.

These transitions were observed in the following cases [23]: Whereas the $^1$H-NMR spectrum of a 1:1 adduct of π-allylnickel bromide and triphenylphosphine clearly shows the characteristics of a π-allyl group, the 1:2 adduct $C_3H_5NiBr \cdot 2P(C_2H_5)_3$ gives the spectrum of a dynamic allyl system. Finally, in the 1:3 adduct $C_3H_5NiBr \cdot 3P(C_2H_5)_3$, the symmetrical allyl system "opens up" (σ-allyl system). However, this case[*(39)*] is observed only when the halogen of the allylnickel bromide becomes part of a complex anion.




These transitions depend, not on the quantity, but rather on the basicity of the phosphine used. Although with an excess of triphenylphosphine a 1:2 adduct is formed, its $^1$H-NMR spectrum shows that it contains a π-allyl system. A 1:2 adduct containing a dynamic allyl system is formed only by the more strongly basic triethylphosphine, *i.e.* the electron configuration of the nickel atom becomes similar to that of the zinc atom, which has a completely filled d-shell.

The π-allylnickel halides become catalytically active only when the halogen atoms form part of a complex anion. This situation can generally be brought about with Lewis acids, and particularly aluminum halides. In polar solvents, complexes such as $C_3H_5NiAlCl_4$ are formed, in which the allyl group is bound as a π-allyl system. These complexes also react with phosphines to form 1:1 adducts in which the phos-

[31] π-Allylnickel halides: German Published Patent Application 1 194417 (Aug. 10th, 1963), Studiengesellschaft Kohle.

[32] a) *E. O. Fischer* and *G. Bürger*, Z. Naturforsch. *16b*, 77 (1961); b) Chem. Ber. *94*, 2409 (1961); c) *G. Bürger*, Dissertation, Universität München 1962.

[33] a) *G. P. Chiusoli*, Angew. Chem. *72*, 74 (1960); b) *E. O. Fischer* and *G. Bürger*, Z. Naturforsch. *17b*, 484 (1962); c) *G. P. Chiusoli* and *S. Merzoni*, Z. Naturforsch. *17b*, 850 (1962); d) *R. F. Heck*, J. Amer. chem. Soc. *85*, 2013 (1963).

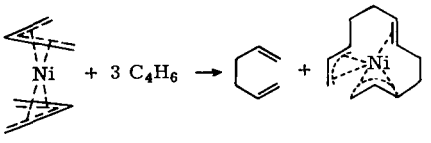
[34] *E. W. Gowling* and *S. F. A. Kettle*, Inorg. Chem. *3*, 604 (1964).

phine molecules clearly interact with the nickel atom. If amines are used instead of phosphines, the complexes dissociate immediately, since aluminum halide-amine complexes are formed preferentially. This behavior illustrates the difference in donor properties of phosphines and amines: whereas phosphines exhibit both donor and acceptor properties, amines are exclusively donors.

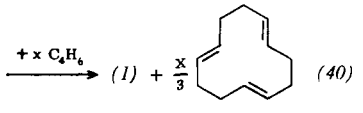
## 6. Catalytic Processes Induced by Allylmetal Complexes [35]

### a) Oligomerization of Butadiene with Bis-(π-allyl)palladium

The synthesis of bis-(π-allyl)nickel *(3)* described in the Introduction was originally intended only to show that two allyl groups can be bonded to a nickel atom, as had been postulated for the intermediate *(1)* in the cyclotrimerization of butadiene. It was subsequently found that bis-(π-allyl)nickel can function as an active catalyst system, *i.e.* as a source of "bare" nickel. Butadiene displaces the allyl groups, which combine to form hexa-1,5-diene, while the butadiene itself forms cyclododecatriene *(40)*.




*(3)* *(1)*

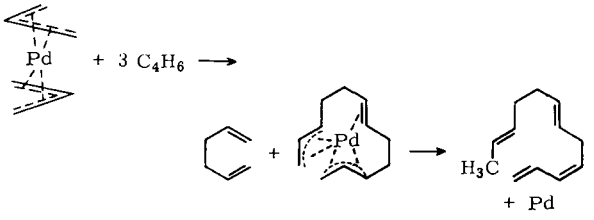



*(40)*

This experiment was repeated later with bis-(π-allyl)-palladium, whose infrared and $^1$H-NMR spectra do not appear at first glance to differ from those of bis-(π-allyl)-nickel. The compounds differ, however, in color, stability, yield, and (understandably, in view of the difference in molecular weight) volatility. Apart from the inner shells, the electronic configurations should be the same, but the crystallographic ionic radii of the metals ($Ni^{2+}$ 0.69 Å; $Pd^{2+}$ 0.80 Å) differ considerably, as do their first ionization energies (Ni 7.61 eV; Pd 8.3 eV).

The catalytic activity of bis-(π-allyl)palladium is comparable to that of the nickel compound at 40 °C, but in this case butadiene does not react to form cyclododecatriene. In a reaction carried out at 40 °C for three days, 30 % of the product consisted of n-dodecatetraenes, which gave only n-dodecane on catalytic hydrogenation. The only other products, apart from traces of vinylcyclohexane, were higher oligomers. At higher temperatures, elementary palladium separated out after a short time.

It can be concluded from the products that the reaction steps involved in the case of bis-(π-allyl)palladium are probably the same as in that of bis-(π-allyl)nickel, *i.e.* butadiene first displaces the allyl groups and is itself trimerized on the palladium. It is possible that an intermediate complex similar to that occurring with the nickel compound is formed, but the chain ends evidently cannot link up in this case to form cyclododecatriene. The subsequent steps are either a hydrogen shift to form dodecatetraene which can react further (to some extent at least, since it is a substituted butadiene) or reaction with further butadiene to form higher oligomers.

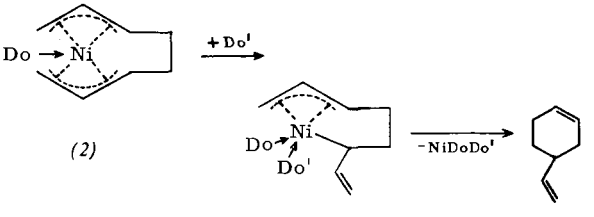



This reaction sequence is supported by the fact that practically the only products are n-dodecatetraenes and higher oligomers. The position of the double bonds in the initially formed dodecatetraene, and hence the position to which the H atom has migrated, cannot be established with certainty, since traces of palladium that separate during the reaction induce migration of double bonds.

It may be very tentatively concluded from this result that the chain ends of the intermediate complex are prevented from comming together because of the greater atomic volume of palladium. The intervention of steric factors is also suggested by the low stability of the "bare" palladium in excess of butadiene, *i.e.* the $C_{12}$ chain does not appear to be such a good ligand system for palladium as for nickel. It must be borne in mind that two separate allyl groups apparently form a more stable complex with palladium than with nickel. Bis-(π-allyl)-platinum, which is still more stable, does not react with butadiene; at higher temperatures, platinum is simply deposited.

By analogy with the dimerization of butadiene on donor-nickel catalysts, experiments were also carried out with bis-(π-allyl)palladium in the presence of donors. As in the case of nickel, it was expected that the donors would activate the catalyst and change the course of the reaction. No appreciable improvement in activity was observed, but the course of the reaction could be fundamentally altered. The greatest effect was obtained with phosphorus trichloride as the donor, added to a solution of bis-(π-allyl)palladium in a molar ratio of 1:1. With this catalyst at 90 °C vinylcyclohexene was practically the only product; control experiments showed the reaction to be catalytic and not thermal.

This result provides a link with the behavior of nickel. We were able to show that donor→nickel catalysts always give vinylcyclohexene when the intermediate *(2)* is

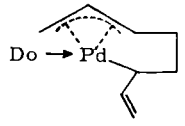



*(2)*

long-lived and when the nickel atom is insufficiently shielded by the donor against attack by other donors, *i.e.* butadiene. Similar intermediate complexes presumably are formed with the palladium compound. However, it must also be borne in mind that the transition

[35] Oligomerization and polymerization of olefins: Belg. Pat. 651 596 (Aug. 7th, 1964), Studiengesellschaft Kohle.

from the π-allyl to the σ-allyl system under the influence of the donor may be easier with palladium than with nickel. In contrast to bis-(π-allyl)nickel it is possible, even with triphenylphosphine, to prepare 1:1 adducts of bis-(π-allyl)palladium in which one of the allyl groups is σ-bonded. The vinylcyclohexene could therefore be derived from the intermediate *(41)*.




*(41)*

The results described give a good indication of the similarities of the bis-(π-allyl) derivatives of nickel and palladium, as well as of the considerable differences between them, which are presumably due in part to steric reasons, but also to a large extent to the difference between the electron shells of the two elements and their interactions with the nuclei.

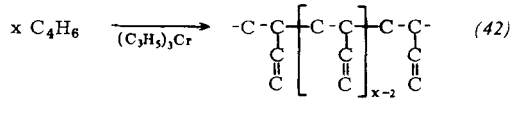
Catalytic reactions proceeding *via* a rapid succession of intermediates separated by low energy barriers appear to be particularly sensitive to influences of the type described, especially since the formation of products such as cyclododecatriene from three molecules of butadiene require that the catalyst atom should exert highly directional forces.

The suitability of "bare" nickel as a matrix for the catalytic formation of cyclododecatriene is shown particularly clearly by the results of X-ray analyses of all-*trans*-cyclododeca-1,5,9-triene and of all-*trans*-cyclododeca-1,5,9-trienenickel(0). The structures, which were determined independently by *Dietrich*[36] (nickel complex) and *Allegra*[37] (hydrocarbon), are practically identical except for the presence of the nickel atom, *i.e.* the nickel atom fits into the center of the ring without altering the cyclododecatriene structure. This is in agreement with the fact that the two compounds appear to form a continuous range of solid solutions, from which the more volatile cyclododecatriene can be sublimed.

### b) Polymerizations with Allylchromium Complexes

Titanium and chromium should form matrices similar to that formed by "bare" nickel for the cyclotrimerization of butadiene, since both elements give catalysts that convert butadiene into cyclododecatriene. However, these matrices must differ sterically, since titanium catalysts give almost exclusively *trans,trans,cis*-cyclododeca-1,5,9-triene, whereas chromium catalysts give mixtures of *all-trans* and *trans,trans,cis*-cyclododecatriene(60:40).

Butadiene cannot be cyclotrimerized with triallylchromium itself. Although this readily soluble complex reacts instantaneously with butadiene, the product is

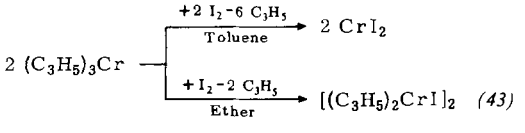



*(42)*

1,2-polybutadiene *(42)*, *i.e.* the reaction is a highly stereoselective polymerization.

Triallylchromium is not a true Ziegler catalyst, since it contains neither halide ions nor organometallic compounds of elements of groups 1 to 3 of the periodic system. Thus the conversion of butadiene into 1,2-polybutadiene by catalysts[38] obtained from chromium acetylacetonate and triethylaluminum is probably due to the much simpler triallylchromium system or the products formed by its reaction with butadiene.

However, the real object of our experiments, *i.e.* the preparation of a cyclotrimerization catalyst, had not been achieved. We had previously isolated the component of a chromyl chloride triethylaluminum catalyst responsible for the formation of cyclododecatriene from butadiene after reaction with 2-butyne in the form of the bis(hexamethylbenzene)chromium cation[39]. The chromium in this complex is formally univalent, and is bonded to a halide ion. In subsequent experiments we replaced one of the three allyl groups in triallylchromium by a halogen atom to obtain a diallylchromium halide as a source of a cyclotrimerization catalyst. Triallylchromium reacts with solutions of elementary iodine at temperatures as low as about 0 °C. The nature of the product depends on the solvent. In non-polar solvents, such as toluene, the only product is $CrI_2$, even when triallylchromium is used in excess. In ether, on the other hand, the reaction proceeds very rapidly with formation of crystalline diallylchromium iodide *(43)*. The diallylchromium halides can also be obtained from triallylchromium and anhydrous hydrogen halides, as was pointed out in Section 2.




*(43)*

Diallylchromium iodide and butadiene in benzene give cyclododecatriene in a yield of about 40 %. The yield can be increased to about 70 % by the use of methylene chloride as solvent or by addition of aluminum halides or alkylaluminum halides. The success of the synthesis appears to depend on disscociation of the dimeric diallylchromium halides.

This is in agreement with the fact that the chloride, which appears to be more strongly associated, gives polymers together with only traces of cyclododecatriene, whereas the iodide, which dissociates more readily, gives considerable quantities of cyclododecatriene. Polar solvents such as methylene chloride or chlorobenzene favor dissociation, and hence also the formation of cyclododecatriene. Aluminum halides or alkylaluminum halides also cause dissociation by formation of the complex $(C_3H_5)_2CrAlX_4$.

Much better catalysts than diallylchromium halides are now available, but this system is making an important contribution to our knowledge of the processes that take place on these catalysts. The cyclotrimerization of butadiene on *(43a)* can be interpreted in the same manner as the cyclotrimerization on "bare" nickel.

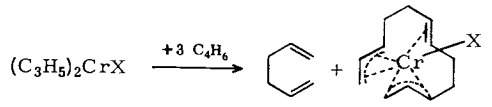
[36] *H. Dietrich* and *H. Schmidt*, Naturwissenschaften *52*, 301 (1965).

[37] *G. Allegra* and *J. W. Bassi*, Atti Accad. naz. Lincei, Rend., Cl. Sci. fisiche, mat. natur. *33*, 72 (1962).

[38] Diolefin polymers: Belg. Pat. 549554 (Juli 14th, 1956), Soc. Montecatini, inventors: *G. Natta* and *L. Porri*.

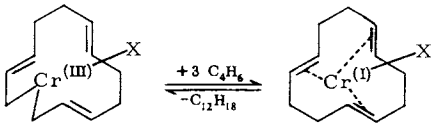
[39] *G. Wilke* and *M. Kröner*, Angew. Chem. *71*, 574 (1959); *M. Kröner*, Dissertation, Technische Hochschule Aachen 1961.

The intermediate *(44)* has not yet been isolated. In the classic formulation, the catalysis would, as in the case of



*(43a)* *(44)*

nickel ($Ni^0 \rightleftarrows Ni^{II}$) be accompanied by a continuous change in the oxidation state of the chromium ($Cr^I \rightleftarrows Cr^{III}$). Thus the matrix provided by the "bare" nickel atom for butadiene is again present in the $Cr^IX$ system.



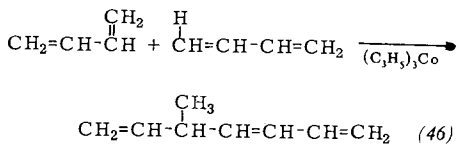
*(45)* *(44a)*

Allylmetal catalysts, like Ziegler catalysts, can induce either polymerizations or oligomerizations, as shown by the above example. Solutions of triallylchromium in *e.g.* hexane polymerize ethylene at 20 °C and *e.g.* 1 to 15 atm, the product being a high-molecular weight polyethylene with nearly the same infrared spectrum as that of Ziegler polyethylene. However, the products have very low solubilities, and therefore probably are cross-linked. The remarkable feature of this result is the fact that ethylene is polymerized under extremely mild conditions by pure soluble triallylchromium in the absence of halide ions or organometallic compounds of elements from groups 1 to 3.

This can be explained in two ways. Either triallylchromium is another new catalyst system for the polymerization of ethylene, or not all views on the mechanism of the Ziegler polymerization of ethylene (which involve the participation of halide ions and the co-operation of the transition metal component with the organometallic component) can be correct.

### c) Polymerizations with Allylcobalt Complexes

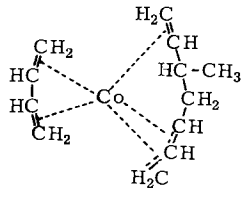
Two types of reactions are observed with allyl compounds of cobalt, with which butadiene may be either selectively dimerized or stereospecifically polymerized [11]. Triallylcobalt can be prepared at low temperatures in the form of golden-red crystals and is readily soluble in hydrocarbons, but starts to decompose at −40 °C. In the presence of butadiene, it is converted into a much more stable complex, so that solutions containing excess of butadiene can be safely heated to about 10 to 20 °C. Under these conditions, however, the butadiene dimerizes to give in more than 90 % yield 5-methylhepta-1,3,6-triene *(46)*, which we had already prepared for the first time with the aid of other catalysts [40].





*(46)*

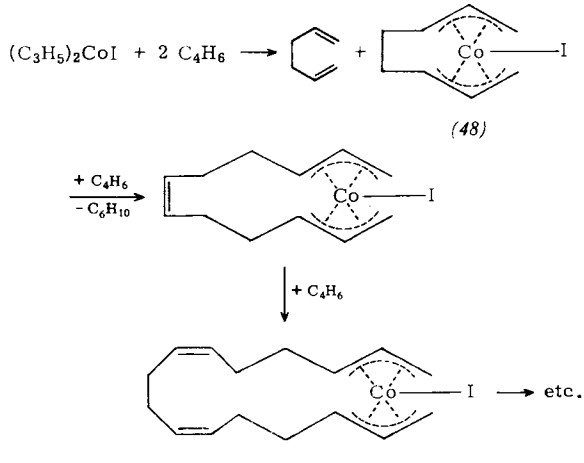
The dimerization proceeds with migration of a hydrogen atom. In the course of investigations on the polymerization of butadiene, *G. Natta, U. Giannini, P. Pino*, and *A. Cassata* [41] isolated the cobalt complex *(47)*. Possibly the same product is formed as an intermediate in the dimerization of butadiene with triallylcobalt.



*(47)*

The second type of reaction on allylcobalt compounds was observed during attempts to replace an allyl group in triallylcobalt by halogen (cf. the experiments with triallylchromium). This replacement can be carried out either with elementary iodine or with hydrogen halides. The same pattern was observed as in the chromium system, *i.e.* the activity of the diallylcobalt halide depends on the halide, the presence or absence of aluminum halide, and the solvent. It appears, therefore, that effects similar to those discussed in connection with chromium are also involved in the case of cobalt. However, the product obtained from butadiene is different; it consists of 1,4-*cis*-polybutadiene together with a little 1,2-polybutadiene; 1,4-*trans*-polybutadiene is absent. The polymerization can also be induced by pure bis(allyl)cobalt iodide. Addition of *e.g.* aluminum bromide leads to a considerable increase in activity and to the formation of essentially pure 1,4-*cis*-polybutadiene. Thus the situation is the opposite of that obtaining for chromium; the pure allyl compound causes dimerization, while the diallylcobalt halides induce polymerization.

The following 1,4-*cis*-polymerization sequence *via* a $C_8$-diallyl system *(48)* has not yet been proved, but it agrees with all the results on the cyclo-oligomerization of butadiene.

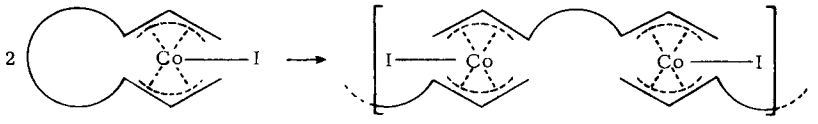


*(48)*

[40] Di- or trimerization of 1,3-diolefins: Austrian Pat. 219580 (Dec. 5th, 1960), Studiengesellschaft Kohle.

[41] *G. Natta, U. Giannini, P. Pino*, and *A. Cassata*, Chim. e Ind. (Milano) *47*, 524 (1965).

It is also quite possible that allyl groups, *i.e.* chain ends, are transferred from one cobalt atom to another so that the ends of a chain may be attached to two different cobalt atoms.



*(49)*

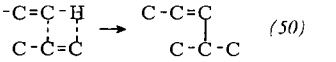
We have studied a number of allyl transfers of this kind[6,13,42]. For example, bis-(π-allyl)nickel exchanges its ligands for those of bis-(π-methallyl)nickel when the two compounds are present in the same solution. Subsequent displacement of the ligands with CO gives 2-methylhexa-1,5-diene as well as hexa-1,5-diene and 2,5-dimethylhexa-1,5-diene. The transfer of allyl groups from one metal to another, *e.g.* from nickel to palladium, has also been observed.

### d) Polymerizations with Activated Allylnickel Halide Systems

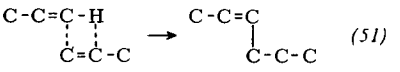
The observation that π-allylnickel halides (cf. Section 5) can act as very active catalysts prompted us to carry out a comprehensive study of these complexes[43]. We first observed catalytic activity[30] when ethylene or propylene was brought into contact with cyclooctatrienylnickel chloride under pressure (about 50 atm) at about 70 °C. The reaction proceeded relatively slowly, and the product consisted mainly of dimers, *i.e.* 2-butene or mixtures of hexenes, methylpentenes, and dimethylbutenes. When the activating influence of aluminum halides, first observed with allylchromium halides, was applied to π-allylnickel halides, very active catalysts were obtained with which ethylene, and even propylene, could be dimerized very rapidly between −30 and −40 °C under reduced pressure. The best results were again obtained in polar solvents such as methylene chloride or chlorobenzene. The yields of dimers were 80 to 85 % for a very low catalyst consumption, and 15 to 20 % of the monomer that had reacted was found as higher oligomers (mainly trimers in the case of propylene).

The catalysts are generally prepared by the following method: dicyclooctadienenickel is allowed to react with *e.g.* allyl bromide to form π-allylnickel bromide, which can be isolated in the crystalline form. This is dissolved in *e.g.* chlorobenzene, and an alkylaluminum dihalide, or most simply an aluminum trihalide, is added to the solution in a molar ratio of 1:1 or 1:2. Propylene is passed into the strongly cooled solution, which is deep red in most cases. 80 % of the resulting dimers consists of 2-methylpentenes and 20 % is n-hexenes *(51)*. Modified catalysts give another mixture containing up to 70% of 2,3-dimethylbutenes, together with 2-methylpentenes and traces of n-hexenes.

The dimerization can be directed by the addition of phosphines. Thus a catalyst containing triphenylphosphine in a molar ratio Ni:P:Al = 1:1:2 leads to the same products as the catalyst without phosphine, but with a smaller content of higher oligomers. Catalysts containing strongly basic phosphines such as triisopropylphosphine lead to a mixture of 2,3-dimethylbutenes *(52)* and 2-methylpentenes *(50)*. The formation of these two products can be explained as follows: In the first case [*(50)*, *(51)*], a C–H bond of the terminal $CH_2$ group of one propylene molecule is activated and adds to the C=C bond of the second. In the second case [*(50)*, *(52)*], the C–H bond on

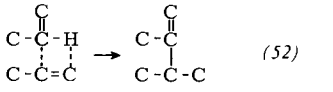


*(50)*

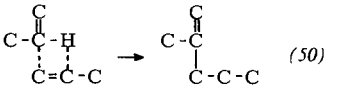


*(51)*

the central C atom of one propylene molecule appears to be activated and to add to the C=C bond of the second.



*(52)*



*(50)*

Model experiments have shown that the dimers initially formed according to the formulae isomerize to varying extents under the influence of the catalysts, the isomerization being confined to the migration of double bonds. These catalytic reactions undoubtedly proceed *via* intermediate complexes in which the monomeric olefins are attached to free coordination positions on the nickel atoms. This is shown by the fact that blockage of these free coordination positions by addition of other donors causes immediate interruption of the catalysis at low temperatures. Thus the simplest of these catalysts (π-allylnickel bromide with $AlBr_3$) can be instantaneously blocked in this way by cycloocta-1,5-diene. The product isolated after the reaction of π-allylnickel tetrabromoaluminate with cyclo-octa-1,5-diene is the complex[23] $\pi\text{-}C_3H_5\cdot Ni\cdot C_8H_{12}\cdot AlBr_4$, which is not catalytically active. In the case of a catalyst system containing Ni:P:Al = 1:1:2, blockage can be effected with a further equivalent of phosphine.

Our experience indicates that this directing influence on the dimerization depends only on the nature (*i.e.* the basicity) of the phosphine. The structure of the dimers formed is not affected by modification of the allyl group or of the Lewis acids used for complex formation with the halide ion.

This method permits the first technically simple preparation of 2,3-dimethylbutenes from the cheap raw material propylene. It provides a technically convenient route to 2,3-dimethylbuta-1,3-diene, which was important some 50 years

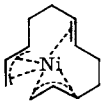
[42] *H. Zimmermann*, Diploma Thesis, Technische Hochschule Aachen 1965.

[43] *G. Wilke* and *B. Bogdanović*, unpublished work; see also [35].

ago, but has since then disappeared from the market because of the excessive cost of production.

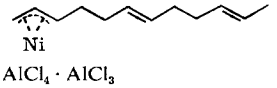
In the pilot plant at our Institute, we have carried out the continuous dimerization of propylene with the new catalysts on a scale of up to 1 ton/24 h. The catalyst used in this work was obtained by a somewhat different method [cf. the cyclotrimerization of butadiene on nickel(0)]: $NiCl_2$ is reduced with $Al(C_2H_5)_3$ in the presence of butadiene; this leads to the formation of the intermediate *(1)* of the cyclotrimerization. The excess of butadiene is removed, and the bis-($\pi$-allyl) system is cleaved with HCl, the diethylaluminum chloride being simultaneously converted into aluminum trichloride. The

$$NiCl_2 + 3\ C_4H_6 + 2\ Al(C_2H_5)_3 \xrightarrow{-2\cdot C_2H_5}$$



$$+\ 2\ (C_2H_5)_2AlCl \xrightarrow{+5\ HCl}$$

*(1)*



$$+\ 4\ C_2H_6$$

$AlCl_4 \cdot AlCl_3$

desired phosphine is added, and the resulting catalyst solution is pumped, together with liquid propylene, into a reactor, from the head of which the product is taken off.

Up to 30000 molecules of propylene (depending on its purity) could be dimerized per nickel atom. An idea of the results obtained in the laboratory and in the pilot plant can be gained from Table 3. Note particularly the considerable reaction rate.

Table 3. Dimerization of propylene with a catalyst based on $C_{12}H_{19}NiAl_2Cl_7$ and a phosphine.

| Pressure [atm] | Temp. [°C] | Throughput [kg $C_3H_6$/g Ni/hour] | Product $C_6$ [%] | Product $>C_6$ [%] |
|---|---|---|---|---|
| 1 | −15 to −20 | 6.25 | 95.5 | 5.4 |
| 4.5–5 | +35 to +40 | 13 | 89.0 | 11.0 |

As a final example of catalytic processes, we mention the polymerization of butadiene with $\pi$-allylnickel halides, which must also be activated with Lewis acids. Butadiene is polymerized very rapidly by $\pi$-allylnickel tetrabromoaluminate, and the product consists mainly of 1,4-*trans*-polybutadiene, together with some 1,2-polybutadiene. The polymerization can be directed. A combination of the catalyst with tricyclohexylphosphine converts butadiene mainly into 1,4-*cis*-polybutadiene. The course of the reaction also depends on the solvent.

## 7. Comparison of Cyclopentadienylmetal and Allylmetal Systems

Allyl-transition metal systems have sometimes been compared with cyclopentadienyl-transition metal systems. Qualitatively there are undoubtedly distinct similarities, but many of the results described above indicate considerable quantitative differences between the two systems. Cyclopentadienylmetal systems are generally characterized by significant stabilities, and hence by low catalytic activities; this is true even if one ignores the extreme case of ferrocene. Allylmetal systems, on the other hand, are not very stable; this property, although a disadvantage from the point of view of synthesis, is of the utmost importance to the high catalytic activity of these complexes. The properties of allylmetal compounds evidently lie between those of stable cyclopentadienylmetal compounds and those of alkyl compounds of transition metals, most of which, if they exist at all, are extremely unstable. The higher stability of the allyl-transition metal compounds may be due to the type of bonding, which is characteristic of the cyclopentadienylmetal compounds; in catalytic processes, however, the transition to the $\sigma$-bonded allyl system, *i.e.* formally to the alkyl-transition metal system, is often important. This intermediate position of the allylmetal compounds is evidently due *inter alia* to two factors: 1. The delocalization energy of the allyl anion according to the HMO theory[44] (0.828$\beta$) is considerably lower than that of the cyclopentadienyl anion (2.472$\beta$), so that the transition to the $\sigma$-bonded system requires much less energy. This takes into account only the ligands, any interactions between these and the metal being disregarded. 2. It was shown for two examples that the catalytic reactions of 1,3-diolefins appear to be associated with a constant change of the oxidation state of the catalyst metal ($Ni^0 \rightleftarrows Ni^{II}$ and $Cr^I \rightleftarrows Cr^{III}$).

However, "redox processes" of this type can take place only if the electron affinities of the metal and the ligand are of roughly the same order of magnitude, so that electrons can easily pass back and forth between the two. This condition seems to be satisfied by the allyl group, but not by the cyclopentadienyl group (high electron affinity). In this connection, the reader is referred to calculations[44] based on the HMO theory, in which the mutual repulsion of the electrons is ignored, and which show that no resonance energy is gained by the transition from the allyl radical to the allyl anion, since the extra electron occupies a non-bonding orbital. In the corresponding transition of the cyclopentadienyl system, on the other hand, the extra electron is accomodated in a bonding orbital, so leading to a gain in resonance energy. Thus the cyclopentadienyl radical has very pronounced electron acceptor properties in relation to metals, whereas the allyl radical does not.

*We are very grateful to Prof. K. Ziegler for the generous support provided for this work, and to Dr. E. G. Hoffmann, Dr. D. Henneberg, and Dr. G. Schomburg, as well as to their co-workers, for the recording and discussion of numerous infrared and proton resonance spectra, mass spectra, and gas chromatograms.*

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German version: Angew. Chem. *78*, 157 (1966)
Translated by Express Translation Service, London

[44] *F. A. Cotton*: Chemical Applications of Group Theory. Interscience Publ., New York-London 1964, p. 133, 156.

# The Biosynthesis of Cyclitols

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*Dedicated to Professor Karl Freudenberg on the occasion of his 80th birthday*

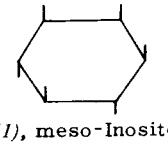
*Information has recently been obtained, mainly with the aid of radioactive compounds, about the biosynthesis of various cyclitols. It was found that the most widely occurring cyclitol, meso-inositol, is biosynthesized by a pathway probably common to all organisms, in which the cyclohexane ring is formed by ring closure between the two terminal carbon atoms of* D-*glucose. Cell-free extracts or enzyme systems that catalyse the conversion of* D-*glucose into meso-inositol can be prepared from various biological materials. The biosynthesis of the other hexahydroxycyclohexanes (inositols) involves meso-inositol as an intermediate. A few steps in the conversion of meso-inositol into other inositols have been studied.*

## A. Introduction

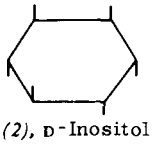
The term "cyclitol" was coined by *Micheel*[1], and denotes carbocyclic polyalcohols in which the hydroxy groups are attached to ring carbon atoms. All naturally occurring cyclitols known at present are derivatives of cyclohexane, the most important being the hexahydroxycyclohexanes or inositols.

In 1850, *Scherer*[2] isolated what he believed to be a sugar from muscle extract, and he named this substance muscle sugar or inositol. It was mainly due to the work of *Maquenne*[3] that this compound came to be recognised as hexahydroxycyclohexane. It was given the name *meso*-inositol[4], and its configuration was established almost simultaneously by two groups of workers in 1942[7,8].

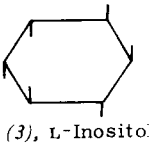
The first of the inositols to be discovered, *i.e. meso*-inositol *(1)*[9], is also the one that is most widely distributed in nature; it probably occurs in all organisms, either in the free form or attached to another residue. *Eastcott*[10] showed that *meso*-inositol is an essential constituent of the growth-promoting mixture for yeast known as "bios". It has been suggested that *meso*-inositol may act as a vitamin for mice and other mammals[11], and it is required in the nutrient medium for various strains of cell cultures of human origin[12]. The principal function of *meso*-inositol is probably to act as a building block for the phosphoinositides, the metabolic role of which has not yet been fully elucidated. These phospholipids were recently found to be involved in the adenosine triphosphate-dependent contraction of



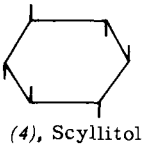
*(1)*, meso-Inositol



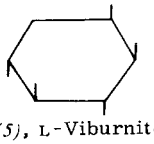
*(2)*, D-Inositol



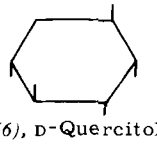
*(3)*, L-Inositol



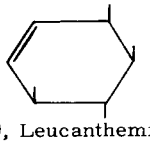
*(4)*, Scyllitol



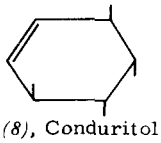
*(5)*, L-Viburnitol



*(6)*, D-Quercitol



*(7)*, Leucanthemitol



*(8)*, Conduritol

[1] *F. Micheel*, Liebigs Ann. Chem. *406*, 77 (1932).

[2] *J. Scherer*, Liebigs Ann. Chem. *73*, 322 (1850); J. prakt. Chem. *50*, 32 (1850).

[3] See *L. Maquenne*: Les sucres et leurs principaux dérivés. Gauthier-Villars, Paris 1900.

[4] Of the nine stereoisomeric hexahydroxycyclohexanes, seven are optically inactive and could therefore be denoted by the prefix *meso*. Although many workers in this field welcomed the suggestion that the substance formerly known as *meso*-inositol should now be called *myo*-inositol [5], this name and the systematic cyclitol nomenclature proposed by the same authors has been generally adopted. The nomenclature of the cyclitols is at present being reviewed by a sub-group of the International Nomenclature Commission for Biochemical Compounds. In the present paper we have used the nomenclature employed in the excellent monography by *Posternak* [6].

[5] *H. G. Fletcher, L. Anderson*, and *H. Lardy*, J. org. Chemistry *16*, 1238 (1951).

[6] *T. Posternak*: Les cyclitols. Hermann, Paris 1962.

[7] *T. Posternak*, Helv. chim. Acta *25*, 746 (1942).

[8] *G. Dangschat* and *H. O. L. Fischer*, Naturwissenschaften *30*, 146 (1942).

[9] Although the cyclitols should be shown in the chair form, the hexagonal form is used here for the sake of claityr.

[10] *E. V. Eastcott*, J. physic. Chem. *32*, 1094 (1928).

[11] See, *e.g.*, *D. W. Woolley*, J. biol. Chemistry *136*, 113 (1940); *139*, 29 (1941); J. exp. Med. *75*, 277 (1942).

[12] *H. Eagle, B. Agranoff*, and *E. E. Snell*, Science (Washington) *123*, 845 (1956); *H. Eagle, V. Oyama, M. Levy*, and *A. E. Freeman*, J. biol. Chemistry *226*, 191 (1957); *R. P. Geyer* and *R. S. Chang*, Proc. Soc. exp. Biol. Med. *95*, 315 (1957).

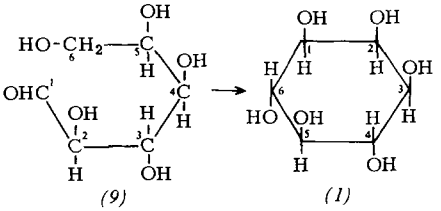
the mitochondria[13]. In general, it must be assumed that cells and organisms requiring *meso*-inositol as a growth promoter or as a vitamin are themselves incapable of producing enough of this substance for the formation of the phosphoinositides.

In higher plants and *e.g.* in bird erythrocytes, *meso*-inositol also occurs as phytic acid (the hexaphosphate of *meso*-inositol) or as salts of this acid. Monomethyl and dimethyl ethers of *meso*-inositol are found in some higher plants and occasionally in the animal kingdom[14].

In contrast to the wide distribution of *meso*-inositol and many of its derivatives, the occurrence of the optically active inositols [D-inositol *(2)* and L-inositol *(3)*] and their methyl ethers [D-pinitol, L-quebrachitol, and L-pinitol] is confined to a few plant families. Scyllitol *(4)* has also been detected both in plants and in animals. Of the cyclitols that are not isomeric with *meso*-inositol and are not derived from an isomer, algae and mussels contain two *C*-methylinositols, mytilitol, and laminitol, while higher plants contain two pentahydroxycyclohexanes, L-viburnitol *(5)*, and D-quercitol *(6)*, and two tetrahydroxycyclohexenes, leucanthemitol *(7)* and conduritol *(8)*.

## B. Biosynthesis of meso-Inositol

*Maquenne* believed that there was a biogenetic relationship between *meso*-inositol and the simple monosaccharides. He pictured the formation of *meso*-inositol as resulting from a kind of aldol condensation between the two ends of a monosaccharide[15]. Since *meso*-inositol has the same configuration as D-glucose *(9)* for four successive carbon atoms, it could be formed by internal aldol condensation of this sugar[16]. As will be shown below, this picture actually appears to fit the facts.



*(9)* *(1)*

The principal techniques used in the study of the biosynthesis of *meso*-inositol are single and multiple labelling with isotopes, the mutant-block method, and kinetic investigations. Radioactive labelling has been used in nearly all the work carried out so far in this field, both with whole organisms and with cell homogenates or enzyme preparations.

According to *Fernandez et al.*[17], D-glucose and its phosphates can be converted into *meso*-inositol by apricot leaves under the influence of ultraviolet radiation. The same authors[18] described an enzyme, "cyclase", which was isolated from the same material and which was reported to bring about the synthesis of *meso*-inositol from D-glucose and from D-glucose phosphates. However, it must be regarded as unlikely that the low conversions involved (less than 1 % for whole plant tissues and even lower for enzyme preparations) should be detectable by a simple colorimetric method, *i.e.* without the use of paper chromatography and without radioactive labelling.

### I. Preliminary Tests Using $^{14}CO_2$ and [$^{14}$C]-D-Glucose

The formation of *meso*-inositol from $^{14}CO_2$ by photosynthesis was first studied in gramineae[19] and leguminosae[20]; 0.07 % of the total radioactivity was incorporated in these experiments. In later work on *Petroselinum*[21], *Pisum sativum*[22] and *Chrysanthemum leucanthemum*[23], much higher activity yields were obtained, the value in the last case being up to 3.5 %. Experiments of this kind give no information about the route followed in the synthesis; they do, however, show the principal sites of biosynthesis, and they also facilitate the choice of plants.

The postulated vitamin function of *meso*-inositol for many animals raises the question of whether the formation of *meso*-inositol in animal tissue is due to biosynthesis in the tissue itself, or is caused by microorganisms. *Halliday* and *Anderson*[24] injected a solution of labelled D-glucose into the leg muscle of rats, and were subsequently able to isolate *meso*-inositol from the whole bodies of the rats with a radiochemical yield of 0.07 %. A similar experiment in which a solution of [u-$^{14}$C]-D-glucose was introduced into the chorion of hens' eggs, which had been pre-incubated for 7 days, led in 64 hours to a 0.01 % incorporation into *meso*-inositol[25]. Human cell cultures (HeLa and KB) that require *meso*-inositol as a growth promoter can synthesize *meso*-inositol from [u-$^{14}$C]-D-glucose. The same is true of mouse fibroblasts, which do not require *meso*-inositol as a growth promoter[26]. In experiments with rats that had been reared germ-free, *meso*-inositol was biosynthesized from labelled D-glucose[27]; 0.03 to 0.08 % of the activity of the D-glucose was built into *meso*-inositol within 3 to 6 hours. This proves that it is the animal tissue, and not the intestinal microflora, that is responsible for the biosynthesis of the *meso*-inositol. In male rats most of the cyclitol is synthesized in the testicle, according to *Eisenberg* and *Bolden*[28].

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[13] *P. V. Vignais, P. M. Vignais*, and *A. L. Lehninger*, J. biol. Chemistry *239*, 2011 (1964); *P. M. Vignais, P. V. Vignais*, and *A. L. Lehninger, ibid. 239*, 2022 (1964).

[14] *D. Ackermann* and *G. Hoppe-Seyler*, Hoppe-Seylers Z. physiol. Chem. *336*, 1 (1964).

[15] See [3], p. 189.

[16] *H. O. L. Fischer*, Harvey Lectures *40*, 156 (1945).

[17] *O. Fernandez, G. Izquierdo*, and *E. Martinez*, Farmac. nueva (Madrid) *9*, 563 (1944).

[18] *O. Fernandez, M. de Mingo*, and *E. Martinez*, Farmac. nueva (Madrid) *10*, 541 (1945).

[19] *K. E. Richardson* and *B. Axelrod*, Plant Physiol. *32*, 334 (1957).

[20] *E. A. Moscatelli* and *J. Larner*, Arch. Biochem. Biophysics *80*, 26 (1959).

[21] *R. Scholda, G. Billek*, and *O. Hoffmann-Ostenhof*, Hoppe-Seylers Z. physiol. Chem. *335*, 180 (1964).

[22] *J. N. Ahuja*, Ph. D. Thesis, Michigan State Univ., East Lansing, 1962.

[23] *H. Kindl*, unpublished work.

[24] *J. W. Halliday* and *L. Anderson*, J. biol. Chemistry *217*, 797 (1955).

[25] *W. H. Daughaday, J. Larner*, and *C. Hartnett*, J. biol. Chemistry *212*, 869 (1955).

[26] *H. Eagle, B. W. Agranoff*, and *E. E. Snell*, J. biol. Chemistry *235*, 1891 (1960).

[27] *N. Freinkel* and *R. M. C. Dawson*, Biochem. J. *81*, 250 (1961).

[28] *F. Eisenberg, Jr.* and *A. H. Bolden*, Nature (London) *202*, 599 (1964).

## II. Incorporation of the Carbon Atoms of D-Glucose into meso-Inositol

In addition to the direct cyclization of D-glucose, there are other biosynthetic routes to be considered, the most important being the formation of *meso*-inositol from two or more smaller fragments. Since evidence for such a mechanism was obtained by *Charalampous* [29] is his work on the biosynthesis of *meso*-inositol in the yeast *Candida utilis*, attempts have been made to distinguish between biosynthesis from smaller components and direct cyclization of D-glucose. These attempts were based on the assumption that in direct cyclization all the carbon atoms of the sugar should be incorporated into *meso*-inositol to the same extent, whereas differences in the extent of incorporation should point to synthesis from fragments.

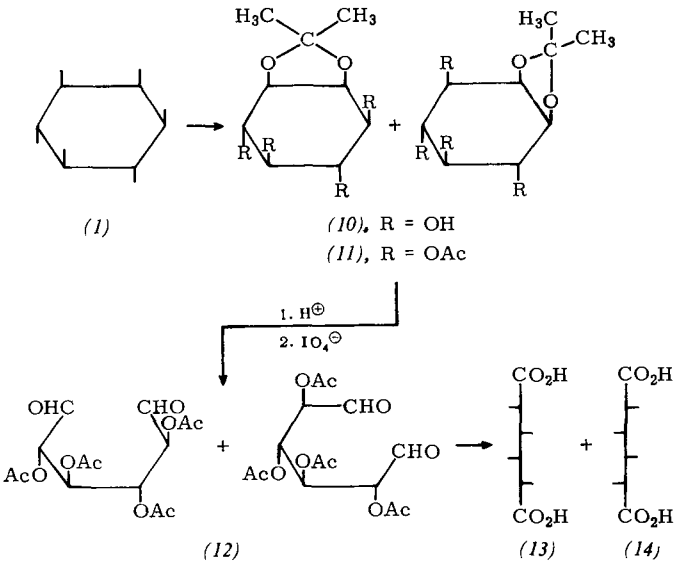
Experiments of this nature with [1-$^{14}$C]-D-glucose, [2-$^{14}$C]-D-glucose, and [6-$^{14}$C]-D-glucose on various subjects gave different results. While *Posternak et al.* [30] and *Imai* [31] observed approximately equal incorporation of the carbon atoms 1, 2, and 6 in rats, *Hauser* and *Finelli* [32] reported that in sections of rat kidney tissue, conversion into *meso*-inositol was 1.8 to 2.4 times as great for [1-$^{14}$C]-D-glucose and [2-$^{14}$C]-D-glucose as for [6-$^{14}$C]-D-glucose. *Charalampous* also found a difference in the case of *Candida utilis* [29]. However, it is doubtful whether the last result can be taken as evidence for the fragmentation of D-glucose before incorporation into *meso*-inositol; it must not be forgotten that both the starting material and the product are subject to metabolism in the whole organism, and even in the section.

## III. Incorporation of Selectively Labelled Precursors and Subsequent Degradation of the meso-Inositol

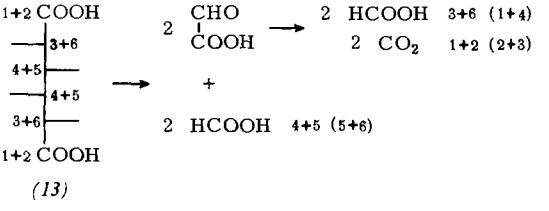
To learn more about the conversion of D-glucose into *meso*-inositol, it was necessary to carry out incorporation tests with selectively labelled D-glucose. The *meso*-inositol formed was then broken down in such a way that the radioactivity of the individual atoms could be determined. Several degradation methods were developed, and in view of their importance in the solution of the problem, we shall now consider these methods critically.

### 1. *Charalampous*' Degradation Method [29]

The *meso*-inositol is degraded to DL-idaric acid *(13)* + *(14)* by a method described by *Dangschat* [8] (Scheme 1a). Further degradation is carried out by a modification of the *Fleury-Lange* method [33] (Scheme 1b): the mixture of stereoisomers is resolved by fractional crystallization of the dibrucine salts, and each of the two sugar acids is oxidized with periodic acid to formic acid and glyoxalic acid. In Scheme 1b, the figures beside the D-idaric acid *(13)* and its oxidation products indicate the original positions of the carbon atoms in the *meso*-inositol; the corresponding figures for L-idaric acid *(14)* are given in brackets.




Scheme 1a. Degradation of *meso*-inositol to DL-idaric acid *(13)* + *(14)*.




Scheme 1b. Periodate oxidation of D- and L-idaric acids.

### 2. *Loewus* and *Kelly*'s Degradation Method [34]

Another selective degradation, using biochemical reactions, was developed by *Loewus* and *Kelly* in the study of the biosynthesis of *meso*-inositol in *Petroselinum*. [1-$^{14}$C]-D-Glucose was injected into leaves, from which *meso*-inositol was isolated two days later; the product contained 0.2% of the total radioactivity.

The labelled *meso*-inositol obtained in this way was allowed to infuse into unripe strawberries, where it was incorporated into the pectin *(16)*, which is formed there in large quantities. An enzyme of microbial origin was then used to degrade the pectin to D-galacturonic acid *(17)*, which was purified by ion-exchange chromatography (gradient elution) [35]. The D-galacturonic acid was reduced with sodium borohydride to L-galactonic acid *(18)*, which was oxidized with permanganate [36].

[29] *F. C. Charalampous* and *P. Abrams*, J. biol. Chemistry *225*, 575 (1957); *F. C. Charalampous*, J. biol. Chemistry *225*, 585, 595 (1957).

[30] *T. Posternak*, *W. H. Schopfer*, and *B. Boetsch*, Arch. Sci. (Genève) *12*, 467 (1959).

[31] *Y. Imai*, J. Biochemistry (Tokyo) *53*, 50 (1963).

[32] *G. Hauser* and *V. Finelli*, J. biol. Chemistry *238*, 3224 (1963).

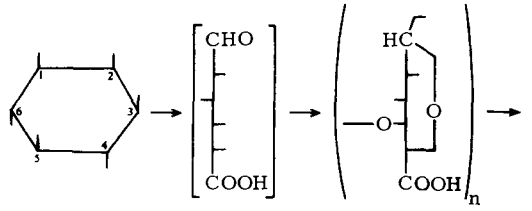
[33] *P. Fleury* and *J. Lange*, J. Pharmac. Chim. *17*, 313 (1933).

[34] *F. A. Loewus* and *S. Kelly*, Biochem. biophys. Res. Commun. *7*, 204 (1962).

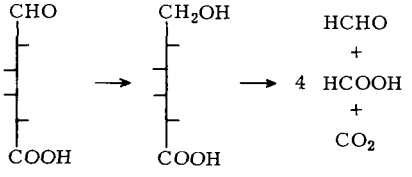
[35] *F. A. Loewus* and *S. Kelly*, Arch. Biochem. Biophys. *102*, 96 (1963).

[36] *C. G. Seegmiller*, *B. Axelrod*, and *R. M. McCready*, J. biol. Chemistry *217*, 765 (1955).

The enzymatic hydrolysis of pectin formed from [2-$^{14}$C]-*meso*-inositol gave [5-$^{14}$C]-galacturonic acid [37]; furthermore, enzymes that degrade *meso*-inositol to D-glucuronic acid occur at least in animal tissue [38] and in one micro-organism [39]. It is very probable, therefore,




*(1)* *(15)* *(16)*




*(17)* *(18)*

that the route from *meso*-inositol to pectin in strawberries involves conversion of the former into D-glucuronic acid *(15)* followed by epimerization to D-galacturonic acid. This establishes the position at which the ring opens; biosynthesis from [1-$^{14}$C]-D-glucose by the route postulated by *Maquenne* and *Fischer* should lead to [6-$^{14}$C]-*meso*-inositol, the degradation of which should proceed *via* [1-$^{14}$C]-D-glucuronic acid to yield [6-$^{14}$C]-L-galactonic acid. After periodate oxidation of the L-galactonic acid, in fact, 81% of the activity was found in the formaldehyde and 11% in the $CO_2$. This randomization of activity must be at least partly due to the biological degradation *via* pectin.

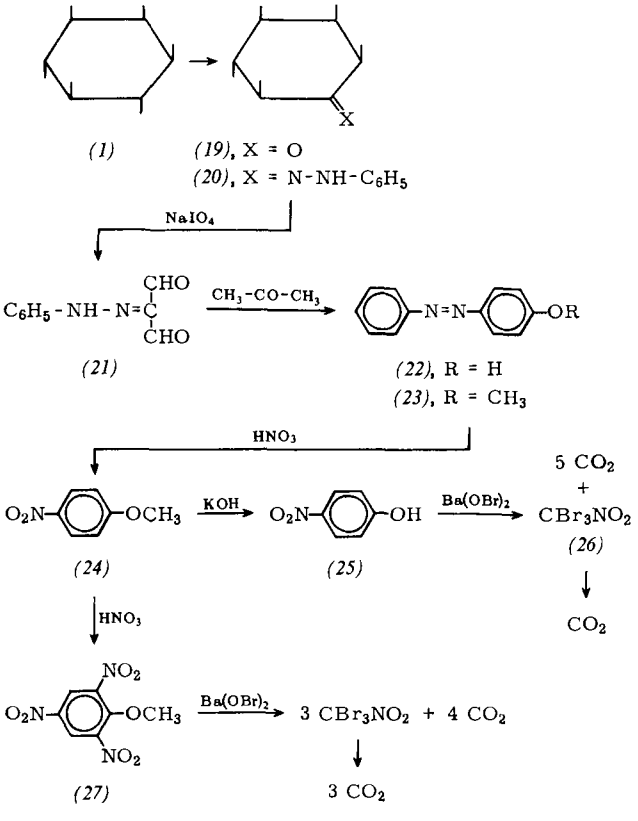
The same degradation route was used to elucidate the biosynthesis of *meso*-inositol in cell-free extracts of animal origin. *Eisenberg* and *Bolden* [40] were able to obtain homogenates from rat testicles that convert D-glucose into *meso*-inositol. These homogenates were incubated for 2 hours with labelled D-glucose. The *meso*-inositol formed was isolated and purified *via* the hexa-acetate. The L-galactonic acid *(18)* obtained by *Loewus-Kelly* degradation was converted into the amide, which gave only 3 moles of formic acid on oxidation with periodate. C-2 of the *meso*-inositol could also be determined indirectly in this way.

When [1-$^{14}$C]-D-glucose was used, 80% of the activity was found in C-6; when [2-$^{14}$C]-D-glucose was introduced, 88% of the activity was found in C-3, C-4, and C-5, and 95% in C-2, C-3, C-4, and C-5, while with [6-$^{14}$C]-D-glucose, 96% of the activity was discovered on C-1. It can be concluded from these results that the *meso*-inositol must be synthesized from D-glucose without fragmentation of the latter, as proposed by *Maquenne* and *Fischer*.

### 3. *Kindl* and *Hoffmann-Ostenhof*'s Degradation Method [42]

Another selective degradation method was developed in our own laboratory for the study of the biosynthesis of *meso*-inositol in mustard plants *(Sinapis alba)*. This method is based on chemical reactions only, and should therefore be free from any inaccuracies due to metabolic processes.

The starting substance in this method is a cyclose (inosose); since all cyclitols can be readily converted into cycloses, the method is generally applicable. In biological or catalytic oxidation ($Pt/O_2$), axial OH groups are preferentially converted into keto groups; nitric acid, on the other hand, converts *meso*-inositol into a racemic mixture of *meso*-inosose-4 and *meso*-inosose-6. The phenylhydrazone *(20)* of the cyclose [*e.g.* (±)-*epi-meso*-inosose *(19)*] is prepared and then oxidized to mesoxaldialdehyde phenylhydrazone *(21)*. To separate the central carbon atom of this $C_3$ fragment from the other two carbon atoms, *(21)* is condensed with acetone




*(1)* *(19)*, X = O; *(20)*, X = N-NH-$C_6H_5$

*(21)* *(22)*, R = H; *(23)*, R = $CH_3$

*(24)* *(25)* *(26)* *(27)*

to obtain *p*-hydroxyazobenzene *(22)*, and this is methylated and then oxidized to *p*-methoxynitrobenzene *(24)*. The *p*-hydroxynitrobenzene *(25)* obtained by demethylation of *(24)* is degraded to tribromonitromethane *(26)*, which contains the central carbon atom of the $C_3$ fragment. Its radioactivity can be measured after oxid-

[37] *F. A. Loewus*, Federat. Proc. *21*, 88 (1962).

[38] *F. C. Charalampous*, J. biol. Chemistry *235*, 1286 (1960).

[39] *A. Sivak* and *O. Hoffmann-Ostenhof*, Biochem. Z. *336*, 229 (1962); *R. Thonet* and *O. Hoffmann-Ostenhof*, Mh. Chem. *97*, 107 (1966).

[40] *F. Eisenberg, Jr.* and *A. H. Bolden*, Biochem. biophys. Res. Commun. *12*, 72 (1963).

[41] *F. Eisenberg, Jr.*, *A. H. Bolden*, and *F. A. Loewus*, Biochem. biophys. Res. Commun. *14*, 419 (1964).

[42] *H. Kindl* and *O. Hoffmann-Ostenhof*, Biochem. Z. *339*, 374 (1964); Abstr.6th intern.Congr.Biochem.NewYork 1964, p. 515.

ation to barium carbonate. If, on the other hand, the radioactivity is expected in the two outer carbon atoms of the $C_3$ fragment, the *p*-hydroxynitrobenzene *(24)* may be degraded *via* 2,4,6-trinitroanisole *(27)*.

Using this method, it was possible to show that in *Sinapis alba* [1-$^{14}$C]-D-glucose gives a *meso*-inositol (0.2% incorporation) in which the radioactivity is located on C-6 (or C-4) [42]. [2-$^{14}$C]-D-Glucose is converted into [5-$^{14}$C]-*meso*-inositol in the same plant [43].

Although *Loewus* and *Kelly*'s findings for *Petroselinum* [34] and our own findings for *Sinapis alba* [42,43] were obtained by different methods, both sets of results indicate that in higher plants, *meso*-inositol is formed by ring closure between C-1 and C-6 of D-glucose, as suggested by *Maquenne* and *Fischer*.

We have recently been able to show that [u-$^{14}$C]-*scyllo*-*meso*-inosose ([u-$^{14}$C]-*meso*-inosose-2) is incorporated into *meso*-inositol to the extent of 25% in the leaves of *Sinapis alba* and to the extent of 40% in the leaves of *Chrysanthemum leucanthemum* [44]. This suggests (but does not prove) that this cyclose may be a precursor in the synthesis of *meso*-inositol in higher plants. A cell-free extract that converts D-glucose into *meso*-inositol has been prepared from mustard plants [45].

Since the experiments on rat-testicle extracts [41], on *Petroselinum* [34], and on *Sinapis alba* [42,43] showed that in both animal tissues and higher plants, *meso*-inositol is formed from D-glucose by linkage of the terminal carbon atoms of the sugar, it was of interest to consider whether this process takes a completely different course in the yeast *Candida utilis*, as had been postulated by *Charalampous* [29].

*Chen* and *Charalampous* [46] recently obtained an enzyme preparation from *Candida utilis* that converts D-glucose and D-glucose 6-phosphate into *meso*-inositol. When the substrate is D-glucose, this reaction occurs only if adenosine triphosphate (ATP), nicotinamide adenine nucleotide (NAD), and $Mg^{2+}$ are present as cofactors; only NAD and $Mg^{2+}$ are required for the conversion of D-glucose 6-phosphate into *meso*-inositol.

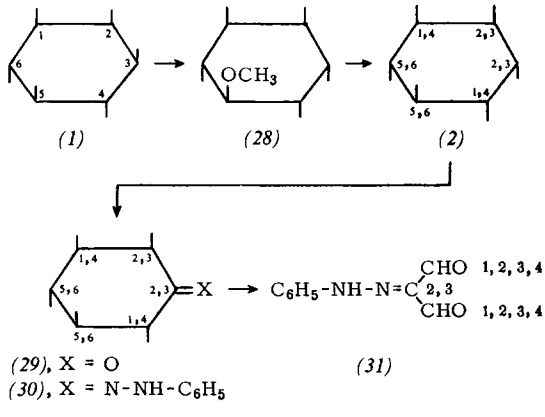
We were able to confirm these results, and we then used this enzyme preparation (with small modifications in its production) for the elucidation of the synthesis of *meso*-inositol. Using our degradation method we were able to show that the enzyme preparation converts [2-$^{14}$C]-D-glucose into [5-$^{14}$C]-*meso*-inositol [47]. Further investigations [48] using differently labelled D-glucose preparations and [1-$^{14}$C]-D-glucose 6-phosphate showed that with D-glucose 6-phosphate, the yield of *meso*-inositol was from 3 to 5 times as great as with D-glucose; moreover, the radioactivity was much less randomized in *meso*-inositol from D-glucose 6-phosphate than in that from D-glucose. This agrees with the results obtained by *Chen* and *Charalampous* [46], and indicates that D-glucose 6-phosphate or a substance formed from it is closer to *meso*-inositol in the biosynthetic pathway than D-glucose itself.

The *meso*-inositol obtained from [1-$^{14}$C]-D-glucose 6-phosphate was degraded *via* mesoxaldialdehyde phenylhydrazone *(21)* and *p*-hydroxynitrobenzene *(25)* (Table 1); 96% of the activity could be traced in this way

Table 1. Distribution of radioactivity in the degradation products of *meso*-inositol synthesized from [1-$^{14}$C]-D-glucose 6-phosphate (A) or [6-$^{14}$C]-D-glucose (B) with enzyme preparations from *Candida utilis* [48]; cf. Scheme 3.

| Compound | Relative specific activity [*(22)* = 1.00] | |
|---|---|---|
| | A | B |
| (±)-*epi*-*meso*-Inosose *(19)* | 2.17 | — |
| *scyllo*-*meso*-Inosose | — | 1.06 |
| (±)-*epi*-*meso*-Inosose phenylhydrazone *(20)* | 2.10 | — |
| *scyllo*-*meso*-Inosose phenylhydrazone | — | 1.03 |
| Mesoxaldialdehyde phenylhydrazone *(21)* | 1.06 | 0.97 |
| *p*-Hydroxyazobenzene *(22)* | 1.00 | 1.00 |
| *p*-Methoxyazobenzene *(23)* | 1.06 | 0.98 |
| *p*-Methoxynitrobenzene *(24)* | 1.06 | 0.96 |
| *p*-Hydroxynitrobenzene *(25)* | 1.14 | — |
| 2,4,6-Trinitroanisol *(27)* | — | 1.01 |
| $BaCO_3$ from C-1 of *(25)* | 1.06 | — |
| $BaCO_3$ from C-2 and C-6 of *(25)* | 0.02 | — |
| $BaCO_3$ from C-4 of *(27)* | — | 0.08 |
| $BaCO_3$ from C-3 and C-5 of *(27)* | — | 0.98 |

to C-6 or C-4 of the *meso*-inositol. To distinguish between these positions, another variant of the degradation method was used. The *meso*-inositol obtained from sugar phosphate labelled on C-1 was infused into the leaves of *Trifolium incarnatum*, which converts *meso*-inositol into D-pinitol *(28)* (4-*O*-methyl-D-inositol) [49]. The D-pinitol was isolated and demethylated to D-inositol *(2)*, and this was then oxidized to *meso*-inosose-3 *(29)*. On periodate oxidation, the phenylhydrazone *(3)* of this inosose yields the fragment mesoxaldialdehyde phenylhydrazone *(31)*, which represents C-1, C-2, C-3, and C-4 of the original *meso*-inositol.




*(1)* *(28)* *(2)*

*(29)*, X = O
*(30)*, X = N-NH-$C_6H_5$

*(31)*

In the degradation of the *meso*-inositol obtained from [1-$^{14}$C]-D-glucose 6-phosphate, this fragment *(31)* was inactive. This, together with the findings reported above proves that C-1 of the D-glucose 6-phosphate becomes C-6 of the *meso*-inositol.

The *meso*-inositol obtained from [6-$^{14}$C]-D-glucose was degraded *via meso*-inosose-2, mesoxaldialdehyde phenyl-

[43] *H. Kindl* and *O. Hoffmann-Ostenhof*, Mh. Chem. *95*, 548 (1964).

[44] *H. Kindl*, unpublished work.

[45] *J. Biedl-Neubacher* and *H. Kindl*, unpublished work.

[46] *I. W. Chen* and *F. C. Charalampous*, Biochem. biophys. Res. Commun. *12*, 62 (1963); J. biol. Chemistry *239*, 1905 (1964).

[47] *J. Neubacher*, *H. Kindl*, and *O. Hoffmann-Ostenhof*, Biochem. J. *92*, 56P (1964).

[48] *H. Kindl*, *J. Biedl-Neubacher*, and *O. Hoffmann-Ostenhof*, Biochem. Z. *341*, 157 (1965).

[49] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Biochem. J. *89*, 31P (1963).

hydrazone *(21)*, and 2,4,6-trinitroanisole *(27)*. The radioactivity was located on C-1 (or C-3) (Table 1).

Thus it has been shown that C-1 of the D-glucose becomes C-6 of the *meso*-inositol, C-2 of the D-glucose becomes C-5 of the *meso*-inositol, and C-6 of the D-glucose becomes C-1 (or C-3) of the *meso*-inositol. There can therefore be little doubt that the biosynthesis of *meso*-inositol in *Candida utilis* also proceeds by direct ring closure between the ends of the sugar molecule. This seems to prove that this pathway is the general route for the biosynthesis of *meso*-inositol. Moreover, *Chen* and *Charalampous* [50] recently deduced the same reaction mechanism from new experiments with their enzyme preparation from *Candida utilis*, and consequently withdrew their earlier conclusions [29].

### IV. The Mechanism of Ring-Closure

Since NAD takes part in the reaction, a redox step should be involved. On grounds of analogy, the ring closure could proceed by an aldol or an acyloin condensation.

Experiments with the enzyme preparation from *Candida utilis* in $^3H_2O$ appear to rule out the possibility of an acyloin condensation. Incorporation experiments with [6-$^3H_2$,6-$^{14}$C]-D-glucose, both in whole plants and with the enzyme extract from *C.utilis*, led to a change in the $^3H/^{14}C$ ratio, which points to an aldol condensation [50a].

*Chen* and *Charalampous* [50b] recently reported the accumulation of *meso*-inositol 1-phosphate from systems of low $Mg^{2+}$ content with the enzyme preparation from *C.utilis*; this phosphate is thought to be an intermediate in the synthesis of *meso*-inositol.

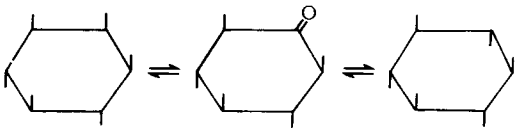
Thus the most likely route for the conversion of D-glucose into *meso*-inositol is as follows (intermediates that have not yet been isolated are printed in brackets):

D-glucose → D-glucose 6-phosphate → [5-keto-D-glucose 6-phosphate] → [1-phospho-*meso*-inosose-2] → *meso*-inositol 1-phosphate → *meso*-inositol.

## C. Biosynthesis of the other Hexahydroxycyclohexanes and their Methyl Ethers

### I. Scyllitol

Since the ingestion of large quantities of *meso*-inositol in the food leads to marked scyllitoluria in human beings, *Helleu* [51] suggested that *meso*-inositol may be converted into scyllitol *(4)* in the body. This was confirmed for rats by experiments with labelled precursors [52]; an equilibrium between the two cylitols evidently exists in the organism, with *meso*-inosose-2 *(31)* as an intermediate. Labelled *meso*-inositol is converted into scyllitol *(4)* in the rat, and labelled scyllitol is converted into *meso*-inositol. When labelled *meso*-inosose-2 *(31)* was introduced, the activity was transferred in varying proportions to both the *meso*-inositol and the scyllitol; the radiochemical yields for *meso*-inositol varied between 2.9 and 12.3 %, while that for scyllitol varied between 0.9 and 46.1 %.



*(1)* *(31)* *(4)*

Similar relationships seem to exist in plants containing scyllitol. When radioactive *meso*-inositol was infused into the leaves of *Calycanthus occidentalis*, the extent to which it was incorporated into scyllitol was almost two orders of magnitude greater than the extent of incorporation of labelled D-glucose [53]; approximately 8 % of *meso*-inosose-2 *(31)* was converted into *meso*-inositol, and 30 % into scyllitol. However, these processes appear to depend on the season; thus incorporation into scyllitol is observed only in spring, while in autumn only the *meso*-inositol becomes radioactive.

### II. D-Inositol and D-Pinitol

We have recently studied the biosynthesis of D-inositol *(2)* and of D-pinitol *(28)* in *Trifolium incarnatum*. This plant was known to contain D-pinitol [54], and small quantities of *meso*-inositol, D-inositol, and sequoyitol (5-*O*-methyl-*meso*-inositol) had also been detected by paper chromatography [49,55]. Labelled D-glucose, D-galactose, and *meso*-inositol were introduced into the plant to find whether it possesses special biosynthetic pathways for D-inositol and D-pinitol, or whether both are formed from *meso*-inositol [55,56]. *Meso*-inositol was incorporated into D-pinitol to a greater extent than was the monosaccharide, *i.e.* *meso*-inositol or a substance formed from it is a direct precursor of the D-pinitol.

The individual steps of the route leading from *meso*-inositol to D-pinitol have also been elucidated [57,58].

[50] *J. W. Chen* and *F. C. Charalampous*, Biochem. biophys. Res. Commun. *17*, 521 (1964).

[50a] *H. Kindl* and *J. Biedl-Neubacher*, unpublished work.

[50b] *J. W. Chen* and *F. C. Charalampous*, Biochem. biophys. Res. Commun. *19*, 144 (1965).

[51] *C. Helleu*, Bull. Soc. Chim. biol. *39*, 633 (1957).

[52] *T. Posternak*, *W. H. Schopfer*, *B. Kaufmann-Boetsch*, and *S. Edwards*, Helv. chim. Acta *46*, 2676 (1963).

[53] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Hoppe-Seylers Z. physiol. Chem. *339*, 28 (1964).

[54] *V. Plouvier*, C. R. hebd. Séances Acad. Sci. Paris *230*, 125 (1950).

[55] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Hoppe-Seylers Z. physiol. Chem. *335*, 180 (1964).

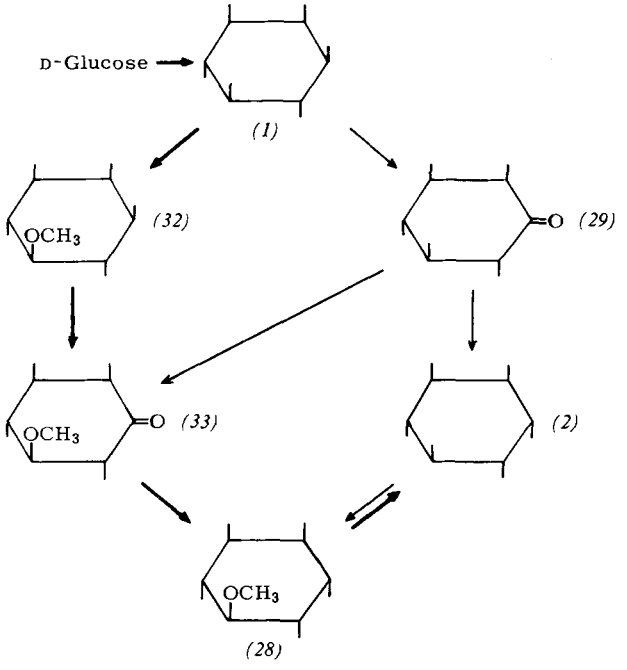
[56] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Hoppe-Seylers Z. physiol. Chem. *337*, 277 (1964).

[57] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Mh. Chem. *94*, 1311 (1964).

[58] The labelled D-pinitol and sequoyitol preparations used in these investigations were obtained by photosynthesis with $^{14}CO_2$ in the same plant; labelled D-inositol was prepared by demethylation of D-pinitol. The biosynthesized radioactive sequoyitol could be converted in good yield into 5-*O*-methyl-*meso*-inosose-3 by catalytic oxidation with air [59].

[59] *K. Heyns* and *H. Paulsen*, Chem. Ber. *86*, 833 (1953); *L. Anderson* and *G. Post*, Abstr. 124th Meeting Amer. chem. Soc. 1958, p. 12D.

Labelled *meso*-inositol is partly incorporated into D-inositol and sequoyitol. Either of these two cyclitols could thus be an intermediate in the conversion of *meso*-inositol into D-pinitol, but each would rule the other out.




Scheme 2. Possible routes for the synthesis of cyclitols in *Trifolium incarnatum*.

It was therefore necessary to decide whether the methyl group enters the molecule before, during, or after the epimerization, *i.e.* whether the substrate for the methylation is *meso*-inositol, *meso*-inosose-3 *(29)*, or D-inositol *(2)*.

Table 2. Incorporation of labelled compounds into D-inositol and D-pinitol in the leaves of *Trifolium incarnatum* [55—57].

| Precursor | Incorporation [%] into | |
|---|---|---|
| | D-pinitol | D-inositol |
| D-Glucose | 0.72 | — |
| D-Galactose | 0.52 | — |
| *meso*-Inositol | 14.2 | 2.1 |
| D-Inositol | 0.1 | (80.7) |
| Sequoyitol | 72.8 | — |
| 5-*O*-Methyl-*meso*-inosose-3 | 31.2 | 6.9 |
| *meso*-Inosose-3 | 1.75 | 50.2 |
| D-Pinitol | (25.8) | 5.9 |

It can be seen from Table 2 and Scheme 2 that labelled D-inositol is not incorporated into D-pinitol. On the other hand, both sequoyitol *(32)* and 5-*O*-methyl-*meso*-inosose-3 *(33)* are converted into D-pinitol in excellent yields. Moreover, when labelled D-pinitol is introduced into the plant, it undergoes partial demethylation to form D-inositol. This establishes the biogenetic relationships of the cyclitols in *Trifolium incarnatum* as those indicated by the heavy arrows in Scheme 2.

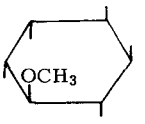
The enzyme system that catalyses the epimerization of sequoyitol to D-pinitol[60] seems to consist of two specific oxidoreductases, the actions of which can be represented by the equations:

sequoyitol + NAD ⇌ 5-*O*-methyl-*meso*-inosose-3 + NADH+H$^+$

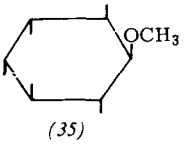
5-O-methyl-*meso*-inosose-3 + NADPH + H$^+$ ⇌ D-pinitol + NADP

### III. L-Inositol, L-Pinitol, and L-Quebrachitol

Experiments on the biosynthesis of L-inositol *(3)* and its methyl ethers have been carried out on two types of *Artemisia*. The common mugwort *(Artemisia vulgaris)* contains L-quebrachitol *(35)*[61]; L-inositol and traces of L-pinitol have also been detected by paper chromatography[62]. In tarragon *(A.dracunculus)*, on the other hand, the most abundant of the cyclitols is L-pinitol *(34)*[61], while L-inositol, L-quebrachitol, and sequoyitol




*(34)*




*(35)*

are also present in varying amounts[62]. When labelled *meso*-inositol is infused into the leaves of both plants, the quantities of radioactive cyclitols found are much larger than after the introduction of labelled D-glucose (Table 3). This suggests that *meso*-inositol or a substance derived from it is an intermediate in the synthesis of L-inositol and its methyl ether. As in the work on the

Table 3. Incorporation of labelled compounds into the cyclitols of *Artemisia vulgaris* and *Artemisia dracunculus* after infusion into the leaves of these plants [62, 63].

| Precursor | Incorporation into | [%] |
|---|---|---|
| *Artemisia vulgaris* | | |
| D-Glucose | *meso*-Inositol | 0.027 |
| | L-Inositol | 0.018 |
| | L-Quebrachitol | 0.27 |
| *meso*-Inositol | L-Inositol | 0.82 |
| | L-Quebrachitol | 13.6 |
| L-Inositol | L-Quebrachitol | 12.4 |
| *Artemisia dracunculus* | | |
| D-Glucose | *meso*-Inositol | 0.02 |
| | L-Inositol | 0.035 |
| | Sequoyitol | 0.02 |
| | L-Pinitol | 0.17 |
| *meso*-Inositol | L-Inositol | 1.31 |
| | Sequoyitol | 1.60 |
| | L-Pinitol | 1.62 |
| Sequoyitol | L-Pinitol | 0.05 |
| L-Inositol | L-Pinitol | 8.04 |

biosynthesis of D-pinitol, the route from *meso*-inositol to the two L-inositol methyl ethers was studied with the aid of labelled forms of the likely intermediates[63]. In contrast to the formation of D-pinitol in *Trifolium*, the epimerization precedes the methylation in the formation

[60] *G. J. Kremlicka*, and *O. Hoffmann-Ostenhof*, Hoppe-Seylers Z. physiol. Chem., in press.

[61] *V. Plouvier*, Ann. pharmac. franc. *7*, 192 (1949); C. R. hebd. Seances Acad. Sci. Paris *243*, 1913 (1956).

[62] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Mh. Chem. *95*, 541 (1964).

[63] *R. Scholda*, *G. Billek*, and *O. Hoffmann-Ostenhof*, Mh. Chem. *95*, 1305 (1964).

of L-inositol methyl ethers; in both types of *Artemisia*, labelled L-inositol *(3)* is incorporated into the corresponding methyl ether in a high radiochemical yield (Table 3).

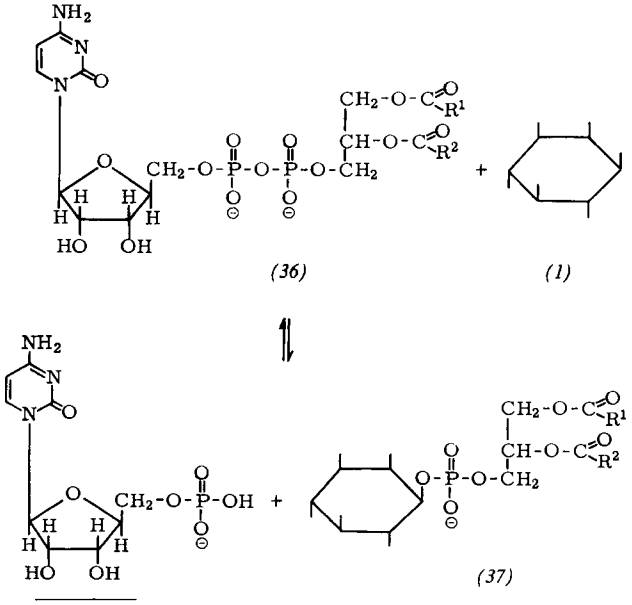
As for the biosynthesis of D-pinitol in *Trifolium*, these results indicate that both types of *Artemisia* contain an epimerase system consisting of two dehydrogenases, and that this enzyme system attacks the *meso*-inositol directly and converts it *via* *meso*-inosose-1 into L-inositol, which is then methylated, as also appears to be proved by the fact that sequoyitol is not incorporated into L-pinitol in *A. dracunculus*.

Thus it seems that the naturally occurring isomers of *meso*-inositol and their methyl ethers are not biosynthesized by independent routes. The first step in every case appears to be the cyclization of D-glucose; only after *meso*-inositol or a very close precursor of the latter has been formed, further rearrangement to give the isomers of *meso*-inositol takes place. No evidence has ever been found to suggest the formation of such a substance directly from D-glucose or from any other monosaccharide, although ring closures of this nature would be feasible.

## D. Phosphorylated Derivatives of meso-Inositol

### I. Phosphoinositides[64]

The route by which *meso*-inositol is incorporated into the phosphoinositides has now been largely established. It is known that this process does not involve *meso*-inositol phosphates as intermediates, although such substances can be detected in the organism[65]. In the synthesis of phosphoinositides, a cytidine diphosphate diglyceride [CDP diglyceride *(36)*] is first formed from phosphatidic acid and cytidine triphosphate (CTP);



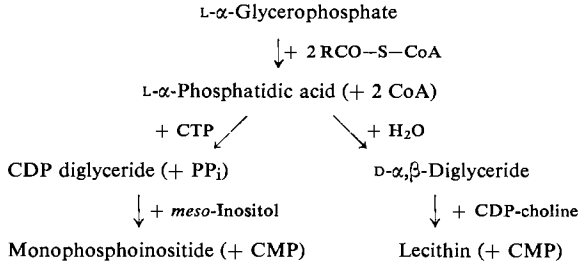
*(36)* *(1)*



*(37)*

this then reacts with free *meso*-inositol to form the monophosphoinositide *(37)* with loss of cytidine monophosphate (CMP). The enzymes responsible for this series of reactions are known[66].

Thus the synthesis of the phosphoinositides is different from that of phospholipids containing nitrogen. In the formation of lecithins and cephalins, the nitrogen bases choline and ethanolamine (the position of which in the phospholipid molecule is formally analogous to that of *meso*-inositol) are first phosphorylated, and the products then react with CTP to form CDP-choline and CDP-ethanolamine, respectively. α,β-Diglyceride, which is formed by hydrolysis of phosphatidic acid, reacts with both compounds to form lecithin and cephalin, with loss of CDP. The enzymes responsible for these reactions are also known[67]. The syntheses of phosphoinositides and lecithins are compared in Scheme 3.




Scheme 3. Biosyntheses of phosphoinositides and of lecithin.

The higher phosphoinositides (diphospho- and triphosphoinositides) are probably formed by stepwise phosphorylation of monophosphoinositide, the phosphate donor being ATP[68–70].

### II. Phytic Acid

Phytic acid, the hexaphosphate of *meso*-inositol, occurs mainly as its calcium and magnesium salts in higher plants, but is also present in the erythrocytes of birds and reptiles. This substance, which supposedly acts as a phosphate reserve, has been known for some time, but very little is known about its biosynthesis. According to *Ahuja*[21] and our own work[71], *meso*-inositol is incorporated into phytic acid in higher plants, but it seems that *meso*-inositol is not a direct precursor of phytic acid: [$^3$H]-*meso*-inositol is not incorporated into phytic acid as an intact unit[71].

The incorporation of radioactive phosphate into phytic acid in birds' erythrocytes proceeds very slowly in the organism[72,73]. No attempt seems to have been made so far to find whether free *meso*-inositol is a direct precursor of phytic acid in this case. Whereas the erythrocytes of mammals always con-

[64] See *G. B. Ansell* and *J. N. Hawthorne*: Phospholipids. Elsevier, Amsterdam 1964.

[65] *G. Hübscher* and *J. N. Hawthorne*, Biochem. J. *67*, 523 (1957).

[66] *H. Paulus* and *E. P. Kennedy*, J. biol. Chemistry *235*, 1303 (1960).

[67] *E. P. Kennedy* and *S. B. Weiss*, J. biol. Chemistry *222*, 193 (1956).

[68] *H. Brockerhoff* and *C. E. Ballou*, J. biol. Chemistry *237*, 49 (1962).

[69] *H. Wagner*, *Ä. Lissau*, *J. Hölzl*, and *L. Hörhammer*, J. Lipid. Res. *3*, 177 (1962).

[70] *R. B. Ellis* and *J. N. Hawthorne*, Biochem. J. *84*, 19P (1962).

[71] *H. Kindl*, unpublished work.

[72] *S. Rapoport*, *E. Leva*, and *T. M. Guest*, J. biol. Chemistry *139*, 633 (1941).

[73] *E. Gerlach*, *A. Fleckenstein*, and *K. J. Freundt*, Pflügers Arch. ges. Physiol. *263*, 682 (1957).

tain relatively large quantities of 2,3-diphosphoglyceric acid, this substance appears to be replaced by phytic acid in the red blood cells of birds.

### E. Other Naturally Occurring Cyclitols

Nothing is known as yet about the biosynthesis of the *C*-methylinositols mytilitol (1-*C*-methylscyllitol) and laminitol (6-*C*-methyl-*meso*-inositol), which occur in algae and in mussels.

Moreover, no detailed studies have been carried out on the pentahydroxycyclohexanes L-viburnitol *(5)* and D-quercitol *(6)* or on the tetrahydroxycyclohexenes leucanthemitol *(7)* and conduritol *(8)*. On phylogenetic grounds, *Plouvier*[74] postulated that in *Anthemideae*, in which L-inositol and its methyl ethers occur together with L-viburnitol and leucanthemitol, L-inositol is a precursor of the other substances. However, preliminary work in our laboratory[75] seems not to substantiate this, but indicates instead that the pentahydroxycyclohexanes are biosynthesized by a special route, which differs from that of *meso*-inositol (and hence also from that of L-inositol) at least in the last step. Labelled *meso*-inositol infused into plants containing L-viburnitol, D-quercitol, or leucanthemitol was not incorporated into these substances, although *meso*-inositol can be epimerized directly to L-inositol.

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Received: January 4th, 1965. [A 495/280 IE]
German version: Angew. Chem. *78*, 198 (1966)
Translated by Express Translation Service, London.

[74] *V. Plouvier*, Bull. Soc. Chim. biol. *45*, 1079 (1963).

[75] *H. Kindl*, unpublished work.

# The Synthesis of Oligo- and Polynucleotides

BY PROF. DR. F. CRAMER

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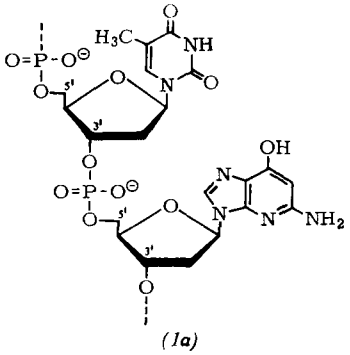
*Dedicated to Professor K. Freudenberg, one of the pioneers of the biopolymers*[1], *on his 80th birthday.*

*Problems and results of the synthesis of oligonucleotides are reviewed. The central role of the nucleic acids in biochemistry is a challenge to synthesize nucleic acids of known base sequence and chain length. Oligomers with various sequences of up to 12 members and homo-oligomers with a maximum chain length of 30 nucleotides can be obtained by chemical synthesis. The enzymatic synthesis of ribonucleic acids can be directed in such a way that polynucleotides with definite sequences are produced.*

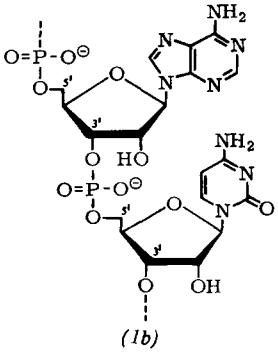
## 1. Structure and Nomenclature

Nucleic acids are mixed polyesters; two basic units are represented by the formulae *(1a)* and *(1b)*.



*(1a)*

Deoxyribonucleic acid (DNA)
Symbol: d-...pTpG...



*(1b)*

Ribonucleic acid (RNA)
Symbol: ...pApC...

The main chemical characteristic of the nucleic acids is the phosphoric ester bond (internucleotide bond), which is responsible for the sensitivity of these substances to hydrolysis. The glycosidic bond between the ribose and the nucleo-bases is acid-labile, particularly so in purine nucleosides. In synthetic work, the amino groups of cytosine and adenine, and sometimes that of guanine, must be taken into account as functional groups. Because of the hydroxy group in the 2′-position of the ribose, ribonucleic acids are particularly alkali-labile.

Abbreviated symbols are used for polynucleotides[2]. Here "p" on the left-hand side of the letter denoting the nucleoside indicates a phosphate residue in the 5′-position of the ribose,

[1] *K. Freudenberg*: Tannin, Cellulose, Lignin. Springer-Verlag Berlin 1933. – Über die blutgruppenspezifische Substanz A. Sitzungsber. Heidelberger Akad. Wiss., math.-naturw. Kl. *1940*, 9. Abhandlung. – Die Stärke *15*, 199 (1963). – High-molecular natural substances, J. Polymer Sci. *16*, 155 (1955).

[2] Terminology and Abbreviations, Tentative Rules: J. biol. Chemistry *237*, 1381 (1962).

and a "p" on the right-hand side of this letter a phosphate residue in the 3′-position. The nucleosides are represented by the following abbreviations: A = adenosine, C = cytidine, G = guanosine, T = thymidine, and U = uridine. In the case of a deoxynucleoside, a "d" is placed before the abbreviation. RNA denotes ribonucleic acid and DNA deoxyribonucleic acid.

## 2. The Problem

The role of DNA as a carrier of genetic information is well known. Only five years ago it was possible to read the following statement about the function of RNA in a review on polynucleotide syntheses [3]: "the role of RNA is still more obscure. It is known only that RNA is responsible for the synthesis of proteins by directing the synthetic process. Here, too, definite sequences of nucleotides seem to determine the synthesis of definite proteins". Meanwhile, the advance of molecular biology [4] has elucidated the functional relationships between the various types of nucleic acids and between these and the biosynthesis of the proteins (Scheme 1).

| | Function | Structural example | Localization |
|---|---|---|---|
| I. DNA | Store of genetic information | d-...pTpApGpCp... | Cell nucleus, chromosome |
| | ↓ transcription (copying) | | |
| II. RNA | Messenger, synthesis of a protein or enzyme | ...pApUpCpGp... | During replication on the DNA, and then on the ribosome |
| | ↓ translation (formation of a protein of definite sequence) | | |
| III. Protein | Enzyme or structural element of the cell | –NH–CH(R¹)–C(=O)–NH–CH(R²)–C(=O)–NH–CH(R³)–C(=O)– | |

Scheme 1. Functions of DNA and RNA in the biosynthesis of proteins.

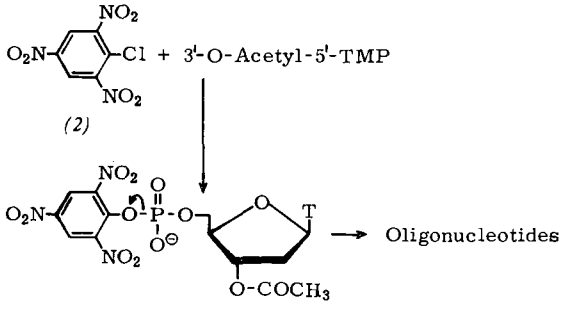
The chemical synthesis of oligo- and polynucleotides is important, since the replication and translation processes in the biosynthesis of proteins can be studied particularly well with synthetic polymers [5]. Definite oligonucleotides are also necessary for studies on base pairing and on the stability of double helices [6]. To decipher the genetic code, the trinucleotides acting as code words must be synthesized or isolated from natural material [7,8]. Determination of the direction of reading of the genetic alphabet requires polynucleotides with definite terminal triplets [7,9]. The mode of action and the specificity of enzymes which split nucleic acids can be studied on dinucleoside phosphates [10]. Oligonucleotides could be used as models for studying mutations on transforming DNA. The secondary structure of polynucleotide strands must be elucidated on relatively simple compounds. Determination of the structure and analysis of the nucleic acid sequence could be aided by the synthesis of fragments.

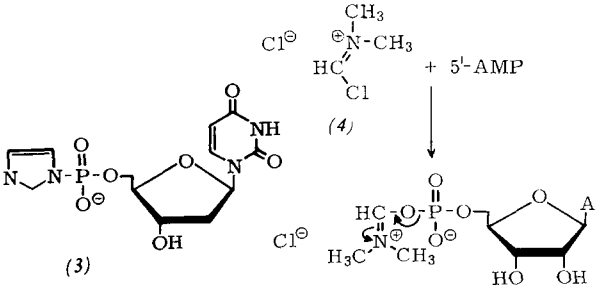
A chemical synthesis of transforming DNA, *i.e.* that containing genetic information, with at leats $10^5$ chain members exceeds human capabilities even with substantial automation of all steps. Even the synthesis of messenger-RNA with at least 500 nucleotides or that of transfer-RNA with approximately 80 chain members appears to be impossible.

## 3. Chemical Syntheses

### 3.1. Phosphorylation Reactions

The classical condensing agent in the synthesis of oligonucleotides is dicyclohexylcarbodiimide (DCC) [11,12]. In addition, numerous other reagents for the preparation of nucleotide esters or oligonucleotides have been tested and have been found to be suitable in special cases; thus, for example, acid chlorides [13,14], trichloro-




[3] *F. Cramer*, Angew. Chem. *73*, 49 (1961).

[4] Reviews in: Progress in Nucleic Acid Research and in Molecular Biology. Academic Press, New York 1963/64, Vol. I–III.

[5] See, for example: *S. Nishimura, D. S. Jones, E. Ohtsuka, H. Hayatsu, T. M. Jacob*, and *H. G. Khorana*, J. molecular Biol. *13*, 283 (1965).

[6] *H. A. Scheraga*, Lecture, Göttingen, September 1965.

[7] *F. Cramer, H. Küntzel*, and *J. H. Matthaei*, Angew. Chem. *76*, 716, 800 (1964); Angew. Chem. internat. Edit. *3*, 589 (1964).

[8] *M. Nirenberg* and *P. Leder*, Science (Washington) *145*, 1399 (1964).

[9] *S. Ochoa*, 2nd FEBS-Meeting Vienna 1965, Abstracts p. 273.

[10] *H. Witzel* and *E. A. Barnard*, Biochem. biophysic. Res. Commun. *7*, 295 (1962).

[11] *H. G. Khorana* and *A. R. Todd*, J. chem. Soc. (London) *1953*, 2257.

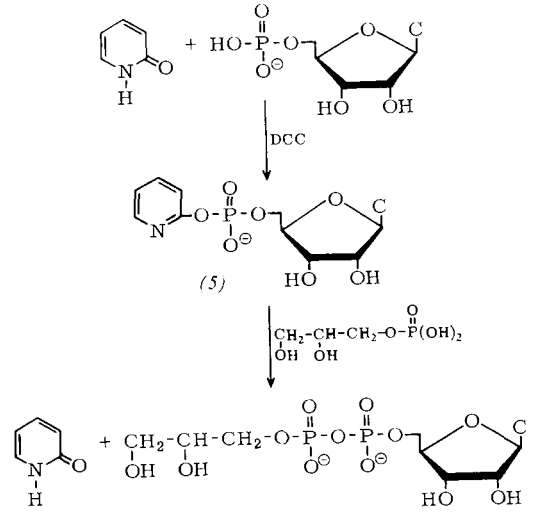
[12] *H. G. Khorana*: Some recent developments in the chemistry of phosphate esters of biological interest. Wiley, New York 1961.

[13] *T. M. Jacob* and *H. G. Khorana*, Chem. and Ind. *1962*, 932.

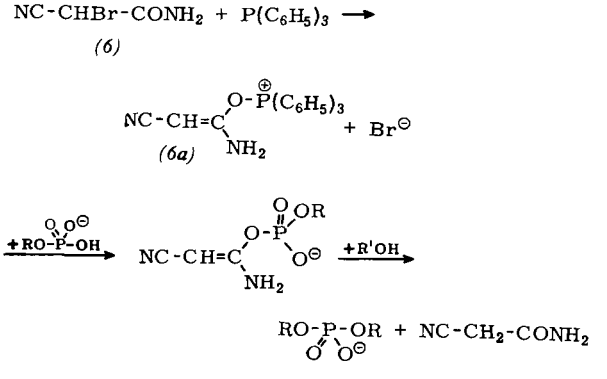
[14] *T. M. Jacob* and *H. G. Khorana*, J. Amer. chem. Soc. *86*, 1630 (1964).

acetonitrile[15,16], Woodward's reagent[17], picryl chloride *(2)*[18], and nucleotide imidazolides *(3)* have been tested for the synthesis of oligonucleotides[19]. Dimethylformamide chloride *(4)* is an esterifying reagent for nucleotides[14,20,21].

New phosphorylation reagents are α-hydroxypyridyl phosphates[22]. α-Hydroxypyridyl esters *(5)* of nucleotides transfer the nucleotide residue to other nucleophiles, *e.g.* to phosphates, so that pyrophosphate



coenzymes are formed. No synthesis of oligonucleotides has yet been carried out with these compounds. A vigorous phosphorylating reagent is a mixture of α-bromocyanoacetamide *(6)* and triphenylphosphine[23]. In a reaction with this mixture, the first step is similar to a Perkow reaction; an intermediate *(6a)* arises which corresponds to the enol phosphate of malonic ester[24],



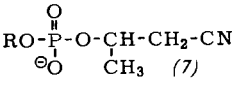
which has earlier been used for the synthesis of oligonucleotides.

The phosphorylating activities of cyclohexyl isonitrile, ethoxyacetylene, bromocyanogen, dichloromalonodinitrile, perfluorooctanecarbonitrile, benzonitrile, benzyl cyanide, and malodinitrile have been investigated[25], but none of these reagents proved to be appreciably superior to those used hitherto. The ynamines 1-dimethylamino-2-phenylacetylene and 1-dimethylamino-3,3-dimethylbut-1-yne, as well as 4-nitrophenyl cyanate, *N*-ethylbenzoiso-oxazolium fluoroborate[25a] as well as *N*(1),*N*(4)-diethyltetrazolium and *N*(1)-ethyl-*N*(4)-methoxyphenyltetrazolium *p*-toluenesulfonates also failed to give satisfactory yields of dinucleoside phosphates[25b].

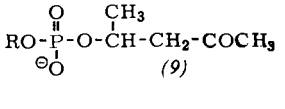
## 3.2. Protecting Groups

### 3.2.1. Protecting Groups for Phosphoric Acids

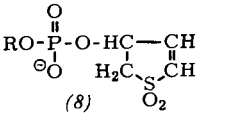
During the linkage of two nucleotides, the phosphoric acid residue of one nucleotide must be protected if the condensation is to proceed in the desired sequence. In general, it is sufficient to prepare the monoester; phosphoric diesters are no longer activated by most condensing agents. Benzyl phosphates[26] can be split by hydrogenation, but a pyrimidine ring may also be hydrogenated under the conditions used. A β-cyanoethyl group[27] can be split off with alkali (β-elimination). Of the alkali-labile esters *(7)–(10)*, R = nucleoside, the esters *(9)* and *(10)* are particularly suitable as protecting groups for phosphoric acid residues in nucleotides[28].



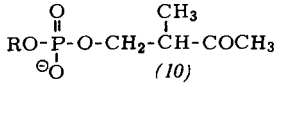
*(7)*



*(9)*

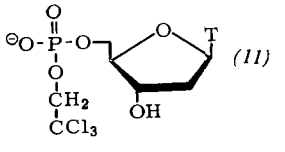


*(8)*



*(10)*

Benzhydryl esters of nucleotides are obtained[29] when nucleotides are treated with diphenyldiazomethane. They can be split with dilute acid. t-Butyl esters are also acid-labile[30]. β,β,β-Trichloroethyl esters of deoxyribonucleotides *(11)* can be split reductively by means of Zn/Cu in acetic acid or in dimethylformamide without



*(11)*

[15] *F. Cramer, W. Rittersdorf*, and *W. Böhm*, Liebigs Ann. Chem. *654*, 180 (1962).

[16] *F. Cramer, H. J. Baldauf*, and *H. Küntzel*, Angew. Chem. *74*, 77 (1962); Angew. Chem. internat. Edit. *1*, 54 (1962).

[17] *F. Cramer, H. Neunhoeffer, K.-H. Scheit, G. Schneider*, and *J. Tennigkeit*, Angew. Chem. *74*, 387 (1962); Angew. Chem. internat. Edit. *1*, 331 (1962).

[18] *F. Cramer, R. Wittmann, K. Daneck*, and *G. Weimann*, Angew. Chem. *75*, 92 (1963); Angew. Chem. internat. Edit. *2*, 43 (1963).

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[22] *W. Kampe*, Tetrahedron Letters *1963*, 2133.

[23] *F. Cramer* and *T. Hata*, Liebigs Ann. Chem., in the press.

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[27] *G. M. Tener*, J. Amer. chem. Soc. *83*, 159 (1961).

[28] *D. Söll* and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 360 (1965).

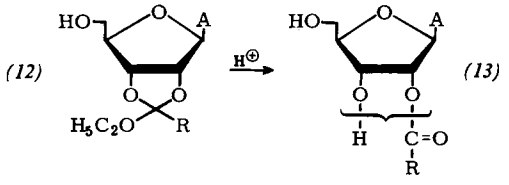
[29] *F. Cramer* and *K.-H. Scheit*, Liebigs Ann. Chem. *679*, 150 (1964).

[30] *F. Cramer, H. P. Bär, H. J. Rhaese, W. Saenger, K.-H. Scheit*, and *G. Schneider*, Tetrahedron Letters *1963*, 1039.

loss of *O*-acetyl or *O*-benzoyl groups [31]. The ethylthio group may be split off oxidatively [32].

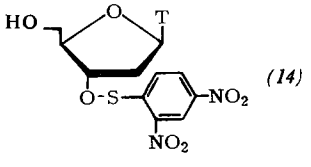
### 3.2.2. Protecting Groups for Hydroxy and Amino Groups

Acetyl and benzoyl derivatives of nucleosides and deoxyribonucleotides can be prepared by the methods customary in carbohydrate chemistry. In the acylation of 3′-ribonucleotides, the formation of cyclophosphates must be avoided [33]. Trityl derivatives or the more easily cleaved methoxytrityl derivates are used for the specific protection of the primary OH group in position 5′ [36]: the 2′-OH group can be masked with dihydropyran [34,36] or with ethyl vinyl ether [35]. The 2′- and 3′-positions of ribose can be protected reversibly by the formation of benzylidene derivatives (*p*-methoxybenzylidene [36] or *p*-dimethylaminobenzylidene groups [37]), which can be easily split off with acids. The 2′,3′-*O*




ethoxymethylene derivatives *(12)*, which can be converted into the 2′- and 3′-*O*-acyl derivatives *(13)* by treatment with acetic acid, serve the same purpose [38–40].

A dinitrophenylsulfenyldeoxyribonucleoside *(14)* has been used in the synthesis of a dinucleotide on a polymeric carrier. Such compounds can be split by thiophenol or Raney nickel [41,42]. Formylnucleosides [30, 43,44] have been synthesized, but have not been used for the synthesis of oligonucleotides.




## 3.3. Synthesis of Oligodeoxyribonucleotides

### 3.3.1. Homopolymers

Homo-oligomers can be prepared by the condensation of thymidylic acid with dicyclohexylcarbodiimide [45], picryl chloride [18], or other reagents. In the resulting mixture of oligomers, the content of the longer chains decreases obeying Poisson's distribution (Fig. 1). The

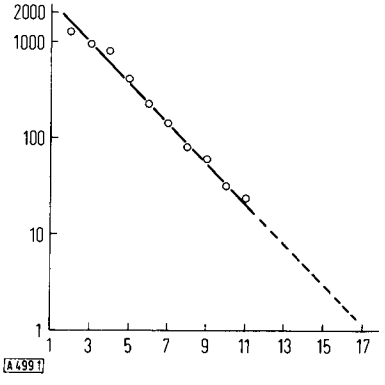



Fig. 1. Chain-length distribution in the product of the polycondensation of thymidylic acid with picryl chloride.
Ordinate: yield of oligonucleotide determined from the extinction at 267 mμ.
Abscissa: number of TMP units in the oligonucleotide chain.

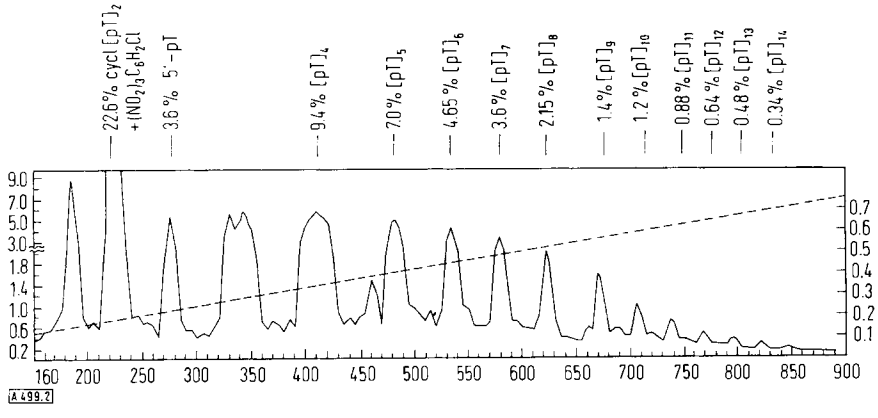



Fig. 2. Column-chromatographic separation of oligothymidylic acids of different chain lengths on DEAE-cellulose. Eluent: aqueous solution of triethylammonium hydrogen carbonate of increasing concentration (the broken line rising from left to right denotes the concentration gradient) [47].
Ordinates: left-hand: extinction at 267 mμ.
right-hand: molarity of triethylammonium hydrogen carbonate.
Abscissa: fraction numbers (25-ml fractions).


[31] *F. Eckstein*, Angew. Chem. *77*, 912 (1965); Angew. Chem. internat. Edit. *4*, 876 (1965).

[32] *A. Nussbaum* and *R. Tiberi*, J. Amer. chem. Soc. *87*, 2513 (1965).

[33] *D. H. Rammler*, *Y. Lapidot*, and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 1989 (1963).

[34] *M. Smith* and *H. G. Khorana*, J. Amer. chem. Soc. *81*, 2911 (1959).

[35] *S. Chladek* and *J. Smrt*, Chem. and Ind. *1964*, 1719.

[36] *M. Smith*, *D. H. Rammler*, *I. H. Goldberg*, and *H. G. Khorana*, J. Amer. chem. Soc. *84*, 430 (1962).

[37] *F. Cramer*, *W. Saenger*, *K.-H. Scheit*, and *J. Tennigkeit*, Liebigs Ann. Chem. *679*, 156 (1964).

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[40] *F. Eckstein* and *F. Cramer*, Chem. Ber. *98*, 995 (1965).

[41] *R. L. Letsinger* and *V. Mahadevan*, J. Amer. chem. Soc. *87*, 3526 (1965).

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[44] *S. Chládek* and *J. Smrt*, Collect. czechoslov. chem. Commun. *29*, 214 (1964).

[45] *G. M. Tener*, *H. G. Khorana*, *R. Markham*, and *E. H. Pol*, J. Amer. chem. Soc. *80*, 6223 (1958).

compounds are separated on columns of DEAE-cellulose [45] (Fig. 2) or on thin-layer plates of polymin-cellulose [48] (Fig. 3). The longest oligomer prepared so far is a polythymidylic acid with 30 chain members [50], which was obtained by condensation with picryl chloride.

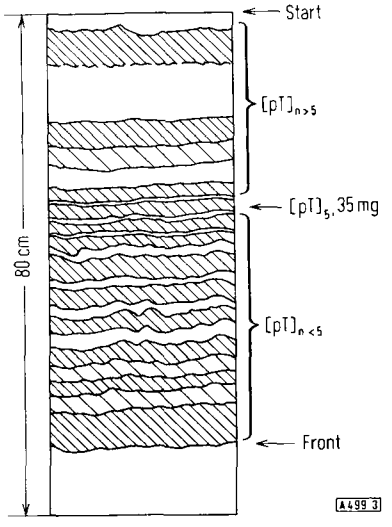



Fig. 3. Thin-layer chromatography of oligothymidylic acids of different chain lengths on polymin-cellulose [48]. The individual bands were eluted and worked up by the $Zn(OH)_2$ method [49].
Solvents: 0.25 M NaCl (2 h), 0.50 M NaCl (2 h), 0.75 M NaCl (2 h), 1.00 M NaCl (2 h), 1.50 M NaCl (2 h).

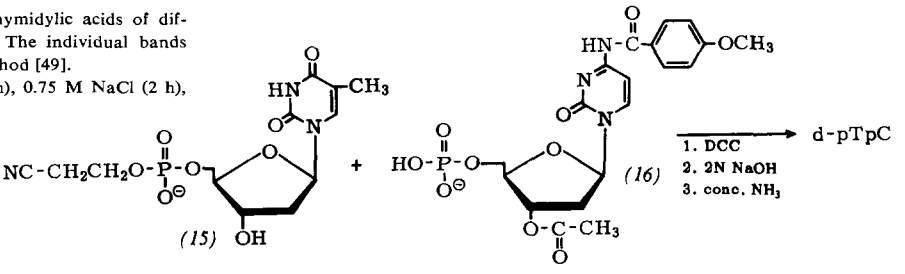
Poly-d-A [51], poly-d-C [52], poly-d-G [53], and poly-T have been synthesized by this process, sometimes in low yields. The oligonucleotides contained in the fractions can be isolated by precipitation with $Zn(OH)_2$ [49]. Graft polymerization can be achieved according to the following scheme [46]:

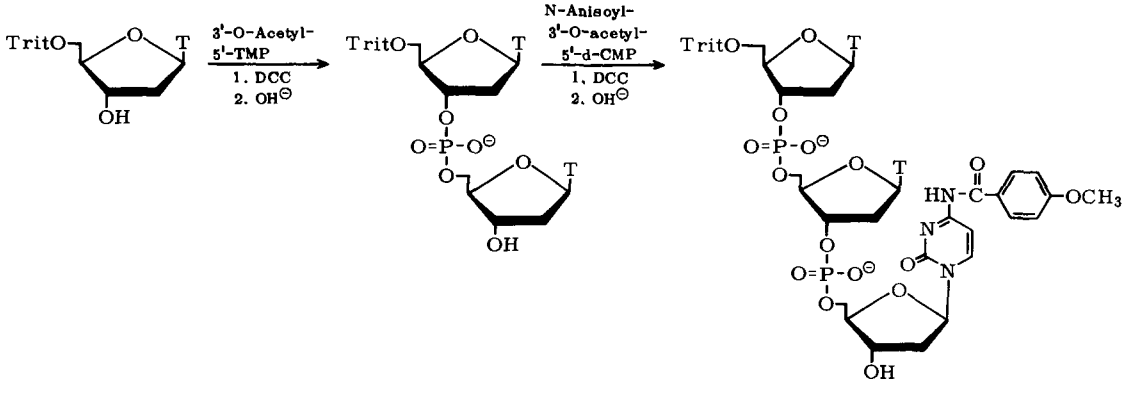
$$n\ pT \xrightarrow[\text{picryl chloride}]{} (pT)_n \xrightarrow[\text{picryl chloride}]{\text{m d-pA}} \text{d-}(pT)_n(A)_m$$

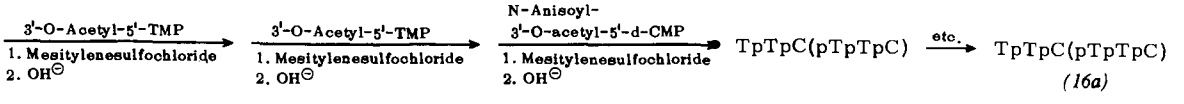
### 3.3.2. Stepwise Synthesis of Oligodeoxyribonucleotides

The condensation of the β-cyanoethyl ester *(15)* of a 5′-nucleotide with a 3′-*O*-acetylnucleotide *(16)* gives a dinucleotide from which the protecting groups can be removed with alkali. The following substances have been prepared in this way:

d-pTpT, d-pGpC, d-pCpG [54], d-pTpA [55], d-pTpG, d-pTpG, d-pTpC, d-pApG, d-pCpA [56], d-pCpT [57], and d-ApTp [55]. For the stepwise synthesis of trinucleoside diphosphates and higher homologues, the 5′-OH group at the beginning of the growing chain must bear a protecting group, *e.g.* the acid-labile trityl group,




which remains in position during all stages of the condensation and is removed only at the end. In this way it has been possible to obtain the dodecanucleotide d-TpTpC(pTpTpC)$_3$ *(16a)* [58], and to synthesize homo-

[46] *K. Daneck*, Göttingen, unpublished work.
[47] *G. Hoffarth*, Göttingen, unpublished work.
[48] *S. Rittner* and *G. Weimann*, Göttingen, unpublished work.
[49] *G. Weimann, K. Daneck*, and *F. Cramer*, Experientia *21*, 417 (1965).
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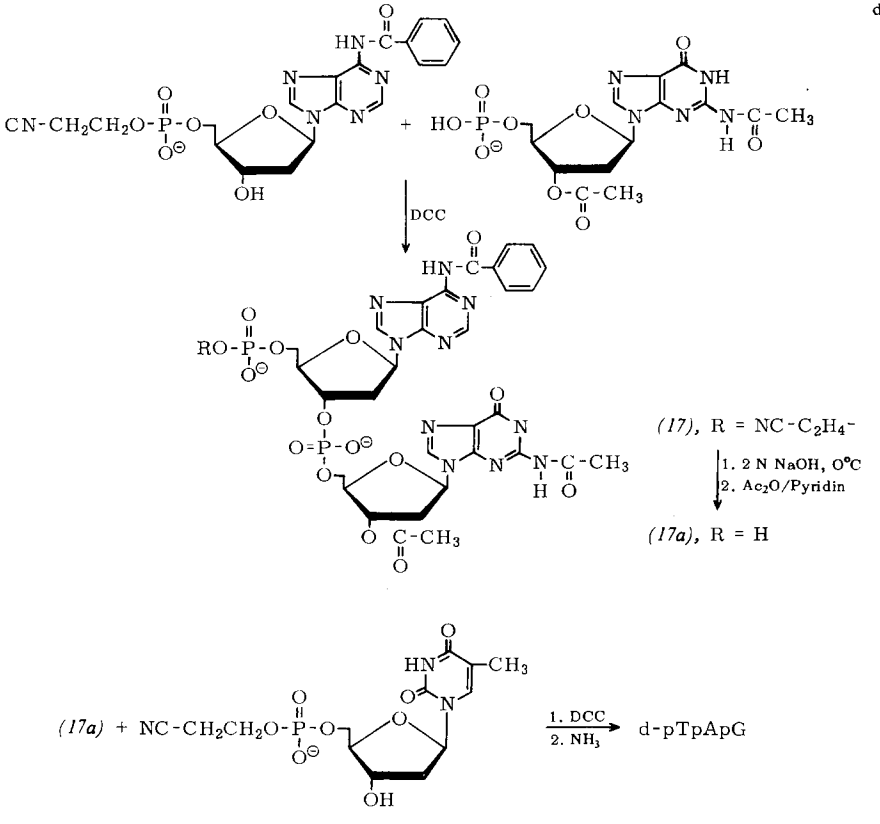
[55] *G. Weimann, H. Schaller*, and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 3835 (1963).
[56] *E. Ohtsuka, M. W. Moon*, and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 2956 (1965).
[57] *H. Schaller* and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 3828 (1963).

logous oligothymidylic acids [59] and, analogously, the oligonucleotides d-TpTpI(pTpTpI)$_3$ [60], d-CpApApCpApA [61], d-GpApApGpApA [61], and d-TpApTpTpT [55].

The problem of the stepwise synthesis of oligonucleotides with a terminal 5′- or 3′-phosphate group, *i.e.* of compounds of the type pXpYpZ or XpYpZp, has been solved less satisfactorily. For this one needs either two protective groups $S^1$ and $S^2$ in the dinucleotide ($S^1$–pXpY–O–$S^2$) which can be eliminated under different conditions or the trinucleoside diphosphate XpYpZ must be re-phosphorylated in the last step of the synthesis. Another possibility [62] consists in first removing all the protecting groups with alkali at the stage of the dinucleotide *(17)*, then acetylating the product, and finally condensing it to the trinucleotide.







### 3.3.3. Block Polymerization

By block polymerization will be understood the condensation of oligonucleotides to higher units. Up to the present time, only dinucleotides have been linked by block polymerization (Table 1) [55]:

$$n\ pXpY \rightarrow (pXpY)_n$$

Important biochemical information has been obtained with these products. For example, (d-pTpA)$_4$ [55] can be used as a template for the Kornberg enzyme [63]. The oligomers act as templates for DNA-polymerase and RNA-polymerase and are used by RNA-polymerase to produce the complementary RNA sequence without errors [64]. In a cell-free system, the messenger-RNA so produced catalyses the synthesis of a polypeptide with an alternating amino acid sequence.

Table 1. Oligonucleotides obtained by the polymerization of dinucleotides [55, 56].

| Dinucleotide | Block polymer | n |
|---|---|---|
| d-pTpA | (d-pTpA)$_n$ | 2–7 |
| d-pTpG | (d-pTpG)$_n$ | 2–6 |
| d-pTpC | (d-pTpC)$_n$ | 2–8 |
| d-pApG | (d-pApG)$_n$ | 2–6 |
| d-pCpA | (d-pCpA)$_n$ | 2–6 |

## 3.4. Synthesis of Oligoribonucleotides

### 3.4.1. Homopolymers

Because of the 2′-OH groups of the ribose residues, the synthesis of oligoribonucleotides is substantially more complicated than corresponding syntheses in the deoxyribose series; the 2′-hydroxy group gives rise to isomerizations and renders the end product alkali-labile. If the exclusive presence of 3′→5′ bonds in the polymer is not required, it is relatively simple to obtain oligomers of the type *(18)* from 2′,3′-*O*-cyclophosphates with diphenyl phosphorochloridate or other vigorously acting acid chlorides as condensing agents [65,66].

These oligomers, which may be valuable for physicochemical studies but which do not behave as natural

[58] *T. M. Jacob* and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 2971 (1965).

[59] *T. M. Jacob* and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 368 (1965).

[60] *S. A. Narang* and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 2981 (1965).

[61] *S. A. Narang*, *T. M. Jacob*, and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 2988 (1965).

[62] *S. Rittner*, Göttingen, unpublished work.

[63] *A. Kornberg*, *L. L. Bertsch*, *J. F. Jackson*, and *H. G. Khorana*, Proc. nat. Acad. U.S.A. *51*, 315 (1964).

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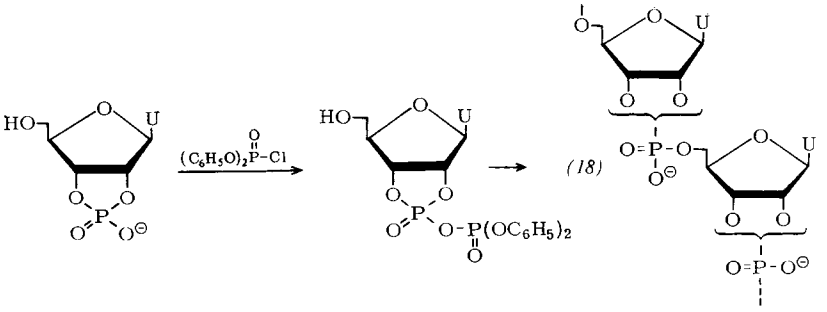
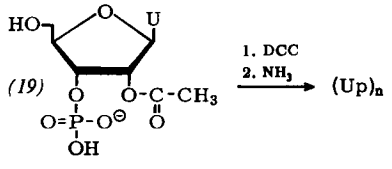


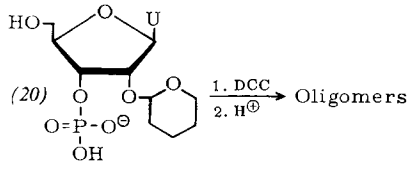
material with respect to most enzymes, have chain lengths of up to 20 units. Addition of chain-terminating 2′,3′-*O*-diacetylnucleosides [66] or 2′,3′-*O*-benzylidene-nucleosides [67] yields oligomers of the type XpXp···XpY with fairly uniform chain lengths.

With polyphosphoric ester as the condensing agent, 3′- or 5′-nucleotides give high-molecular compounds [69] which do not possess the biological properties of polynucleotides; they are obviously cross-linked and partially substituted, and are not degraded by ribonuclease [50, 70].

If isomerizations are to be avoided, the 2′-position must be protected. In this way, 2′-*O*-acetyl-3′-uridylic acid *(19)* can be polymerized up to the decanucleotide, although not in very satisfactory yields [68], and 2′-*O*-tetrahydropyranyl-3′-uridylic acid *(20)* has been con-



densed to oligomers from which, however, the tetrahydropyranyl group can be removed only with difficulty and not without isomerization [36]. Guanosine derivatives protected in the 2′-position have also been prepared [71, 72].

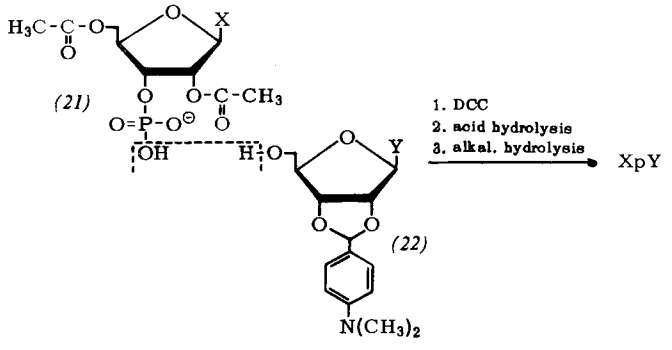


### 3.4.2. Stepwise Synthesis of Oligoribonucleotides

#### 3.4.2.1. *Dinucleoside Phosphates and Analogous Compounds*

Dinucleoside phosphates (XpY) have been synthesized by various methods:

2′,5′-Di-*O*-acetyl-3′-nucleotides *(21)* [73] can be condensed with *p*-methoxybenzylidene- or *p*-dimethylaminobenzylidenenucleosides *(22)* [36, 73a]. At the present time this is probably the most useful procedure for the preparation of dinucleoside phosphates. However, it is impossible to extend the chain further at the 5′-hydroxy group liberated by alkaline hydrolysis, since the acetyl



group in the 2′-position of the nucleotide is also removed. This disadvantage is not associated with the following two procedures:

A 5′-*O*-methoxytrityl-2′-*O*-acetyl-3′-nucleotide *(23)* is esterified with a 2′,3′-di-*O*-benzoylnucleoside *(24)* [74]. The methoxytrityl group can be removed from the dinucleoside phosphate *(25)* with acid without the acetyl or benzoyl groups being split off. Further condensation with a 2′,5′-di-*O*-acetyl-3′-nucleotide *(26)* then gives the trinucleoside diphosphate XpYpZ. In this way, the 64 possible nucleotide triplets have been synthesized [80] and used for the complete deciphering of the genetic code [81]. The tetranucleoside triphosphate UpApUpU has been obtained by the same method [82].

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[67] *K. H. Scheit* and *W. Kampe*, Göttingen, unpublished work.

[68] *C. Coutsogeorgopoulus* and *H. G. Khorana*, J. Amer. chem. Soc. *86*, 2926 (1964).

[69] *G. Schramm*, *H. Grötsch*, and *W. Pollmann*, Angew. Chem. *74*, 53 (1962); Angew. Chem. internat. Edit. *1*, 1 (1962).

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[71] *D. B. Straus* and *J. R. Fresco*, J. Amer. chem. Soc. *87*, 1364 (1965).

[72] *D. B. Straus*, J. Amer. chem. Soc. *87*, 1375 (1965).

[73] *D. H. Rammler* and *H. G. Khorana*, J. Amer. chem. Soc. *84*, 3112 (1962).

[73a] *F. Cramer*, *H. J. Rhaese*, *S. Rittner*, and *K.-H. Scheit*, Liebigs Ann. Chem. *683*, 199 (1965).

[74] *Y. Lapidot* and *H. G. Khorana*, J. Amer. chem. Soc. *85*, 1363 (1963).

[75] *R. Lohrmann* and *H. G. Khorana*, J. Amer. chem. Soc. *86*, 4188 (1964).

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[78] *G. Schneider*, Dissertation, Technische Hochschule Darmstadt 1965.

[79] *K.-H. Scheit* and *F. Cramer*, Tetrahedron Letters *1964*, 2675.

[80] *H. G. Khorana*, *D. Söll*, *R. Lohrmann*, *E. Ohtsuka*, and *H. Haytsu*, personal communication.

[81] *H. G. Khorana*, personal communication.

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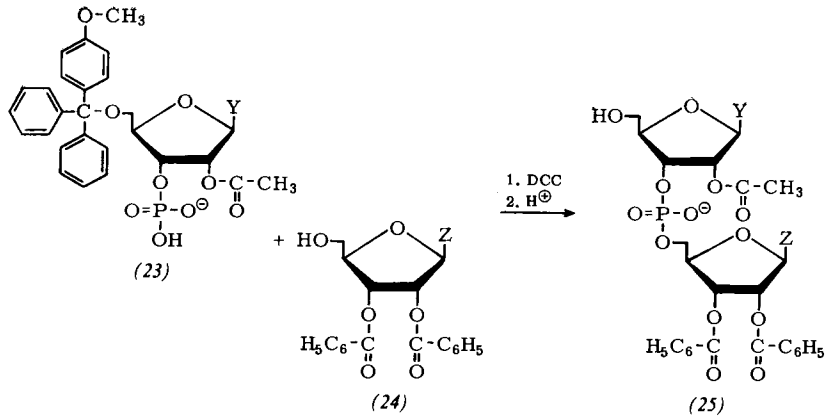
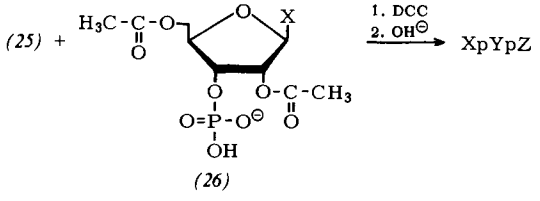
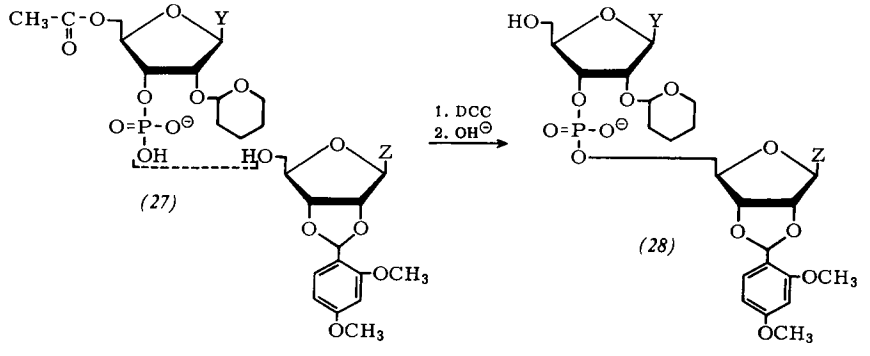


(23) + (24) → (25)

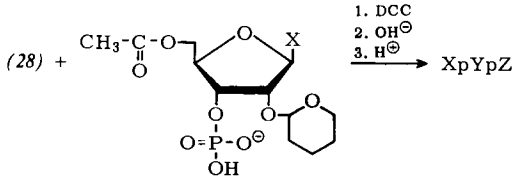


(25) + (26) → XpYpZ

Another method, which again allows subsequent extension of the chain, starts from a 5′-*O*-acetyl-2′-*O*-tetrahydropyranyl-3′-nucleotide *(27)* [83]. After the first condensation, the 5′-*O*-acetyl group can be split off by alkaline hydrolysis. The chain *(28)* may be extended by



(27) → (28)



(28) → XpYpZ

one nucleoside by means of another condensation [84]; UpUpU and CpUpU have been obtained in this way. However, in the case of higher oligonucleotides it is difficult to remove the tetrahydropyranyl groups completely. Nevertheless, it has been possible to obtain a hexanucleoside pentaphosphate, UpUpUpUpUpU, although only in low yield [85].

Table 2 lists the dinucleoside phosphates obtained by various methods.

[83] *J. Smrt* and *F. Šorm*, Collect. czechoslov. chem. Commun. *28*, 61 (1963).

[84] *F. Cramer* and *S. Rittner*, Tetrahedron Letters *1964*, 107.

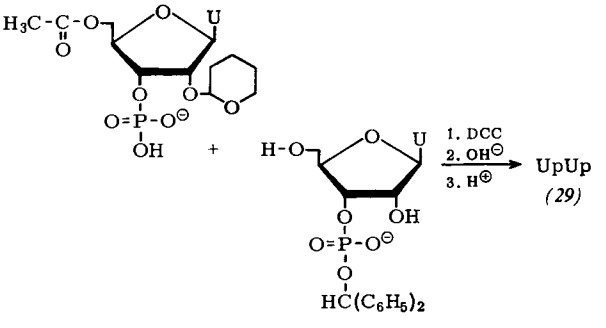
[85] *J. Smrt* and *F. Šorm*, Collect. czechoslov. chem. Commun. *29*, 2971 (1964).

Table 2. Dinucleoside phosphates prepared by various methods.

| | | | |
|---|---|---|---|
| UpU [36, 73a, 76, 79] | UpC [73, 79, 83] | UpA [36, 73a, 77, 79] | UpG [77] |
| CpU [75, 76, 78, 83] | CpC [77, 78] | CpA [73, 75, 77] | CpG [75, 77] |
| ApU [73a, 79] | ApC [79] | ApA [73, 73a, 79] | |
| GpU [75] | GpC [75] | GpA [75] | GpG [75] |

### 3.4.2.2. *Diribonucleotides*

In many cases, the enzymatic or alkaline hydrolysis of the ribonucleic acids leads to oligonucleotides with terminal 3′-phosphate groups. Various routes to their synthesis have been attempted. The first diribonucleotide *(29)* was obtained by the benzhydryl ester method [86]. UpAp, ApAp [86, 87], CpAp, and CpUp [78] have been synthesized in basically the same way. Dinucleotides possessing a 2′,3′-*O*-cyclophosphate grouping (that can be opened by ribonuclease) in the terminal



[86] *F. Cramer* and *K.-H. Scheit*, Angew. Chem. *74*, 717 (1962); Angew. Chem. internat. Edit. *1*, 510 (1962).

[87] *F. Cramer, K.-H. Scheit*, and *H. J. Rhaese*, Liebigs Ann. Chem., in the press.

position and an internucleotide bond (which is stable to ribonuclease), *i.e.* dinucleotides of the type XpPyp [*], are obtained by condensation of the 2',3'-*O*-cyclophosphates with protected 3'-nucleotides [89]. The β-cyanoethyl group has also been used for the protection of the terminal phosphate residue [88], but there is a danger of isomerization when it is split off under alkaline conditions. CpUp, ApUp, IpUp [89], UpUp, UpCp, and CpUp [88] have been prepared by this method.

The synthesis of diribonucleotides with 5'-terminal phosphate groups requires the phosphorylation of a protected dinucleside phosphate [76]. Here, many preparative problems remain to be solved.

## 4. Enzymatic Syntheses

Enzymatic syntheses of nucleic acids are treated here only to the extent that they lead to the synthesis of polymers of a definite sequence. It is impossible to go into all details with respect to biochemistry and molecular biology.

### 4.1. Synthesis of DNA

#### 4.1.1. DNA-Polymerase (Kornberg Enzyme; E.C. 2.7.7.7.)

An enzyme has been isolated from *E. coli* [90–92] which catalyses the synthesis of high-molecular polydeoxyribonucleotides when all four 5'-triphosphates – namely d-ATP, d-GTP, d-CTP, and d-TTP – and a DNA template are present.

The native DNA double strand is a poor primer for the polymerization by the purified enzyme (which is substantially free from DNases). Much more suitable is DNA slightly digested by pancreatic DNase and subsequently denatured by brief heating to 77 °C. From this and other findings, it has been concluded that the natural function of the DNA-polymerase is that of a repairing enzyme. *In vitro*, up to 20 °C, the Kornberg enzyme in fact repairs only gaps in the double strand of DNA [92a], the intact strand serving as a template. At higher temperature, however, excessive polymerization extending beyond repair begins, leading to branchings on the DNA. Under these conditions, the net amount of DNA synthesized may reach twenty times the amount of the template. All results, particularly the molar ratio of the bases in the DNA template and in the newly synthesized DNA [93], point to the fact that base-paired double strands are always produced in this polymerization.

No synthesis of DNA takes place in the absence of a DNA template. If, however, the polymerase from *E. coli* is incubated without a DNA template but with d-ATP and d-TTP in the presence of $Mg^{2+}$ ions, the formation of a high-molecular compound is observed after a lag phase of 2–6 hours (depending on the concentrations of enzyme and substrate). Chemical analysis (base ratio and determination of the nearest neighbors) [92,94] and physicochemical investigations [95] have shown that the product consists of complementary double strands in which d-Ap and d-Tp units alternate [poly-d-(AT)]. On the other hand, incubation with d-GTP and d-CTP does not give an alternating poly-d-(GC) double strand but a double-stranded polymer consisting of complementary homopolymeric d-G and d-C strands [92,96].

The enzyme has also been used to copy short-chain synthetic oligodeoxyribonucleotides, *i.e.* to obtain long-chain complementary polynucleotides. Even a heptanucleotide d-$(pA)_7$, in the presence of a template $(pT)_{11}$, acts as a primer for the enzymatic formation of high-molecular poly-d-A. It seems therefore that the template can be shifted with respect to the growing nucleotide chain (slipping mechanism) [63]. In a few cases, it has been possible with the aid of chemically synthesized oligodeoxyribonucleotides to prepare polydeoxyribonucleotides with strictly alternating base sequences (Table 3) [97].

Table 3. Polydeoxyribonucleotides obtained enzymatically from chemically synthesized oligodeoxyribonucleotides.

| Template and primer | Substrate | Product |
|---|---|---|
| $(pT)_{11}$:d-$(pA)_7$ | d-ATP | Poly-d-A (50–100 nucleotides) |
| $(pT)_{11}$:d-$(pA)_7$ | d-ATP<br>d-TTP | d-$(pA)_n$:d-$(pT)_n$<br>M.W. $6 \times 10^6$ |
| d-$(pTpC)_5$:d-$(pApG)_5$ | d-ATP<br>d-TTP<br>d-CTP<br>d-GTP | d-$(pTpC)_n$:d-$(pApG)_n$<br>M.W. $> 10^6$, $S_{20,w} - 16$ |

#### 4.1.2. "End-Addition Enzyme"

In addition to a DNA-dependent (template-dependent) DNA polymerase, a second DNA-polymerizing enzyme, the "end-addition enzyme", has been detected in purified extracts of calf thymus. It has been separated from the DNA-dependent DNA polymerase on a hydroxylapatite column [98,99]. The "end-addition enzyme" extends

[*] Py = pyrimidine nucleoside.

[88] *J. Smrt* and *F. Šorm*, Collect. czechoslov. chem. Commun. *28*, 2415 (1963).

[89] *D. Söll* and *H. G. Khorana*, J. Amer. chem. Soc. *87*, 350 (1965).

[90] *A. Kornberg, I. R. Lehman, M. J. Bessman*, and *E. S. Simms*, Biochim. biophysica Acta *21*, 197 (1956).

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[92] *C. C. Richardson, C. L. Schildkraut, H. V. Aposhian*, and *A. Kornberg*, J. biol. Chemistry *239*, 222 (1964).

[92a] *C. C. Richardson, R. B. Inman*, and *A. Kornberg*, J. molecular Biol. *2*, 46 (1964).

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[99] *M. Yoneda* and *F. J. Bollum*, J. biol. Chemistry *240*, 3385 (1965).

oligodeoxyribonucleotides by the repeated addition of deoxyribonucleotide units to long homologous chains:

$$pTpTpT + n\ d\text{-}ATP \xrightarrow{\text{end-addition enzyme}} d\text{-}pTpTpTpApApApA.....$$

The rate of this polymerization decreases in the sequence d-ATP > d-ITP > d-CTP ≫ d-TTP and d-GTP. d-CTP is incorporated only in the presence of $Co^{2+}$ ions [100]. The oligonucleotides acting as primers must have a minimum length of three nucleotides; at the same concentration of enzyme, the length of the newly formed chain depends on the substrate/primer ratio.

### 4.2. Synthesis of RNA

#### 4.2.1. DNA-Dependent RNA Polymerase (E.C. 2.7.7.6)

A DNA-dependent RNA polymerase is present in bacteria and other tissues [101–105]. It requires a DNA template and all four ribonucleoside 5′-triphosphates. The polyribonucleotides synthesized are single-stranded and of high molecular weight. Their composition is determined by the composition of the DNA template. *In vitro*, the enzyme copies DNA single and double strands. If single strands are copied, the base composition of the product is complementary to that of the template. If synthetic polydeoxyribonucleotides with a known base sequence, *e.g. (30)* or *(31)*, are used as templates, complementary polyribonucleotides also having definite base sequences are obtained [64]. Which strand of the DNA is used as a template depends on the nature of the nucleoside triphosphate offered. The ribonucleic acids produced have contributed to the deciphering of the genetic code.

"Translation" into the complementary polyribonucleotides can also be effected with RNA polymerase starting from templates consisting of trideoxyribonucleotides [5, 106]. A template of only 9 nucleotides (3 triplets) is sufficient to synthesize a complementary polyribonucleotide with more than 150 nucleotide units. Here again a slipping of the oligomeric template during the synthesis has been postulated.

The chemical synthesis of polydeoxyribonucleotides is substantially simpler than that of polyribonucleotides. Using the described enzyme, it is possible to utilize the information contained in chemically synthesized polydeoxyribonucleotides for the enzymatic synthesis of polyribonucleotides and thus to circumvent the difficulties associated with the chemistry of the ribopolymers.

#### 4.2.2. Polynucleotide Phosphorylase (E.C. 2.7.7.8)

##### 4.2.2.1. *Homopolynucleotides*

Polynucleotide phosphorylase polymerizes nucleoside diphosphates to polynucleotides in which the bases are distributed at random:

$$n\ XDP \rightleftharpoons (XMP)_n + n\ P_i$$

The enzyme requires no template [107]. It has been isolated from *Azotobacter vinelandii* [108, 109] and from *Micrococcus lysodeicticus* [110]. The enzyme from *Micrococcus lysodeicticus* possesses somewhat different properties, and is easier to purify. Even after 500-fold concentration, the enzyme from *Azotobacter vinelandii* contains ca. 3% of a firmly bound oligonucleotide, which may have the function of a prosthetic group [111]. Both enzymes are specific for ribonucleoside 5′-diphosphates; even chemically modified 5′-diphosphates can be used as substrates [112]. If several nucleoside 5′-diphosphates are present, they are incorporated into the polymer at random, with the exception of GDP [113] which is incorporated preferentially [114].

Highly purified enzyme preparations require a primer which must be at least a dinucleoside phosphate; less highly purified preparations and crude extracts contain sufficient oligonucleotides to act as primers [115, 116]. A net synthesis of polynucleotides is possible with crude extracts from *Azotobacter vinelandii* if the process is carried out in 1–2 M

[100] *F. Bollum*, Federat. Proc. *24*, No. 2, part I, p. 1207 (1965).

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[108] *M. Grunberg-Manago* and *S. Ochoa*, Federat. Proc. *14*, 221 (1955).

[109] *M. Grunberg-Manago, P. J. Ortiz*, and *S. Ochoa*, Science (Washington) *122*, 907 (1955).

[110] *R. F. Beers, Jr.*, Federat. Proc. *15*, 13 (1956).

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[112] *S. P. Colowick* and *N. O. Kaplan*: Methods in Enzymology. Academic Press, London, New York 1962, Vol. VI, p. 716.

[113] *H. Küntzel*, Göttingen, unpublished work.

[114] *M. F. Singer, R. J. Hilmoe*, and *M. Grunberg-Manago*, J. biol. Chemistry *235*, 2705 (1960).

[115] *S. Mii* and *S. Ochoa*, Biochim. biophysica Acta *26*, 445 (1957).

[116] *M. F. Singer, L. A. Heppel*, and *R. J. Hilmoe*, Biochim. biophysica Acta *26*, 447 (1957).

urea [117, 118] (the optimum concentration of urea is different for the individual homopolynucleotides [119]). The reason for this is that the crude extract contains ureases, which raise the concentration of ammonium ions by decomposition of the urea to such an extent that the phosphate produced ($P_i$) is precipitated with the magnesium ions present. In this way the equilibrium

$$n\ XDP \rightleftharpoons (XMP)_n + n\ P_i$$

is displaced to the side of the polymer [121, 122]. The optimum conditions for the synthesis of polynucleotides with crude extracts from *Azotobacter vinelandii* are: addition of $NH_4^+$ ions in the form of ammonium hydrogen carbonate and a pH of 9.15, together with an increase in the concentration of magnesium ions so that the phosphate can be precipitated quantitatively as ammonium magnesium phosphate. Under these conditions, the yield of polynucleotide is almost quantitative (Fig. 4) [120].

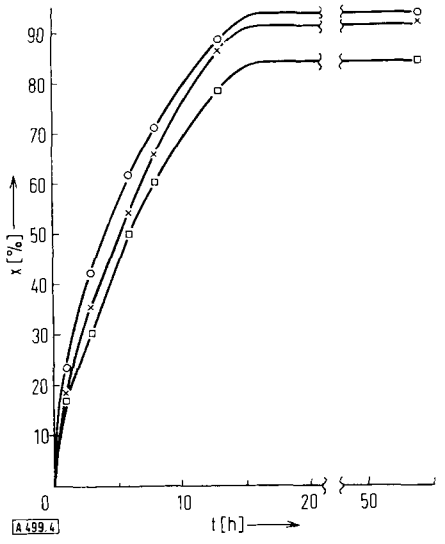


Fig. 4. Course of the synthesis of polynucleotides with a crude extract from *Azotobacter vinelandii* in the presence of equimolar (referred to the nucleoside diphosphate added) amounts of $Mg^{2+}$ and a 208-fold molar excess of ammonium hydrogen carbonate [120].
o—o Poly-C; ×—× Poly-A; □—□ Poly-U.
Ordinate: yield of polymer [%].
Abscissa: time [hours].

### 4.2.2.2. *Polynucleotides with Definite Terminal Triplets and Oligoribonucleotides*

The fact that polynucleotide phosphorylase is not specific with respect to nucleo-bases can be utilized to obtain polymers with definite triplets at the 3'-end [7]. For this purpose, a nucleotide is incorporated randomly into the polymer, and the latter is subsequently split specifically at the site of this nucleotide. For example:

UDP + GDP (30:1)
↓ Polynucleotide phosphorylase
....pUpUpUpGpUpU....pUpUpGpU....
↓ $T_1$ ribonuclease
....pUpUpUpGp + UpU....pUpUpGp + U....
↓ Phosphatase
....pUpUpG

As a check, the terminal guanosine in the example shown here was split off by the periodate method and determined [123]. Polymers synthesized in this way are shown in Table 4. One of these polymers, namely ...ApApC, has been used to determine the direction of reading of the messenger-RNA [9]. In the case of G-containing polymers, in particular, the base ratio in the product does not completely correspond to that in the substrate mixture (Table 4), *i.e.* part of the chains have "wrong" ends, which must be be ascribed to the presence of endonucleases which split the polynucleotide in the homologous part of the chain.

Table 4. Polynucleotides with definite triplets at the 3'-end [124].

| Polynucleotide | Substrate ratio | Base ratio in the polymer | Average chain length [nucleotides] | Chains with pXpXpX ends [%] |
|---|---|---|---|---|
| Up...UpUpG | 30:1 | 20:1 | 17 | 12 |
| Cp...CpCpG | 30:1 | 27:1 | 24 | 13 |
| Ap...ApApG | 30:1 | 19:1 | 14 | 33 |
| Ap...ApApC | 30:1 | 28:1 | 26 | 9 |
| Ap...ApApU | 30:1 | 37:1 | 31 | 17 |
| Ip...IpIpC | 30:1 | 26:1 | 23 | 12 |
| Ip...IpIpU | 30:1 | 36:1 | 29 | 15 |

Purified polynucleotide phosphorylase [125] requires a primer [126, 127] and extends a nucleoside diphosphate to a homopolymer with a definite triplet at the 5'-end [128], *e.g.*:

$$GpU + ppU \xrightarrow{37\,^\circ C,\ 48\ h} GpUpUpUpUpUp...U$$

Polynucleotide phosphorylase from *M. lysodeicticus* [127] (protein content 1.45 mg/l, $\varepsilon_{280}:\varepsilon_{260} = 1.76$) is used. The charges (1 ml of solution) contain

24 μmole of nucleoside diphosphate,
0.5 μmole of primer (dinucleoside phosphate),
150 μmole of Tris buffer (pH 8.1),
0.8 μmole of EDTA,
6 μmole of $MgCl_2$, and
0.11mg of polynucleotide phosphorylase.

The following polymers have been obtained under these conditions [124]:

ApG + ADP → ApGpApApAp... A
UPG + UDP → UpGpUpUpUp... U
GpA + ADP → GpApApApAp... A
GpA + UDP → GpApUpUpUp... U
ApU + ADP → ApUpApApAp... A
ApU + UDP → ApUpUpUpUp... U
ApA + UDP → ApApUpUpUp... U
UpC + APD → UpCpApApAp... A
GpC + ADP → GpCpApApAp... A
GpC + UDP → GpCpUpUpUp... U
UpG + ADP → UpGpApApAp... A
CpU + ADP → CpUpApApAp... A
GpU + ADP → GpUpApApAp... A
GpU + UDP → GpUpUpUpUp... U

[117] *F. Cramer* and *K. Randerath*, Biochim. biophysica Acta *61*, 346 (1962).

[118] *F. Cramer* and *K. Randerath*, Nature (London) *196*, 1209 (1962).

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[128] *H. Küntzel*, Göttingen, unpublished work.

The chains are 50 to 100 nucleotides long, depending on the amount of primer and the experimental conditions.

Polynucleotide phosphorylase can also be used for the synthesis of short chains. With the primer-dependent enzyme from *M. lysodeicticus*, a dinucleoside phosphate is extended by only a few units if the reaction takes place in 0.4 M NaCl [129] and is allowed to proceed until the few long chains formed initially have been converted by phosphorolysis into a large number of short chains [129]:

ApU + ADP (1:4)
↓ Polynucleotide phosphorylase, 2 h
ApUpApA...A (high molecular weight)
↓ +ApU (unused primer) Polynucleotide phosphorylase, 24 h

ApU (small amount) + ApUpa (main product) + ApUpApA + ApUpApApA + a small amount of polynucleotides of higher molecular weight.

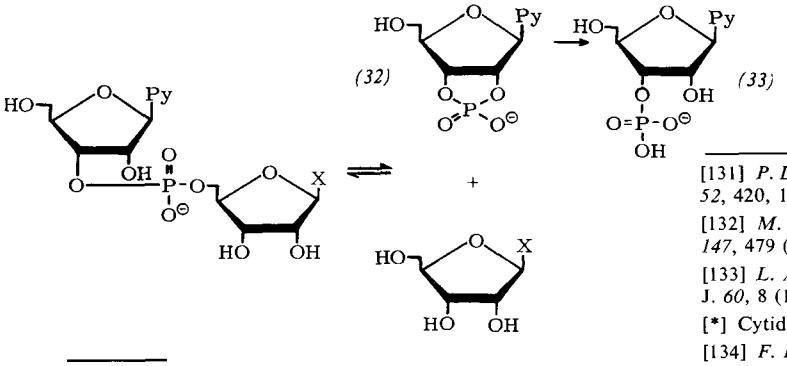
When a highly purified polynucleotide phosphorylase is used and the ratio of primer to nucleoside diphosphate equals 1:1 or 2:1, trinucleoside diphosphates are obtained in yields of 5 to 15% [130].

The trinucleoside diphosphates XpYpZ can be separated chromatographically from more highly polymerized material and unused primer. Fourteen trinucleoside diphosphates have been synthesized in this way, and have contributed to the deciphering of the genetic code [131, 132]. The method is suitable in principle for the synthesis of all 64 nucleotide triplets.

#### 4.2.2.3. *Reversible Action of Ribonucleases*

Pancreatic ribonuclease splits the internucleotide bonds of ribonucleic acids close to the sites of the pyrimidine bases. The 2',3'-*O*-cyclophosphates *(32)* arising as intermediates are hydrolysed by the enzyme to the pyrimidine nucleoside 3'-phosphates *(33)*. The first step of the hydrolysis is reversible [133], if the concentration of the cyclophosphate is greater than 0.1 M. The 2',3'-*O*-cyclophosphate then gives methyl esters of nucleoside 3'-phosphates with methanol, and dinucleosides are produced with nucleosides. The following products were found in the reaction of the 2',3'-*O*-cyclophosphate of cytidylic acid with cytidine [133]:

| | Cp | CpC | CpC>p [*] | CpCpC |
|---|---|---|---|---|
| % | 3.5 | 4.5 | 9 | 1 |

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Uridine 2',3'-*O*-cyclophosphate reacts similarly [134] (Table 5).

Table 5. Synthesis of UpU from uridine 2',3'-*O*-cyclophosphate [134]: a solution of 65 mg of the cyclophosphate, 300 mg of uridine, and 1.4 mg of ribonuclease in 20 ml of water was kept at pH 7.0 and 4 °C. Figures in % of the cyclophosphate used.

| Time [h] | Up [%] | UpU [%] | U>p [a] [%] |
|---|---|---|---|
| 1.75 | 36 | 26 | 38 |
| 2.5 | 45 | 29 | 26 |
| 3.5 | 48 | 28 | 24 |
| 6.0 | 54 | 26 | 20 |
| 25 | 78 | 10 | 12 |
| 54 | 83 | 7 | — |

[a] Uridine 2',3'-*O*-cyclophosphate

Mixed oligomers such as CpU and CpCpU (0.8% yield) can also be prepared [134].

Still more pronounced is the reversible action of $T_1$ ribonuclease [135]. Guanosine 2',3'-*O*-cyclophosphate is partially polymerized in concentrated solution to oligoguanylic acids. In the presence of an excess of nucleotide with a free 5'-hydroxy group, dinucleoside phosphates of the type GpX are produced, and with dinucleoside phosphates one obtains trinucleoside diphosphates of the type GpXpY [79]. In addition, small amounts of higher oligonucleotides ...GpGpXpY are formed. The further growth of the chain can be prevented if the 5'-position of the guanosine 2',3'-*O*-cyclophosphate is blocked by acetylation [136]. GpU and GpC have been obtained in 16 and 15% yields, respectively, in this way.

*Own investigations that have been cited in this review are the result of a fruitful collaboration with my colleagues whom I should like to thank above all. Thanks are also due to Dr. Reinhard, Dr. Eckstein, and Dr. Lezius for their assistance in preparing the manuscript. The investigations were supported financially by an initial grant from the Rockefeller Foundation (1958), by several grants of the Deutsche Forschungsgemeinschaft, the Bundesministerium für Wissenschaftliche Forschung, and the Fonds der Chemischen Industrie.*

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German version: Angew. Chem. *78*, 186 (1966)
Translated by Express Translation Service, London

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[132] *M. R. Bernfield* and *M. W. Nirenberg*, Science (Washington) *147*, 479 (1965).

[133] *L. A. Heppel, P. R. Whitfield*, and *R. Markham*, Biochem. J. *60*, 8 (1955).

[*] Cytidyl-3'→5'-cytidine 2',3'-*O*-cyclophosphate.

[134] *F. Fittler*, Göttingen, unpublished work.

[135] *F. Egami* and *K. Sato-Asano*, Biochim. biophysica Acta *29*, 655 (1958).

[136] *K.-H. Scheit*, Göttingen, unpublished work.

# The Passivity of Metals

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*After a survey of the various factors, depending both on the metal and on the attacking substance, that can influence the anodic dissolution of metals, the nature of the passive layer is discussed on the basis of electrochemical and optical studies. Passivation is characterized by a rapid decrease in the anodic current density as the Galvani tension is increased; this is due to the presence of a monomolecular layer, which prevents the metal ions from passing across the phase boundary. The growth of this layer is strongly influenced by transport processes, particularly within the layer itself. The kinetics of the passivation and activation processes can be explained by the simultaneous occurrence of competing reactions which depend on the potential; exchange adsorption appears to play some part in the passive behavior of metals towards various acids.*

## Introduction

Titanium, zirconium, niobium, and tanatalum, as well as their alloys, have an even greater affinity (*i.e.* a very large decrease in free energy $\Delta G$; Table 1) for oxygen, water, and acids than the more common metals iron, aluminum, chromium, nickel, and copper. Nevertheless Ti, Zr, Nb, and Ta react with oxygen, water, acids, or other chemicals very slowly or not at all, *i.e.* they are passive; this is the only reason that the growing use of these metals in chemical engineering and in reactor engineering is possible.

It is generally known that reactions between substances having a high affinity for one another ($\Delta G \ll 0$) may proceed very slowly because of high reaction barriers, *i.e.* high activation energies (*e.g.* the reaction of $H_2$ with $O_2$ or of Fe with S at room temperature). The resistance of (base) metals towards components of the atmosphere or towards other substances for which they have a high affinity is known in general as passivity. This very general definition, which also applies to electrochemical reactions of the metals, makes no stipulation as to the reasons for this inhibition, which differ widely in nature, and which are not yet fully understood.

Table 1. Values of $\Delta G_{298}$ for the reaction $x\,M + y/2\,O_2 \rightarrow M_xO_y$.

| $M/M_xO_y$ | $\Delta G_{298}$ (kcal/mole) | $M/M_xO_y$ | $\Delta G_{298}$ (kcal/mole) |
|---|---|---|---|
| $Ag/Ag_2O$ | − 2.69 | $Mo/MoO_3$ | −162.0 |
| $Al/Al_2O_3$ | −376.8 | $Nb/Nb_2O_4$ | −362.4 |
| $Al/Al_2O_3 \cdot H_2O$ | −435.0 | $Nb/Nb_2O_5$ | −432.0 |
| $Al/Al_2O_3 \cdot 3\,H_2O$ | −547.9 | $Ni/NiO_2$ | − 47.5 |
| $Au/Au_2O_3$ | + 39.0 | $Ta/Ta_2O_5$ | −470.6 |
| Co/CoO | − 51.0 | $Th/ThO_2$ | −280.1 |
| $Cr/Cr_2O_3$ | −250.2 | $Ti/TiO_2$ | −203.8 |
| Cu/CuO | − 30.4 | $Ti/Ti_2O_3$ | −346.0 |
| $Cu/Cu_2O$ | − 35.0 | $V/V_2O_3$ | −271.0 |
| Fe/FeO (wüstite) | − 58.4 | $V/V_2O_4$ | −318.0 |
| $Fe/Fe_2O_3$ (hematite) | −177.1 | $V/V_2O_5$ | −344.0 |
| $Fe/Fe_3O_4$ (magnetite) | −242.4 | W/$WO_3$ (yellow) | −182.5 |
| Mg/MgO | −136.1 | $W/WO_2$ | −118.3 |
| Mn/MnO | − 86.8 | Zn/ZnO | − 76.1 |
| $Mn/MnO_2$ | −111.4 | $Zr/ZrO_2$ | −244.4 |
| $Mn/Mn_3O_4$ | −306.0 | | |

[1] *Ch. Schönbein* and *M. Faraday*, Philos. Mag. (3) *9*, 53, 57, 100 (1836).

*Schönbein* and *Faraday*[1], who coined the term "passivity", regarded the phenomenon as being due to the presence of an oxide layer. This theory has been shown to be correct in principle. The corrosion of metals in the presence of water (which is nearly always present, if only as an adsorbed layer) is regarded as an electrochemical reaction comprising the anode process (a) and the cathode process (b).

$$M(s) + x\,H_2O \rightleftarrows M^{n+}(x\,H_2O) + n\,e^- \quad (a)$$

$$n\,H_2O + n\,e^- \rightleftarrows n/2\,H_2 + n\,OH^- \quad (b)$$

$$M(s) + (x+n)\,H_2O \rightleftarrows M^{n+}(x\,H_2O) + n\,OH^- + n/2\,H_2 \quad (c)$$

In acidic solutions, other anions may naturally be present instead of $OH^-$. According to these equations, the rate of reaction of the metal depends partly on the rate of reduction of water, or more generally on the rate of the cathode process, but since this process cannot generally be regarded as characteristic of the reactivity of the metal, the phenomenon of passivation is usually studied by examination of the anode process. The decrease in the free energy as a result of this process is known as the "electrochemical affinity", and it can be made as large as desired by increasing the anodic polarization of the metal (*i.e.* by withdrawing electrons); the rate of the anode reaction (a), as measured by the current density, can then be found.

The general definition of passivity still remains valid when this approach is used, and can be expressed in the form proposed by *Lange* and *Göhr*[2]: Passivity is the state of a metal surface in which the rate of corrosion is very low, in spite of an appreciable positive chemical affinity. Where the reaction of a metal is inhibited only because the cathode process is retarded by a high hydrogen overvoltage (*e.g.* zinc in acids), the metal should not be referred to as passive.

It is difficult to define the passivity of a metal on the basis of a measuring technique, and particularly on the basis of the current density-potential curves, which are

[2] *E. Lange*: Thermodynamische Elektrochemie. Hüthig Verlag, Heidelberg 1962, p. 360–371.

generally used for the characterization of passivity [3]. Since the reasons for inhibition can vary widely even in the case of the anode process, it is practically impossible to limit the concept of passivity on this basis, as was emphasized earlier by *Franck* [3].

If we wish to assess the reactivity, and hence the passivity, of a metal towards water and aqueous solutions, the above definition requires that the free energy of the reaction or the position of the equilibrium should be known. Since Equation (c) can be written in the form (d), the position of the equilibrium depends also on the

$$M(s) + n\,H^+ + (n\,A^-) \rightleftarrows M^{n+} + n/2\,H_2 + (n\,A^-) \qquad (d)$$

hydrogen ion concentration (or activity). The electrochemical equilibria relevant to the reactivity of metals have been compiled [4] as a function of pH and in potential-pH diagrams. Comparison of the affinity $A = -\Delta G$ with the rate of reaction (which is usually found from the current density) gives a measure of the passivity, but yields no information about its cause.

Since the surfaces of all metals (including the noble ones [5a,5b]) react very rapidly with oxygen to form an oxide or at least a chemisorbed film of oxygen, the old oxide layer theory of *Faraday* may be a valid explanation for the passivity of metals if the oxide layer prevents the attacking substance from reaching the metal surface and is not broken down by aqueous solutions.

However, not only do the metals behave differently in the same medium, but their reactivities depend very strongly on the attacking substance (*e.g.* chloride ions).

If the oxide layer acted simply as a layer separating the reactants, the passivity provided by this protective layer should be the same in all aqueous media. In reality, however, a given metal often behaves differently in different solutions, even when the oxide layer is destroyed by the solution. To obtain a better understanding of the differences in passivity, therefore, it is necessary to study the kinetics of the formation and breakdown of passive layers, as well as the kinetics in general of the electrode processes (a) and (b) involved in the dissolution of metals. The process (a), which is typical of all metals, can be used for the assessment of the specific passivity and is studied by means of galvanostatic and potentiostatic current-potential curves.

The advantage of potentiostatic measurements [6a–7] is that the whole of the potential range in question can be swept continuously without danger of a sudden, very marked change in the metal/reference electrode Galvani tension, such as occurs in galvanostatic measurements when a certain current is reached.

## I. Factors Affecting the Anodic Dissolution of Metals

### 1. The Crystallinity of the Surface

As in any heterogeneous reaction, the rate of an electrochemical reaction at the metal/solution (or moisture/film) interface is proportional not only to the concentrations, but also to the area of the interface. If the rate of the reaction is to be expressed, as usual, by the current density (mA/cm²), it must be possible to find the area of the interface at any moment. Increasing anodic polarization of a metal originally not possessing a passive layer generally gives a "stationary" current density-potential curve of the type shown in Fig. 1. The current density gradient in the active region and the current density itself after the fall in the passive region depend not only on the nature of the metal, its purity, and the structure of its surface, but also to a large extent on the composition of the electrolyte.

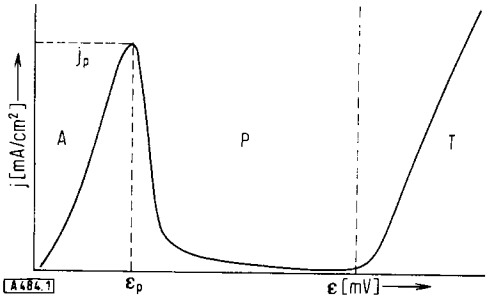


Fig. 1. Typical potentiostatic current density-potential curve for passivation. j = current density = current/geometrical surface area; $\varepsilon$ = Galvani tension between the anode and the reference electrode; A = active region; P = passive region; T = transpassive region; $j_p$ = passivation current density; $\varepsilon_p$ = passivation potential.

Curves of this type, which are used for the examination of the electrode kinetics [8], are not strictly stationary, since the current is never quite constant. It is usual, therefore, to fix a time after which the current is read (5, 30, 60 min or more). The curves obtained in this way sometimes differ considerably [9]. A common practice is therefore to sweep the entire potential range continuously and at a constant speed, and to register the current-potential curve with a pen-type recorder [6b, 10]. This "potentiodynamic" or "potentiokinetic" method is very convenient and time-saving for comparative studies, but the curves still depend on the rate at which the potential is increased.

The current density-potential curves are subject to an error due to the fact that the true surface area is natur-

[3] *K. J. Vetter* in *H. Fischer, K. Hauffe*, and *W. Wiederholt*: Passivierende Filme und Deckschichten. Springer, Berlin-Göttingen-Heidelberg 1956, p. 72, and the comment by *K. Nagel*, p. 90; *U. F. Franck*, Werkstoffe u. Korrosion *9*, 504 (1958).

[4] *M. Pourbaix*: Atlas d'Équilibres Électrochimiques à 25 °C. Gauthier-Villars et Cie., Paris 1963.

[5a] *Ch. Weissmantel, K. Schwabe*, and *G. Hecht*, Werkstoffe u. Korrosion *12*, 353 (1961).

[5b] *Ch. Weissmantel*, Habilitation Thesis, Technische Universität Dresden, 1963.

[6a] *H. Gerischer*, Angew. Chem. *70*, 285 (1958); *W. Vielstich* and *H. Gerischer*, Z. physik. Chem. N.F. *3*, 16 (1955); *4*, 10 (1955); *N. D. Greene* and *R. B. Leonard*, Electrochim. Acta *9*, 45 (1964); *A. Bewick* and *M. Fleischmann, ibid. 8*, 89 (1963); *W. M. Schwarz*, Analytic. Chem. *35*, 1770 (1963); *M. Pourbaix* and *F. Vandervelden*, Rapport Technique CEBELCOR, RT 98, 1961.

[6b] *Ya. M. Kolotyrkin, I. E. Bryksin, G. M. Florianovič*, and *A. N. Čemodanov*, Probl. fiz. Khim. *3*, 14 (1963).

[7] *P. Delahay*: New Instrumental Methods in Electrochemistry. Interscience Publishers, New York 1954; *G. Charlot, J. Badaz-Lambling*, and *B. Trémillon*: Electrochemical Reactions. Elsevier, Amsterdam-New York 1962.

[8] *K. J. Vetter*: Elektrochemische Kinetik. Springer, Berlin-Göttingen-Heidelberg 1961.

[9] *R. Littlewood*, Corrosion Science *3*, 99 (1963).

[10] *N. D. Greene* and *R. B. Leonard*, Electrochim. Acta *9*, 45 (1964); *M. Pourbaix*, Werkstoffe u. Korrosion *15*, 821 (1964).

ally greater than the geometrical area. The rugosity factor, which is generally assumed to be between 1.5 and 4, would not affect the shape of the curve if it remained constant. In reality, however, the nature of the attack on the metal surface, and hence also the rugosity factor, may vary appreciably with the potential, as can be seen, for example, in Fig. 2. Whereas the surface of

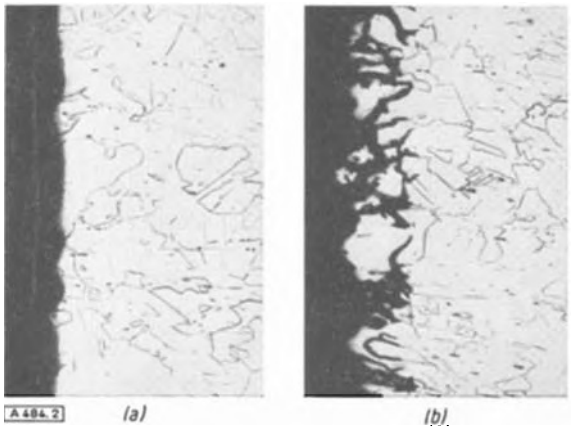


Fig. 2. Attack on nickel after anodic polarization in 5 N $H_2SO_4$ at 25 °C (a) at $E_H$ = 300 mV and (b) at $E_H$ = 1450 mV (against the standard hydrogen electrode). Section perpendicular to the attacked surface. Magnification 150 ×.

nickel is uniformly dissolved at +300 mV, pronounced grain boundary corrosion is found at +1450 mV under the same conditions and when the same quantity of nickel has passed into solution [11]. Uniform surface attack begins again at still higher potentials. Stable surface oxide films would scarcely be able to withstand this concentration of acid (5 N). In any case it is clear that in view of this considerable dependence of the rugosity factor on the potential, any conclusions regarding the kinetics of the electrode process can be only qualitative. The grain boundaries and sub-grain boundaries of the metal (which is generally polycrystalline) are naturally very important.

Structure defects (sub-microscopic fissures) can affect anodic attack on polycrystalline materials. A polished nickel surface (cross section of a rod) with no microscopically visible defects exhibited a granular surface with holes after anodic polarization in 0.7 N sulfuric acid at 60 °C, although the solution was free from halide ions. A 5.5 mm layer was then cut off, and the electrode was anodically polarized under the same conditions; the holes reappeared in the same positions. The rod evidently contained defects running in an axial direction. Since the diameter of a hole is some 50 times as great as that of a crystallite, this attack could hardly be due to impurities concentrated at the boundaries, as has been suggested.

On the other hand, structural defects of this type may be the cause of remarkable "memory effects" in relation to passivity, if electrolyte enters these cracks. For example, a nickel electrode that had been anodically polarized in hydrochloric acid was thoroughly cleaned and its surface ground; when this electrode was subsequently polarized in sulfuric acid, it had a much higher passivation current density $j_p$ (cf. Fig. 1) than an electrode of the same material that had not been in contact with hydrochloric acid. This has been assumed [12] to result from the penetration of electrolyte anions into normal metal structures; however, this explanation is unacceptable, since it has been shown that for "smooth" surfaces of polycrystalline metals, the intensity ratio of $\beta$ to $\gamma$ radiation from $^{82}Br^-$ ions absorbed from the solution does not change [13]. If the $^{82}Br^-$ ions had penetrated into the grain boundaries, the absorption of the $\beta$ radiation by the metal should have led to a marked decrease in this ratio. Autoradiographic studies [14] have shown, however, that anions are preferentially adsorbed at the grain boundaries of the metal surface (60 to 70% of the total adsorption). Since (as we shall see later) the breakdown of the passive layer begins with the adsorption of anions, the grain boundaries play an important part in the transition from the passive to the active state.

Even single crystals of metal can differ enormously in their anodic behavior, owing to differences in the behavior of the lattice planes, defects and dislocations, or traces of impurities. The adsorption of anions depends on the surface energy of the metal atoms in the various lattice planes, and is much less pronounced for the (111) plane of nickel than for the (110) and (100) planes, as has been shown with the aid of $^{14}CN^-$ and $H^{35}S^-$ ions [15]. In autoradiographs of a polycrystalline iron surface on which $^{35}S$ vapor was adsorbed, *Lacombe* [16] obtained differences in blackening that corresponded to the etch micrograph (Fig. 3).

*Piontelli* [17] showed, for nickel and lead, that during anodic (and cathodic) polarization, the difference in the surface energies of the various lattice planes gives rise

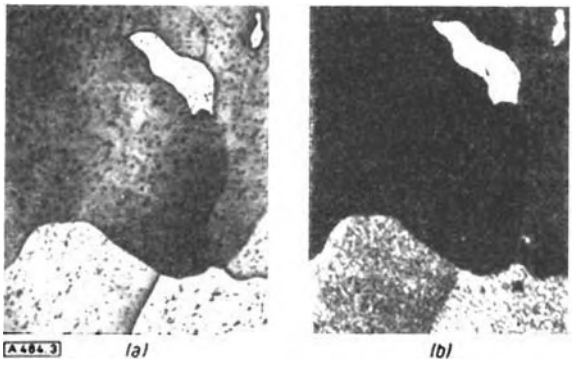


Fig. 3. (a) Etch micrograph of a sample of polycrystalline iron. (b) Autoradiograph of the same sample after adsorption of sulfur vapor labelled with $^{35}S$. Magnification 10 ×.

[11] *E. Kunze*, Dissertation, Technische Universität Dresden, 1956.

[12] *N. A. Balašova*, Dokl. Akad. Nauk S.S.S.R. *103*, 639 (1955); Z. physik. Chem. *207*, 340 (1957); Zh. fiz. Khim. *32*, 2266 (1958); Elektrochim. Acta *7*, 559 (1962).

[13] *C. Herold*, Dissertation, Technische Universität Dresden, 1964; Z. physik. Chem., in press.; *W. Nowak*, Dissertation, Technische Universität Dresden, 1963.

[14] *K. Schwabe*, Electrochim. Acta *6*, 223 (1962).

[15] *W. Nowak*, Dissertation, Technische Universität Dresden, 1963.

[16] *P. Lacombe*, Corrosion et Anticorrosion *8*, 215 (1960).

[17] *R. Piontelli* and *G. Poli*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 320 (1958); *R. Piontelli*, *G. Poli*, and *G. Seravalle* in *E. Yaeger*: Transactions of the Symposium on Electrode Processes. J. Wiley and Sons, New York 1961.

to different overvoltages and to different patterns of attack and deposition. The reactivity of an atom on the surface of the metal in this case must obviously be assessed in the same way as in the case of the catalytic activity of a contact; consequently, differences in behavior must be expected even in the same lattice plane, as a result of defects, dislocations, *etc.* [18].

### 2. Influence of the Solvent

The effect of the solution on the kinetics of the anode process depends on the activities of the hydrogen ions, the metal ions, and the anions at the interface. These activities are not the same as those found in the bulk of the solution, and they vary with time and with potential. Moreover the activities (particularly that of the hydrogen ions) are strongly dependent on the presence of other ions, especially metal ions [19]. Thus the current, $i_a$, measured potentiostatically against a reference electrode at a constant Galvani tension and at a constant concentration of the various reactants depends on a number of factors:

$$i_a = \Phi(f_i, \varepsilon, a^{o}_{H^+}, a^{o}_{M^{n+}}, a^{o}_{A^-}, t) \qquad (e)$$

$f_i$ = effective surface area of the electrode; $\varepsilon$ = Galvani tension between the working electrode and the reference electrode; $a_0$, a = activities of the ions at the interface and in the bulk of the solution; t = time; and

$$f = \varphi_1(t, \varepsilon); \; \varepsilon = \varphi_2(a_{H^+}, a_{M^{n+}}, a_{A^-}, t)$$

$$a_{M^{n+}} = \varphi_3(t); \; a_{H^+} = \varphi_4(t, a_{M^{n+}})$$

$$a^{o}_i \neq a_i$$

Thus conflicting views are held [20] regarding even the kinetics of the anodic dissolution of iron. Owing to the strong interionic interactions, the activity coefficients of the ions are very different from unity, and must therefore be taken into account. This was demonstrated in the anodic dissolution of iron in $HClO_4$, where the hydrogen ion activity at a constant $HClO_4$ concentration was changed by a factor of more than 100 by the addition of large quantities of $NaClO_4$ [21]. The anode current density was found to depend on the hydrogen ion concentration in accordance with

$$j_{Fe} = K_+ a^{z}_{H^+} \exp K' \qquad (f)$$

where $K_+$ and $K'$ are proportionality factors ($K'$ contains characteristic electrode-kinetic factors such as the transition factor and transition valence). The order of the reaction with respect to the hydrogen ion activity is $z \approx -2$ at constant $H^+$ concentration.

The rapid build-up of high metal salt concentrations in the diffusion layer as a result of the anodic dissolution leads to large changes in the hydrogen ion activity [19]. A number of variants of the pulse technique are used to avoid changes at the site of the surface reaction due to diffusion and transport, since these changes are generally the slowest of all the processes, and would therefore be rate-determining. For example, the Galvani tension may be measured during the passage of a short pulse of current, or the decay of polarization may be measured after the current has been switched off; alternating current methods, *e.g.* with square pulses, are used in many cases, the inhibiting processes being studied by means of impedance measurements [22]. However, the formation and breakdown of passive layers are often controlled by slower changes taking place on the surface of the electrode. The situation is further complicated by the fact that we must now consider two interfaces (metal/passive layer and passive layer/solution: "multiple electrodes") and transport processes through these layers.

For these reasons it is not possible to give a qualitative and quantitative interpretation for, or even to predict, the passivity of metals under any given conditions. Nevertheless, important information about the nature of the passive layer and about its formation and breakdown has been obtained by the study of simple systems.

## II. Nature and Properties of Passive Layers. Chemisorbed Film or Oxide Phase?

Only a few years ago it was generally thought that in order to prevent dissolution of the metal, the passive layer must be an independent phase, generally an oxide phase [6, 23]. It was usually assumed in accordance with *Müller*'s covering theory [24] that during the anodic dissolution of the metal, a porous salt layer is deposited on the anode when the concentration of the salt in the diffusion layer rises above the saturation limit. The current density (and hence the polarization) at the parts of the anode that are not covered is then so high that a new process, *e.g.* that represented by Equation (g),

$$M + OH_2 \rightarrow MO + 2\,H^+ + 2\,e^- \qquad (g)$$

begins. This new process leads to the formation of the actual non-porous passive layer, the oxide phase itself.

[18] *F. F. Volkenstein*, Zh. fiz. Khim. *22*, 311 (1948); *23*, 917 (1949). The difficulty of reaching theoretical, and in particular quantum-mechanical, conclusions regarding the energy states at the surface of a crystal can be seen in *J. Koutecký*, Angew. Chem. *76*, 365 (1964); Angew. Chem. internat. Edit. *3*, 496, (1964).

[19] *K. Schwabe*, Österr. Chemiker-Ztg. *65*, 339 (1964).

[20] *T. Hurlen*, Acta chim. scand. *14*, 1533 (1960); *K. E. Heusler*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 582 (1958); *A. Frumkin*, *B. Kasanov*, and *B. Burstein*, Discuss. Faraday Soc. *1*, 259 (1947); *J. O.M. Bockris*, *D. Drazioc*, and *A. Despic*, Electrochim. Acta *4*, 325 (1961).

[21] *K. Schwabe* and *Ch. Voigt*, Werkstoffe u. Korrosion, in press; *K. E. Heusler*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 582 (1958); *K. Schwabe*, J. electrochem. Soc., in press.

[22] *P. Delahay*, Ann. Rev. physic. Chem. *8*, 229 (1957); *H. Gerischer*, *ibid. 12*, 227 (1961); *P. Delahay* in: Advances in Electrochemistry and Electrochemical Engineering. Vol. 1, Electrochemistry. Interscience Publishers, New York-London 1961, p. 233; *W. H. Reinmuth*, Analytic. Chem. *36*, 211 R (1964); *N. Tanaka* and *R. Tamamushi*, Electrochim. Acta *9*, 963 (1964); *Yu. N. Michalylovskij*, Zh. fiz. Khim. *37*, 937 (1963).

[23] International colloquium on the passivity of metals, held at Schloss Heiligenberg (Germany) on September 2nd to 7th, 1957; *A. M. Sukhotin*, Usp. Khim. *25*, 312 (1956).

[24] *W. J. Müller*: Die Bedeckungstheorie der Passivität der Metalle und ihre experimentelle Begründung. Verlag Chemie, Berlin 1933.

*Bonhoeffer* [25] improved this theory by careful experimental and theoretical studies on iron. It was also shown in the course of this work [26], however, that the quantity of electricity required for the cathodic reduction of the passive layer formed on iron in $HNO_3$ corresponds to a monomolecular layer. In the case of metals exhibiting so-called chemical passivity (Fe, Co, Ni, Cr) it was unanimously accepted that the passive layer was an oxide. The chemically passive metals are characterized by a steep increase in current in the transpassive region (cf. Fig. 1), accompanied by evolution of $O_2$ or formation of a higher valence state of the metal. In so-called mechanical passivity (Al, Ta, Ti, Zr), the passive range is very much wider; the current generally rises very gradually, the rise often starting only at a potential of about 20 V or more, and the passive layer being broken down in places by spark discharge [27]. This type of passivity can be obtained with all metals that do not form higher valence states, if the metals are anodically polarized in saturated solutions of their salts [28]. Salt barrier layers are formed in many cases [29], and the structures of these layers have a marked influence on the beginning of the current increase. In any case, the salt barrier layers give rise to appreciable inhibition only if they are formed directly from the metal, and not *via* the solution [28].

The study of the passive oxide layers on Fe, Ni, and Cr is difficult, since these layers are very thin and can change during the isolation process. Many attempts have been made to study these layers by optical and electron-optical methods [30]. However, these studies are all open to the objection that the layers observed may not have been the same as the layers responsible for passivation, particularly when they were not studied in the passive state, *i.e.* in the solution itself, but (as in most cases) were isolated by dissolution of the metal. Even optical measurements carried out during the passivation process are not very informative, as has been shown by *Kruger* [30], who observed the presence of oxide layers even before the passive state had been reached. Polarization measurements on light reflected from the passive layer on iron [31] indicated that the layer is between 10 and 80 Å thick. Roughly the same result was obtained by the optical measurement of the layer thicknesses on nickel, chromium, and chromium-nickel stainless steels [31, 32]. Electron-diffraction studies by *Pfisterer*, *Politycky*, and *Fuchs* [33] on passive layers produced on nickel by treatment with chromosulfuric acid indicated an average thickness of 12 Å.

The thickness of the passive layer cannot be reliably determined by cathodic reduction. In the first place, it is not certain that the electricity required in order to reach the active state is used only for the reduction of the passive layer [34] (some may be used, *e.g.*, to reverse the charge of the double layer); secondly, the active state may be reached after the passive layer has been removed from only part of the surface; and finally, it is necessary to make more or less arbitrary assumptions regarding the rugosity factor. Further, local currents may also contribute to the reduction of the oxide layer [35]. The layer thicknesses found by cathodic reduction are approximately the same as, or in some cases smaller than, those found by optical methods [26, 36].

About the same thicknesses are found from the quantity of electricity required for passivation by anodic polarization. *Arnold* and *Vetter* [37] found that the quantity of electricity required to break down a passive layer on nickel is 4 millicoulomb/cm², corresponding roughly to a monomolecular "oxide layer". If, on the other hand, the nickel is polarized to the range in which evolution of oxygen begins, 28 millicoulomb/cm² is required according to *Okamoto* and *Sato* [38], corresponding to an oxide layer about 40 Å thick and having a rugosity factor of 3 [37]. *Franck* and *Weil* [39] had already shown, from the spontaneous widening of the activation range in passive iron wires, that the thickness of the passive layer depends on the potential. Using anodic coulometry *Nagayama* and *Cohen* [40] recently found layer thicknesses of 10 to 30 Å on iron in alkaline borate solutions.

Another method of determining the thickness of a passive layer during its formation is based on the measurement of the change in capacitance of the double layer [41] during anodic polarization. An oxide phase with a thickness that differs appreciably from that of the adsorption layer should, if it is firmly attached to the metal, show its presence by a reduction in capacitance. *Hackerman* and *Popat* [42] have shown, however, that the anodic capacitance-potential curves for Ni, Fe, and Cr/Ni steels are the same as that for Pt, which certainly

[25] *K. F. Bonhoeffer*, Z. Elektrochem. angew. physik. Chem. *47*, 147 (1941); *59*, 594 (1955); *U. F. Franck*, Werkstoffe u. Korrosion *9*, 504 (1958).

[26] *H. Beinert* and *K. F. Bonhoeffer*, Z. Elektrochem. angew. physik. Chem. *47*, 536 (1941).

[27] *A. Güntherschulze* and *H. Betz*, Z. Physik *91*, 70 (1934); *92*, 367 (1934).

[28] *K. Schwabe*, Habilitation Thesis, Technische Hochschule Dresden, 1933. The view that the dissolution can be appreciably inhibited only by an oxide or a salt formed directly from the metal was subsequently confirmed by *R. Piontelli*, Werkstoffe u. Korrosion *3*, 191 (1952).

[29] *K. Schwabe* and *F. Lohmann*, Z. physik. Chem. *215*, 158 (1960/61).

[30] *J. O. Bockris*, *M. A. V. Devanathan*, and *A. K. N. Reddy*, Proc. Roy. Soc. (London) *279*, A, 1378 (1964); *J. Kruger*, J. electrochem. Soc. *110*, 654 (1963); *A. K. N. Reddy*, *N. Genshaw*, and *J. O. Bockris*, J. electroanalyt. Chem. *8*, 406 (1964); *A. K. N. Reddy*, *M. G. B. Rao*, and *J. O. Bockris*, J. chem. Physics *42*, 2246 (1965).

[31] *L. Troustad*, Trans. Faraday Soc. *29*, 502 (1933); *31*, 1151 (1935); *L. Troustad* and *T. Hövenstad*, Z. physik. Chem. *A 170*, 172 (1934).

[32] *E. M. Mahla* and *N. A. Nielsen*, Trans. electrochem. Soc. *93*, 1 (1948); *T. N. Rhodin*, Corrosion *12*, 123, 465 (1956).

[33] *H. Pfisterer*, *A. Politycki*, and *E. Fuchs*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *63*, 257 (1959).

[34] *K. F. Bonhoeffer*, Z. Elektrochem. angew. physik. Chem. *47*, 147 (1941); *H. Beinert* and *K. F. Bonhoeffer*, *ibid. 47*, 441 (1941).

[35] *K. F. Bonhoeffer* and *K. J. Vetter*, Z. physik. Chem. *196*, 127 (1950).

[36] Regarding measurements of this nature on nickel, cf. *G. Siemens*, Diploma Thesis, Technische Universität Dresden, 1961.

[37] *K. Arnold* and *K. J. Vetter*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 407 (1960); *Ya. J. Turyan* and *Yu. S. Gorodeckij*, Dokl. Akad. Nauk S.S.S.R. *117*, 655 (1957); *M. A. V. Devanathan* and *M. Selvaratnam*, Trans. Faraday Soc. *56*, 1820 (1960); *G. Siemens*, Diploma Thesis, Technische Universität Dresden, 1961.

[38] *G. Okamoto* and *N. Sato*, J. electrochem. Soc. Japan *27*, E 125 (1959); Trans. Japan Inst. Metals *1*, 16 (1960).

[39] *U. F. Franck* and *K. Weil*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *56*, 814 (1952).

[40] *M. Nagayama* and *M. Cohen*, J. electrochem. Soc. *109*, 781 (1962).

[41] For the procedure for the measurement of differential double-layer capacities, cf. *P. Schubert*, Z. Chem. *4*, 11 (1964).

[42] *N. Hackerman* and *P. V. Popat*, J. physic. Chem. *65*, 1201 (1961).

does not form an oxide phase under these conditions. Aluminum, on the other hand, behaves as would be expected if an oxide layer were formed [43] (see Fig. 4).

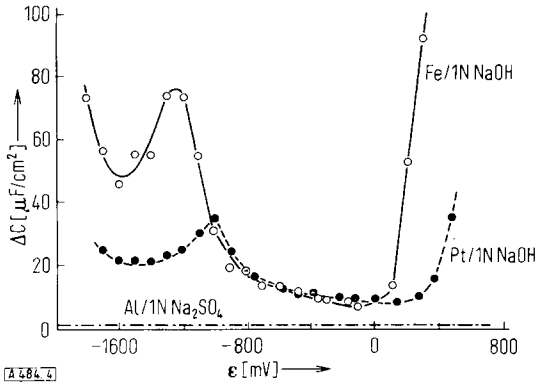


Fig. 4. Capacitance-potential curves of the anodic double layer on Fe, Pt, and Al at 25 °C. $\Delta C$ = differential double layer capacitance; $\varepsilon$ = Galvani tension, measured against a saturated $Hg/Hg_2SO_4,Na_2SO_4$ electrode.

The steep increases in capacitance at the cathodic and at the anodic ends of the curve can be attributed to the liberation of $H_2$ and $O_2$, respectively (high pseudo-capacitance due to the transition current).

The differences from the trough-shaped capacitance curves observed in neutral solutions [43a, 43b], *i.e.* the presence of the maximum at about −1200 mV, is probably due to the absorption of $OH^-$ ions. A similar maximum was observed by *Hackerman* [43c].

It follows that the passive layer on iron, nickel, and chromium (if an oxide layer is in fact formed) cannot consist of more than a few layers of molecules. The energy relationships in extremely thin layers are by no means comparable to those in the bulk materials [44]. If, therefore, the inflection in the potential curve, and particularly the Flade potential [28] of iron, is used as an argument for the existence of oxide phases because they point to equilibria between the metal and the oxide, it must be borne in mind that the free energies calculated from these inflections will not be the same as those corresponding to an equilibrium reaction such as that represented by Equation (h). Moreover, the activities at the surface of the metal are unknown, and the electrode processes are not generally reversible. In fact, the

$$M + n\,H_2O \rightleftharpoons MO_n + 2\,n\,H^+ + 2\,n\,e^- \qquad (h)$$

inflection of the Galvani tension of iron found by *Flade* [45] (from potential-time curves) when the external current was switched off after passivation of the iron in, *e.g.*, sulfuric acid is nowhere near the equilibrium Galvani tension $E_H$ [*] of any of the iron oxides.

$$Fe/FeO: E_H = -0.060\ V;$$
$$Fe/Fe_3O_4: E_H = -0.082\ V;$$
$$Fe/Fe_2O_3: E_H = -0.040\ V \text{ at pH } 0$$

The Galvani tension $E_{H_F}$ of iron against the standard hydrogen electrode during the transition from the passive to the active state (Flade potential) varies with the pH as expected in a reversible reaction of this type:

$$E_{H_F} = (0.580 - 0.058)pH \qquad (i)$$

It is therefore necessary to make further assumptions, the most important of which is that the passive layer consists of two oxides, the iron being in equilibrium with a layer of $Fe_3O_4$, which in turn is in equilibrium with an overlying $\gamma$-$Fe_2O_3$ layer [46]. The Galvani tension calculated from the corresponding $\Delta G$ values is much closer to the experimental Flade potential (+0.580 V at pH 0), but it is difficult to imagine two oxide phases in a layer between 10 and 30 Å thick, particularly since the equilibria must have been reached in fractions of a second during the passivation. Assumptions involving iron oxides with particularly high energies and containing excess oxygen have also failed to yield a satisfactory explanation for the activation or passivation potentials [47].

Different oxide phases have also been postulated for nickel, on the basis of the passivation and activation Galvani tensions, but no such pronounced inflections are found as in the case of iron. On the other hand, up to five activation Galvani tensions have been found for very pure nickel in sulfuric acid when the current was switched off [48]. The Galvani tension corresponding to the Flade potential of iron is more negative in the case of nickel, and changes linearly with pH. *Okamoto* and *Sato* [49] found for the passivation of nickel:

$$E_{H_F} = (0.48 - 0.060)pH \qquad (k)$$

Since the activation and passivation Galvani tensions of nickel again do not agree with values calculated from equilibria between the metal and a single oxide, *Okamoto* and *Sato* [50] recently postulated that the passive layer consists of several oxides, *i.e.* NiO and $Ni_3O_4$, and possibly also $Ni_2O_3$. However, multiphase passive layers are even less likely in this case, owing to the thinness of the layers.

[43] *M. Paul*, Dissertation, Technische Universität Dresden, 1965.

[43a] *W. L. Kheifets* and *B. S. Krasikov*, Dokl. Akad. Nauk S.S.S.R. *94*, 101 (1954).

[43b] *M. C. Bansa* and *N. Hackerman*, J. electrochem. Soc. *111*, 114 (1964).

[43c] *P. V. Popat* and *N. Hackerman*, J. physic. Chem. *65*, 1201 (1961).

[44] *A. Mayer*: Physik dünner Schichten, Vol. 1 and 2. Wissenschaftl. Verlagsges., Stuttgart 1950 and 1955; *R. Suhrmann, G. Wedler, et al.*, Z. physik. Chem. N.F. *10*, 184 (1957); *35*, 47, 155 (1962); *36*, 165 (1963); *42*, 187 (1964); *V. M. Novakovsky*, Electrochim. Acta *10*, 353 (1965).

[45] *F. Flade*, Z. physik. Chem. *76*, 513 (1911); *U. F. Franck*, Habilitation Thesis, Universität Göttingen, 1954.

[*] The subscript H indicates that the potential is referred to the standard hydrogen electrode.

[46] *H. Göhr* and *E. Lange*, Naturwissenschaften *43*, 12 (1956); Z. Electrochem., Ber. Bunsenges. physik. Chem. *61*, 1291 (1957).

[47] Cf. *K. J. Vetter*, Z. physik. Chem. *202*, 1 (1953), and the objections of *W. Schottky*, Z. physik. Chem. N.F. *4*, 165 (1955).—*G. H. Cartledge*, J. physic. Chem. *60*, 1571 (1956); *A. Krause*, Naturwissenschaften *47*, 202 (1960).

[48] *L. F. Trueb, G. Trümpler*, and *N. Ibl*, Helv. chim. Acta *44*, 960 (1961).

[49] *G. Okamoto* and *N. Sato*, J. electrochem. Soc. Japan *25*, 199 (1957); J. Japan Inst. Metals *23*, 662 (1959).

[50] *G. Okamoto* and *N. Sato*, J. Japan Inst. Metals *24*, 179 (1960).

For chromium, which goes into solution as $CrO_4^{2-}$ in the transpassive state, *Lange* and *Weidinger*[51] also assumed that the passive layer consists of two oxides or hydroxides [$Cr(OH)_2/Cr(OH_3)$], the chromate formed in the transpassive range being derived from the $Cr(OH)_3$, in accordance with Equation (l). Once again this theory is opposed by the extreme thinness of the

$$Cr(OH)_3 \rightarrow CrO_3 + 3\,H^+ + 3\,e^- \qquad (l)$$

layer, as well as by deviations from the equilibrium Galvani tensions.

However, if oxide phases of this nature are morphologically and thermodynamically improbable in the stationary passive state, which is the only state in which the thickness of the layers can be measured directly, there is even less justification for regarding them as the primary causes of passivation, *i.e.* of the negative current-potential characteristic, since even fewer layers of molecules would have to be sufficient in that case. This brings us to the view favored by *Uhlig*[52], *Kolotyrkin*[53], *Schwabe*[54a,54b], and other autors, *i.e.*, that the primary cause of passivation is chemisorbed layers of oxygen, or more generally, monomolecular surface layers that inhibit the phase transition.

According to *Uhlig*, when an anodic potential is applied to iron, a layer of chemisorbed atomic oxygen is formed and this is followed by a layer of chemisorbed molecular oxygen, as indicated in Equation (m).

$$Fe + 3\,H_2O \rightleftarrows Fe(O{-}O_2)_{ads} + 6\,H^+ + 6\,e^- \qquad (m)$$

From the heat of chemisorption of the oxygen/iron system, *Uhlig*[55] calculated the standard contact potential and found $E_H = +0.56$ V; this value agrees fairly closely with that found by experiment (0.58 V). Equation (m) also predicts the experimentally observed dependence on pH. The fact that the Flade potential varies with the metal surface and with the electrolyte (particularly in the case of nickel) can be explained by the difference in the heats of adsorption. *Uhlig*'s calculated values for the "thicknesses" of the chemisorbed films can also be reconciled with the experimental values if it is borne in mind that an oxide phase may be formed over this chemisorbed layer in the stationary state. $Fe^{3+}$ ions may be formed in the passive state in accordance with Equation (n), and these would be converted by hydrolysis into iron oxide. The experimental

$$Fe_2(O{-}O_2)_{ads} + 6\,H^+ \rightarrow 2\,Fe^{3+} + 3\,H_2O \qquad (n)$$

potentials obtained for nickel can also be essentially explained by a chemisorbed layer of oxygen, although they cannot be readily reconciled with the calculated values in this case[56].

*Kolotyrkin*[53] carried out impendance and double-layer capacitance measurements on chromium, nickel, and stainless steel, partly based on investigations by *Kabanow*[57,58], and found that the dissolution of these metals was inhibited by activated adsorption of oxygen from the water; he pointed out the analogy with the inhibition of the oxidation of $H_2$ on Pt electrodes coated with oxygen. *Trümpler*[59] has also recently postulated chemisorbed oxygen as the primary cause of passivation, on the basis of impendance measurements carried out mainly on anodically polarized nickel.

An argument advanced against the chemisorption theory is that a monomolecular chemisorbed layer could not form a continuous covering, and so could not cause passivation, since this would be counteracted by the dissolution of the oxide film in the steady state. A perfectly non-porous covering layer could exist only while the thickness of the layer was increasing[6]. However, if the chemisorbed layer of oxygen is formed from the water in accordance with Equation (o), then since the

$$M + OH_2 \rightleftarrows MO_{ads} + 2\,H^+ + 2\,e^- \qquad (o)$$

surface of the metal in an aqueous solution is completely covered with adsorbed water dipoles, this reaction should give a non-porous passive layer at least above a certain anode potential, provided that the dissolution process is not promoted by the displacement of the water or the oxygen by other strongly adsorbed molecules or ions. In the case of the base metals moreover, the reaction (p) must also be expected to occur. Even films of iron formed by evaporation in a high vacuum react in-

$$M + OH_2 \rightleftarrows MO + H_2 \qquad (p)$$

stantaneously with water vapor in accordance with Equation (p) to form $H_2$, which can be detected mass-spectrometrically[56].

Studies on the protection of iron surfaces by dibenzyl sulfoxide show that a monomolecular adsorbed layer is sufficient to inhibit completely the dissolution of the metal[60][*].


[51] *H. G. Weidinger* and *E. Lange*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 468 ,1165 (1960).

[52] *H. H. Uhlig* and *J. J. Lord*, J. electrochem. Soc. *100*, 216 (1953); *H. H. Uhlig* and *A. Geary*, *ibid. 101*, 215 (1954); *H. H. Uhlig* and *T. O. Connor*, *ibid. 102*, 562 (1955); *H. H. Uhlig*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 626, 700 (1958).

[53] *Ya. M. Kolotyrkin*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 664 (1958); Zh. fiz. Khim. *34*, 1121 (1960); *Ya. M. Kolotyrkin* and *N. Ya. Bune*, Z. physik. Chem. *214*, 264 (1960).

[54a] *K. Schwabe* and *G. Dietz*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 751 (1958); *K. Schwabe*, Z. physik. Chem. *214*, 343 (1960).

[54b] *K. Schwabe*, Electrochim. Acta *3*, 186 (1960).

[55] *H. H. Uhlig* and *P. F. King*, J. electrochem. Soc. *106*, 1 (1959).

[56] *J. Osterwald* and *H. H. Uhlig*, J. electrochem. Soc. *108*, 515 (1961).

[57] *B. N. Kabanov* and *D. I. Leikis*, Zh. fiz. Khim. *20*, 995 (1946); *C. A. Rosencvejg* and *B. N. Kanabov*, *ibid. 22*, 513 (1948); *V. V. Lossev* and *B. N. Kabanov*, *ibid. 28*, 824, 914 (1954).

[58] *B. N. Kabanov* and *D. I. Leikis*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 660 (1958).

[59] *L. F. Trueb* and *G. Trümpler*, Helv. chim. Acta *44*, 1433 (1961).

[60] *K. Schwabe*, Dechema-Monographien *45*, 273 (1963).


[*] It has been observed repeatedly that monomolecular layers of inhibitors can effect almost complete inhibition of corrosion [see, *e.g.*, *G. Karagounis* and *H. Reis*, Z. Electrochem. Ber. Bunsenges. physik. Chem. *62*, 865 (1958)]. What is possible in inhibition (*i.e.* prevention of the reaction of a metal in an aggresive medium by the addition of a foreign substance to the medium) is even more likely to occur in passivation (*i.e.* prevention of reaction in an aggresive medium by the metal itself).

It has been shown [54,54a,61], for nickel and chromium in sulfuric acid, that the Galvani tensions of the passivity range can be maintained and inhibited dissolution can be observed if, during the anodic polarization, the electrodes are ground with a corundum disk so that more metal is removed mechanically in a given time than is carried into solution by the current. However, the current-voltage curve is still found to be typical of those observed during passivation. Although the current is much higher in the passive range than for an unground electrode, it is still at least two orders of magnitude smaller than it should be at the same potential on the basis of the trend of the curve in the active range (see Fig. 5). It follows that neither a porous salt layer nor an

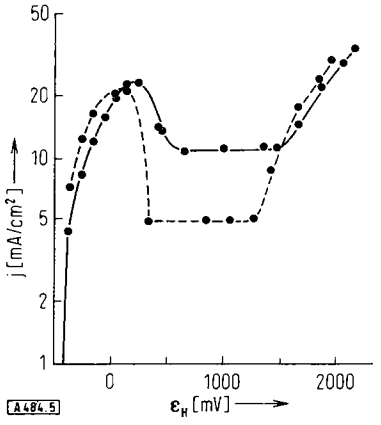


Fig. 5. Potentiostatic current density-potential curves for a ground Cr electrode in 1 N $H_2SO_4$ [61]. Quantity of Cr reacting at the anode *ca.* $2.7 \times 10^{-6}$ g cm$^{-2}$ sec$^{-1}$; $\varepsilon_H$ = potential, measured against a standard hydrogen electrode.
• - - - • Rate of abrasion = $2.2 \times 10^{-5}$ g cm$^{-2}$ sec$^{-1}$.
• ·-·-· • Rate of abrasion = $4.4 \times 10^{-5}$ g cm$^{-2}$ sec$^{-1}$.

oxide phase is a necessary condition for passivation, since if the anodic polarization is adequate and if water is preferentially adsorbed, any metal atom that is exposed mechanically is immediately re-covered by oxygen. The high current densities that are required for passivation when the electrode is ground in acids could not be achieved in the case of iron [62]. In alkaline solution, however, the electrode could not be activated by grinding, owing to the preferential adsorption of $OH^-$.

If we accept that passivation, at least in the cases of iron, nickel, and chromium, is primarily due to chemisorbed layers, oxide phases may still be gradually formed in the steady passive state, since a corrosion current flows even in the passive state, owing to the passage of metal ions through the chemisorbed layer. However, these layers are not the cause of the marked inhibition of the dissolution of the metal, although they hinder the access of the ions required for the dissolution. Consequently, the mechanism of conduction in these layers (in the cases of Ni, Fe, and Cr) is also of minor importance; the main factor is the junction between the metal and the oxide phase, which can be regarded as a chemisorbed layer. Chemisorbed layers on the surface of an ideal single crystal are probably non-porous, but penetration of the metal ions will be easier at edges, grain boundaries, and other points of high energy. An effect of this nature due to lattice defects was used by *Pryor* [63] to explain the Flade potential in a passivating $\gamma$-$Fe_2O_3$, and a similar effect would explain the marked dependence of the passivity on the pretreatment of the metal surface.

The growth of a passive layer is greatly influenced by its conduction mechanism [64,68]. If the oxide is an electronic semiconductor, the migration of the metal ions through oxide layers of appreciable thickness will require a higher anode potential than the process (q). Oxy-

$$2\,H_2O \rightarrow O_2 + 4\,H^+ + 4\,e^- \qquad (q)$$

gen will therefore be liberated, unless further oxidation of the metal ions in the passive layer, and hence breakdown (r) down to the chemisorbed film, is possible.

$$2\,MO + OH_2 \rightarrow M_2O_3 + 2\,H^+ + 2\,e^- \qquad (r)$$

If the Galvani tension is suitable, the reactions (q) and (r) can occur simultaneously. Further, the higher oxide may have an additional inhibiting action if it grows directly on the metal (secondary passivation) [65]. In the cases of Fe, Ni, Cr, and Co, it appears that the electronic conductivity of the passive layer formed during the steady passive state normally predominates over the passage of ions to such an extent that a further increase in voltage leads to an increase in the current and to reactions (q) and (r) (cf. Fig. 1). In the case of Al, Ta, Ti, and Zr [66], on the other hand, the electronic conductivities of the oxides are so low that, at the high field strengths that prevail [67], metal ions are transported through the passive layer to the solution side, where their hydrolysis leads to the growth of the layer. Consequently, the current does not increase to the breakdown point as the voltage is increased (cf. Fig. 9).

The first step in the passivation of very base metals is based mainly on reaction (p). If the passive state is maintained for long periods, oxide phases, sometimes containing different oxidation states, are observed. Thus in

[61] *K. Schwabe, K. Müller,* and *A. Loge,* Electrochim. Acta *8,* 193 (1963).

[62] *K. Schwabe,* Z. physik. Chem. *214,* 343 (1960).

[63] *M. J. Pryor,* J. electrochem. Soc. *106,* 557 (1959).

[64] Cf. in particular *L. Young*: Anodic Oxide Films. Academic Press, London-New York, 1961. Regarding the junction between the two phases, see also *J. H. van der Merwe,* Proc. physic. Soc., Sect. A *63,* 616, (1950).

[65] Regarding the secondary passivation of Ni, cf. *E. Kunze* and *K. Schwabe,* Corrosion Science *4,* 169 (1964); *A. U. MacRae,* Surface Sci. *1,* 319 (1964).

[66] The anodic oxide layers on these metals, particularly Al, Nb, and Ta, were studied earlier by *A. Güntherschulze* and *H. Betz,* Z. Physik *91,* 70 (1934); *90,* 367 (1934), in connection with their use as rectifiers in electrolytic condensers. For work on other metals, the reader is referred to more recent publications:
For Ta, cf. *P. G. H. Draper* and *W. M. Jacobs,* Trans. Faraday Soc. *59,* 2888 (1963); *L. D. Calvert* and *P. G. H. Draper,* Canad. J. Chem. *40,* 1943 (1962); *J. Elze* and *G. Oelsner,* Metall *16,* 111 (1962); *D. Mohler* and *R. G. Hierst,* J. electrochem. Soc. *108,* 347 (1961); *L. Young,* Proc. Roy. Soc. (London), Ser. A *263,* 395 (1961); *L. Apker* and *E. A. Taft,* Physic. Rev. (2) *88,* 58 (1952); *H. Maissinsky,* Métaux et Corrosion *23,* 15 (1948);
For Nb, cf. *P. G. H. Draper,* Electrochim. Acta *8,* 847 (1963); *H. S. Isaacs* and *J. S. Llewelyn Leach,* J. electrochem. Soc. *110,* 680 (1963); *R. Bakisa, ibid. 107,* 653 (1960); *A. I. Stalov,* Zh. prikl. Khim. *36,* 3, 588 (1963); *A. I. Stalov* and *T. B. Bondareva,* Dokl. Akad. Nauk S.S.S.R. *147,* 1137 (1962); *L. Young,* Canad. J. Chem. *38,* 1141 (1960).
For W, cf. *H. J. Booz,* Metall *11,* 511 (1957). – Comparative studies on Ti, Zr, and Mo oxide films, as well as oxide films on alloys of Ti, have been carried out by *V. V. Andreeva* and *N. A. Alekseeva,* Dokl. Akad. Nauk S.S.S.R. *134,* 106 (1960).

[67] *E. J. Verwey,* Physica *2,* 1059 (1935); *N. F. Mott,* Trans. Faraday Soc. *43,* 429 (1947).

[68] *U. F. Franck* in *W. Schottky*: Halbleiterprobleme, Vol. II. Friedr. Vieweg u. Sohn, Braunschweig 1955, p. 2147.

the case of titanium, *Tomashov*[69] observed TiO, $Ti_3O_5$, $Ti_2O_3$, and $TiO_2$, several oxidation states being present at the same time in some cases. The occurrence of high field strengths in very thin passive layers with low ionic conductivities during anodic polarization explains *Güntherschulze* and *Betz*'s observation[66] that the thickness of such layers on aluminum and on tantalum increases exponentially with the applied potential. Even where the surface layer is electronically conducting, a high field strength (diffusion potential) can lead to an exponential relationship between the rate of growth of the layer and the voltage [see Equation (s)], as has been shown for iron by *Vetter*[70] and *Weil*[71]; this is due to the much higher mobility of the electrons in relation to the defects.

$$dx/dt \propto \exp(K\Delta U/x) \qquad (s)$$

(x = thickness of layer; $\Delta U$ = voltage; K = constant).

Oxide layers on aluminum and on tantalum exhibit a rectifying effect towards anode currents. *Van Geel*[72] has described the $Al_2O_3$ layer as a semiconductor diode consisting of an n- and a p-conducting layer. *Sasaki*[73] explains the behavior of the rectifying layer on tantalum by assuming that the layer consists of a very thin n-conducting layer containing an excess of metal on the metal side, an ionically conducting layer in the middle, and a p-conducting layer containing an excess of oxygen in contact with the electrolyte. This explains not only the rectifying effect, but also the dependence of the capacitance on the potential. However, owing to the change in the situation with different electrolytes, as well as for other reasons, doubt has been expressed regarding the interpretation of the rectification as a semiconductor effect[74–76]. It must be remembered in practice that the secondary passive layers, which are polycrystalline oxides or salts exhibiting pores and cracks, always contain water or electrolyte solution in their capillary system.

Thus with the aid of a microthermobalance, *Okamoto*[77] found that even the passive layers on stainless steels contain from 30 to 50 % of water. Where the layers contain such large quantities of electrolyte, an appreciable proportion of the current will be transported by the ions. At the field strengths encountered in ionically conducting salt or oxide layers ($10^6$ to $10^7$ V/cm), on the other hand, it is necessary to take into account the appreciable increase in the resistance of the layer as a result of the electroosmotic expulsion of water from its capillary system. This process, which *Müller*[78] regards as the cause of the rectifying effect of aluminum oxide layers, has also been observed in investigations on zinc in saturated $ZnSO_4$ solution and on aluminum in ammonium borate solution, using electrolytes containing $^3H_2O$[79]. The passive layers were formed in water containing $^3H_2O$, the anode current was switched off when the steady state was reached, and the electrode was allowed to stand for a short time, washed with dioxane, and transferred to an electrolyte containing no $^3H_2O$. When the isotope-exchange equilibrium was reached, a field was applied with the passivated electrode as the anode; the $^3H_2O$ content of the solution increased rapidly. It can be seen from Fig. 6 that this increase is proportional to the applied

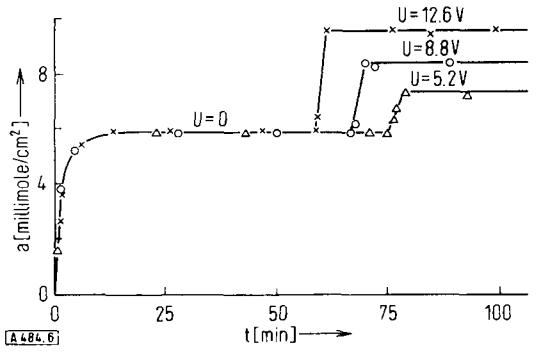


Fig. 6. Anodic loss of water from the passive layer on zinc in saturated $ZnSO_4$ solution, as a function of time and of the applied potential. a = surface concentration of water given off from the oxide layer.

potential. Passive layers on aluminum in borate solution also give up water. The fact that even anhydrous sulfuric acid labelled with $^{35}S$ is electroosmotically expelled[79] invalidates *Güntherschulze*'s objection[80] that electroosmotic dehydration cannot be considered as a cause of the rectifying effect in aluminum, because aluminum exhibits this effect even in practically anhydrous $H_2SO_4$. The elimination of charge carriers from the phase boundary by electroosmotic dehydration is similar to the "cut-off" state in a semiconductor diode (Fig. 7). The anions are carried away from the interface with the water, while the cations are removed by transport, the electrons being removed on the metal side. In any case, water

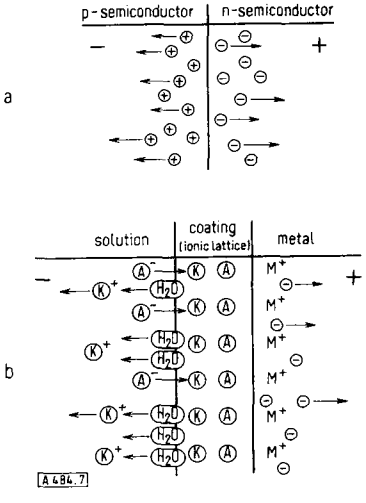


Fig. 7. Rectifying action of a passive layer (b) and the analogy with a semiconductor diode in the "cut-off" state (a). K = cation, A = anion.

[69] *N. D. Tomaschow, R. M. Altovskij*, and *M. Ya. Kushnerev*, Dokl. Akad. Nauk S.S.S.R. *141*, 913 (1961); *N. D. Tomaschow, G. P. Tomaschowa*, and *R. M. Altovskij*, Z. physik. Chem. *214*, 312 (1960). – For the anodic behavior of Ti, see also *W. R. Fischer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 803 (1958), and *R. Otsuka*, J. sci. Res. Inst. (Tokyo) *54*, 97 (1960); *51*, 73 (1957). – For passivity in alkaline solutions see *I. Sanghi* and *S. Visvanathan*, Electrochim. Acta *7*, 567 (1962). – For the behavior of Ti towards halide ions, see *I. Dugdale* and *J. B. Cotton*, Corrosion Science *4*, 397 (1964).

[70] *K. J. Vetter*, Z. physik. Chem. *202*, 1 (1953); Z. Elektrochem., Ber. Bunsenges. physik. Chem. *58*, 230 (1954).

[71] *K. G. Weil*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *59*, 74 (1955).

[72] *W. Ch. van Geel*, Physica *17*, 761 (1951). – Regarding the ionic conduction mechanism in anodic oxide films, see in particular *L. Young*: Anodic Oxide Films. Academic Press, London-New York 1961, and *J. F. Duenwald*, Physics Chem. Solids *2*, 55 (1957).

[73] *Y. Sasaki*, Physics Chem. Solids *13*, 177 (1960).

[74] *N. Schottky* in: Halbleiterprobleme, Vol. I. Friedr. Vieweg u. Sohn, Braunschweig 1954, p. 313.

[75] *A. W. Smith*, Canad. J. Physics *37*, 591 (1959).

[76] *L. Young*, Trans. Faraday Soc. *55*, 842 (1959).

[77] *G. Okamoto, T. Shibata, T. Ishikawa*, and *M. Nagayama*: Report 2nd Internat. Conference on Metallic Corrosion, New York, March 11th–15th, 1963.

[78] *W. J. Müller* and *K. Konopicky*, Z. physik. Chem. *A 141*, 343 (1929).

[79] *K. Schwabe*, Naturwissenschaften *49*, 56 (1962); *K. Schwabe* and *Nguyen Quy*, Mber. dtsch. Akad. Wiss. Berlin *5*, 372 (1963).

[80] *A. Güntherschulze*, Z. physik. Chem. *A 143*, 62 (1929).

plays an important part, not only in the formation of the primary passive layer, but also in the transport of current in the secondary layer.

The passivity of a metal is strongly dependent on the nature of the aqueous electrolyte, and particularly on the pH value and on the anions present. However, investigations on this aspect of passivity have so far failed to provide an explanation. The specific effect of the electrolyte can be best understood on the basis of the mechanism of formation and breakdown of the passive layer.

## III. Kinetics of the Passivation and Activation Processes

If we regard passivation as being due primarily to the coating of the metal with an initially monomolecular film of a compound formed from the metal and bound to it two-dimensionally, while phases growing over this film[81] can provide powderful additional inhibition of the dissolution of the metal, but are not essential to passivation, the question arises of why the protective action varies from one metal and from one corrosive medium to another.

Following the fundamental work carried out by *Mott* and *Cabrera*[82], the kinetic inhibition observed during the oxidation of metals with dry oxygen has been the subject of a number of studies and theoretical interpretations[56,83]. Difficulties are encountered in the quantitative interpretation of the different rates of oxidation, since metals with very high affinities for oxygen (Al, Ta, W) frequently have much lower oxidation rates than metals (*e.g.* Cu) with lower affinities[84]. The principal factor involved here is the transport of the reactants through the boundary layer.

The kinetics of the anodic formation of oxide phases, and in particular of rectifying layers, have been studied by *Vermilyea*[85], *Young*[86], and *Dewald*[87]. However, these studies have explained neither the difference in the stabilities of these layers towards the same attacking agent, nor the differences in the action of different media on the same passive layer.

*Schwabe* has considered these questions in connection with the passivation of iron, nickel and chromium, and regards chemisorption as the primary and essential cause of passivation. The specific effect of the attacking agent (the anion in the case of acids) must become operative during the passivation, and not simply during the attack on the passive layer. In the case of a nickel anode, for example, passivation does not occur in HCl even at very high current densities; in $H_2SO_4$ or $HClO_4$ at the same concentration, however, passivation occurs at relatively low current densities, the current density falling off rapidly with increasing potential (Fig. 8).

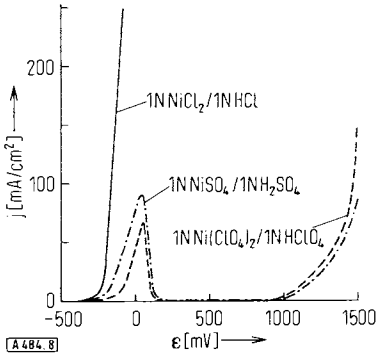


Fig. 8. Effect of the anion on the current density-potential curves for polished nickel electrodes in acidic solutions of nickel salts. ε is measured *versus* a saturated calomel electrode.

$Cl^-$, $Br^-$, and $I^-$ ions have been repeatedly observed [88–89b] to have a particularly corrosive action on the metals of the iron group, even in alkaline electrolytes, in which these metals are very stable in the absence of halide ions. This attack generally leads to pitting, even in the case of Cr/Ni steels. We shall confine ourselves here to a few possible explanations for the activating effect of halide ions on Fe, Ni, and Co, although the effects of these ions on metals such as titanium and zirconium have also been studied recently. The last two metals are particularly affected by fluoride ions, which have hardly any activating effect on the metals of the iron group[90]. This alone indicates the extreme complexity of the situation in relation to the attacking medium, and in particular the anion (Fig. 9). In the case of the iron metals, the chemisorption theory of the passive layer has been found to be capable of explaining the effect of the anion if the activation can be assumed to be due to the displacement of chemisorbed oxygen.

During active dissolution, not only must water molecules be available for the hydration of the metal atom, but anions must also be available to maintain electro-

[81] *K. Schwabe*, Electrochim. Acta *3*, 186 (1960). If the lattice dimensions of the new phase formed by the junction agree with those of the metal lattice and if the new phase can orient itself with the metal lattice (epitaxy), it will remain firmly bound to the junction; cf. *A. Neuhaus*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *56*, 453 (1952).

[82] See the detailed presentation by *N. F. Mott* and *N. Cabrera*, Rep. Progr. Physics *12*, 163 (1949).

[83] *K. Hauffe*: Reaktionen in und an festen Stoffen. Springer, Berlin-Göttingen-Heidelberg 1950, p. 110; *R. Suhrmann, G. Wedler*, and *H. J. Heyne*, Z. physik. Chem. N.F. *22*, 336 (1959).

[84] *Ch. Weissmantel, K. Schwabe*, and *G. Hecht*, Werkstoffe u. Korrosion *12*, 353 (1961).

[85] *D. A. Vermilyea*, Acta metallurg. *1*, 282 (1953); *2*, 482 (1954); *5*, 113 (1957); J. electrochem. Soc. *102*, 655 (1955); *104*, 140, 427, 485 (1957).

[86] *L. Young*: Anodic Oxide Films. Academic Press, London-New York 1961.

[87] *I. F. Dewald*, Acta metallurg. *2*, 340 (1954); J. electrochem. Soc. *162*, 1 (1955); Physics Chem. Solids *2*, 55 (1957).

[88] *Ya. M. Kolotyrkin*, Usp. Khim. *31*, 322 (1962); Corrosion *8*, 261 (1963); *Ya. M. Kolotyrkin, G. V. Golovina*, and *G. M. Florianovich*, Dokl. Akad. Nauk S.S.S.R. *148*, 1106 (1961); *G. Trümpler* and *R. Keller*, Helv. chim. Acta *44*, 1691, 1785 (1961); *G. Herbsleb* and *H. I. Engell*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 881 (1961); *H. I. Engell* and *N. D. Stolica*, Z. physik. Chem. N.F. *20*, 113 (1959); *E. Brauns* and *W. Schwenk*, Werkstoffe u. Korrosion *12*, 73 (1961); *U. F. Franck*, *ibid. 11*, 401 (1960).

[89a] Regarding halide ions in alkaline solutions, see *T. I. Popova* and *B. N. Kabanov*, Zh. fiz. Khim. *35*, 1295 (1961); *K. Schwabe* and *R. Radeglia*, Werkstoffe u. Korrosion *13*, 281 (1962).

[89b] *K. Schwabe*, J. elektrochem. Soc. *110*, 663 (1963).

[90] Regarding the action of $Cl^-$ on Ti, see *N. D. Tomashov* and *R. M. Altovskij*, Zh. fiz. Khim. *33*, 610 (1959). – For the action of $F^-$ on Zr, see *M. E. Straumanis, W. J. James*, and *A. J. Neiman*, Corrosion *15*, 286t (1959). – For the action of halide ions on Zr see *V. A. Gil'man* and *Ya. M. Kolotyrkin*, Dokl. Akad. Nauk S.S.S.R. *143*, 640 (1962); *137*, 642 (1961).

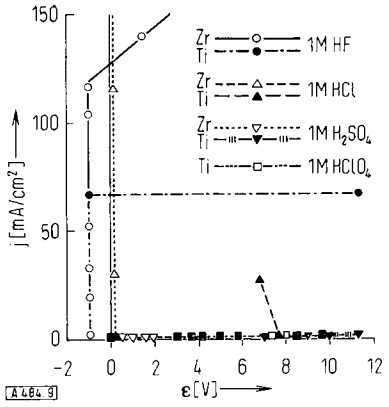


Fig. 9. Current density-potential curves for titanium and zirconium in HCl, $H_2SO_4$, HF and $HClO_4$. ε is measured against a saturated calomel electrode.

neutrality. In any case, the water dipoles adsorbed in the double layer cannot remove metal atoms from the lattice as cations unless anions are also available in the solution to compensate the charge [91]; the water molecules, on the other hand, can give up oxygen to form the passive layer (see page 191).

However, anions are also specifically adsorbed on the metal surface, with partial dehydration and incorporation into the inner Helmholtz double layer [92]. It is fairly safe to assume that this adsorption favors the anodic transition-reaction with active dissolution of the metal. Thus if we start with a metal surface free from oxygen, the anion that is most strongly adsorbed on the metal will be the first to contribute to the uninhibited anodic dissolution. Of the anions of the strong acids HCl, $H_2SO_4$, and $HClO_4$, the $Cl^-$ ion is the most rapidly and the most strongly adsorbed, as has been shown with the aid of radioactively labelled anions [93]. The general case involves the displacement of adsorbed water dipoles or of chemisorbed oxygen by the anions in question. This can be seen from the fact that the saturation state on Pt and on Ni, which always corresponds to only 30 to 40% of a monolayer (provided that there is no chemical reaction, *e.g.* with $HS^-$), is reached only after several hours. Table 2 shows the quantities of anions adsorbed on Pt from aqueous solution in 1000 min

Table 2. Adsorption of various anions on Pt sheets from $2 \times 10^{-3}$M $Na^+$ solutions. Exposure time $10^3$ min.

| Ion | $10^{-10}$ g ions/cm² of true surface |
|---|---|
| $HS^-$ | 17.0 |
| $I^-$ | 9.1 |
| $CN^-$ | 8.6 |
| $HPO_4^{2-}$ | 6.3 |
| $Cl^-$ | 2.1 |
| $SO_4^{2-}$ | 1.3 |
| $ClO_4^-$ | 0.8 |

[91] *Ya. M. Kolotyrkhin*, Usp. Khim. *31*, 322 (1961); J. electrochem. Soc. *108*, 209 (1961) has also stressed the fact that the anions must be involved in the dissolution of the metal.

[92] *D. C. Grahame*, Chem. Reviews *41*, 441 (1947); J. Amer. chem. Soc. *74*, 1207 (1952).

[93] *K. Schwabe*, *K. Wagner*, and *Ch. Weissmantel*, Z. physik. Chem. *206*, 309 (1957).

under the same conditions. Further, it can be shown with the aid of radioactively labelled ions that after the metal has been precoated with ions of one type, these can be displaced by more strongly adsorbed ions. This effect is evident in Fig. 10.

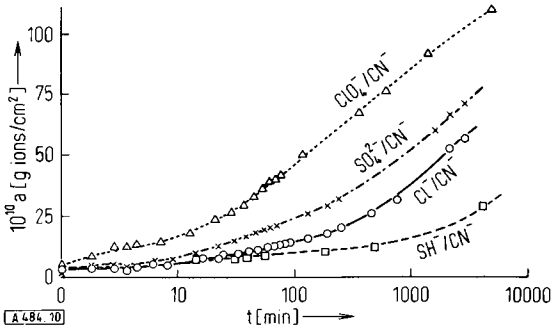


Fig. 10. Adsorption of $CN^-$ ions to pre-adsorbed films on platinum.

This strong adsorption is obviously not enough in itself to bring about anodic dissolution, since the still more strongly adsorbed $CN^-$ even inhibits the anodic dissolution of iron in neutral and alkaline solutions [94]. It may be that the anions are not so strongly chemisorbed, with the displacement of water, that they prevent hydration. It should also be borne in mind that the adsorption depends on the potential of the metal [95]; the anions can be completely desorbed by the use of a sufficiently negative Galvani tension. *Kolotyrkin* [96] postulated that the adsorption can lead to anodic dissolution only above a critical Galvani tension; below this critical potential adsorbed ions can even inhibit corrosion, a phenomenon that is attributed in some cases to the hindrance of the cathode process (increase in the $H_2$ overvoltage [97]). The adsorption of the anions will increase with increasing anodic polarization, but the passivating reaction (o) may at the same time become more pronounced, with the result that the anions may again be displaced.

Fig. 11 shows the increase in the adsorption of $I^-$ on a nickel plate in the active range, and the rapid decrease

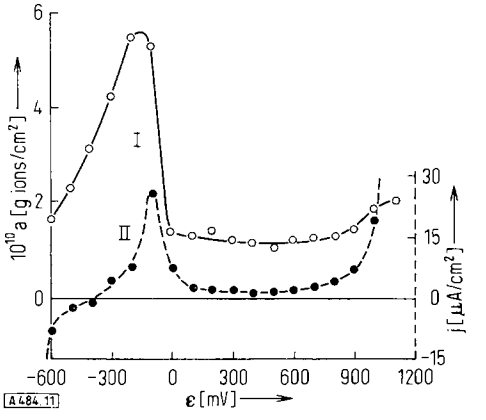


Fig. 11. Curve I: Dependence of the adsorption of $^{131}I$ on Ni plates, at pH 4.3 in 0.1 M $Na_2SO_4$ solution, on the Galvani tension. Curve II: Corresponding current density-potential curve; ε is measured against a saturated calomel electrode. The current densities are based on 1 cm² of true surface.

[94] *W. Schmidt* and *C. Steinbach*, unpublished work.

[95] *A. N. Frumkin*, Dokl. Akad. Nauk S.S.S.R. *154*, 143 (1964); *N. A. Balashova*, Z. physik. Chem. *207*, 340 (1957); *K. Schwabe* and *W. Schwenke*, Electrochim. Acta *9*, 1003 (1964).

[96] *Ya. M. Kolotyrkin*, Usp. Khim. *31*, 322 (1962).

[97] *Z. A. Iofa*, *E. I. Ljachoveckaja*, and *K. Sarifov*, Dokl. Akad. Nauk S.S.S.R. *84*, 543 (1952); *Z. A. Iofa* and *G. B. Rožděstvenskaja*, *ibid. 91*, 1159 (1953).

in adsorption on passivation [98]. In any case, during the anodic dissolution of an oxide-free metal, the slower the anodic dissolution, the more pronounced will be the passivating reaction in comparison with the anodic transition reaction with the chemisorbed anions. Thus anodic polarization gives rise to two competing anode processes, one being the active dissolution of the metal with hydration and with the aid of the anions, and the other being the formation of an adsorbed film of oxygen from the water. If this passivating reaction predominates, the metal becomes completely covered by the passive layer, and the characteristic rapid decrease in current is observed. The contribution of reaction (o) to the anode process increases with the inhibition of active dissolution (in the absence of the passive layer). A measure of this is the exchange current density of the process (t), *i.e.* the lower the current density, the greater

$$M + n\,H_2O \rightleftharpoons M^{y+} + n\,H_2O + y\,e^- \qquad (t)$$

is the contribution of reaction (o). The exchange current densities reported for Fe, Ni, and Cr are 6 to 10 orders of magnitude smaller than that reported for silver [99]. Thus there is no passivation of a polished Ag anode in $HClO_4$ even at current densities of more than 1 A/cm² [60]. However, the passivating reaction also competes with the displacement of adsorbed oxygen by activating anions, in accordance with Equation (u) (in

$$[^{\ominus\ominus}M^{(++)}\ {}^{\ominus\ominus}M^{(++)}] - O_{ads} + 2\,A^- + H_2O \rightarrow [^{\ominus\ominus}M^{(++)}] + M^{2+} + 2\,A^- + 2\,OH^- \qquad (u)$$

which brackets denote the metallic phase). This process leads to the removal of the chemisorbed oxygen layer and the reactivation of the metal. Finally, another process that competes with reaction (o) is the chemical dissolution of the metal by acids:

$$[^{\ominus\ominus}M^{(++)}] - O_{ads} + 2\,H \rightarrow H_2O + M^{2+} \qquad (v)$$

Thus the passivation, which inhibits both itself and the active dissolution, is stopped by reactions (u) and (v) [54b, 100]. If the metal is originally covered with oxygen, the active dissolution must be preceded by the displacement of the oxygen by activated anions. In any case, even if the active dissolution can follow the anodic polarization, it is also inhibited by the formation of a blocking layer of salt or oxide directly from the metal when the concentration rises above the saturation point [28]. In this case we generally find an anodic rectifying effect (*e.g.* Zn in saturated $ZnSO_4$ solution). The high polarization caused by salt layers can lead in some cases to the formation of compounds of higher valence.

Thus the competition of various activating and passivating reactions gives rise to a large number of possibilities for the formation or breakdown of passive layers [*]:

The metal will in general be covered with oxide; this oxide layer must be removed by reactions (u) or (v), or both, before active dissolution according to Equation (t) can occur. The re-passivation reactions (o) and (p), however, compete with (u) and (v). If the former are faster than the latter, no activation can take place. It should further be noted that reaction (o) depends on potential and is accelerated by increasing anodic polarization. The same applies to the active anodic dissolution according to Equation (t). When the latter, and particularly the passage of metal ions across the phase boundary, is not inhibited, reaction (o) will not take place after removal of the passivating oxide layer, and eventually solid salt will be deposited on the metal surface. Since it is an ionic conductor, this salt acts as an electrical barrier layer, and a marked current decrease results (*e.g.* zinc in zinc sulfate [103]). A substantial current increase with increasing potential occurs only when the layer has undergone dielectric breakdown or a transition in which, *e.g.*, ions of higher charge are formed. The latter occurs with lead in sulfuric acid, where $PbSO_4$ is converted into electronically conducting $PbO_2$. With iron in $FeCl_2$ solution, the blocking layer of $FeCl_2$ initially formed is removed [100a] at higher Galvani tensions by the reaction

$$[Fe^{(++)} - Cl_2^{(--)}] + Cl^- \xrightarrow{H_2O} Fe^{3+} + 3\,Cl^- + e^- \qquad (w)$$

If the active anodic dissolution is strongly inhibited (overvoltage), however, the reaction (o) can cause re-passivation and a decrease in current long before saturation is reached on increase of Galvani tension; Equation (v) shows that the passivating potential will depend on pH. If the passive layer is a good electronic semiconductor, reaction (q) will initiate another current increase above the oxygen potential; such an increase can also be caused by formation of higher oxidation states in the passivating oxide (*e.g.* in Cr). Ionically conducting oxide layers which are not oxidizable, however, block the current until dielectric breakdown occurs.

In case the passivating reactions (o) and (p) are much faster than the activating ones (u) and (v), activation is not possible; the base metals (Ti, Al, *etc.*) remain passive in neutral or weakly acidic solution on anodic polarization, since they react faster according to Equa-

[98] *C. Spenner*, unpublished work.

[99] *T. P. Hoar* in *J. O.M. Bockris*: Modern Aspects of Electrochemistry, No. 2. Butterworths Scientific Publications, London 1959, p. 274.

[100] Similar views have also been expressed in the meantime by *W. A. Mueller*, J. electrochem. Soc. *107*, 157 (1960), and by *Ya. M. Kolotyrkin*, Usp. Khim. *31*, 322 (1962).

[*] The diverse anodic behavior of metals can be explained quantitatively [54b] on the basis of the competing activating and passivating surface reactions, and the typical negative current-potential characteristic can be similarly derived.

[100a] *D. Tschö*, Diploma Thesis, Technische Hochschule Dresden, 1959; *K. Schwabe* and *V. Ebersbach*, Electrochim. Acta, in press.

[101] *K. Schwabe* and *R. Radeglia*, Werkstoffe u. Korrosion *13*, 281 (1962).

[102] Chemisorbed oxygen layers may also be particularly stable because of the feasibility of localized bonding to the metal and transverse bonding of the oxygen atoms to one another; cf. *K. Schwabe* and *Ch. Weissmantel*, Mber. dtsch. Akad. Wiss. Berlin *5*, 23 (1963).

[103] For investigations on zinc in saturated zinc sulfate solutions, cf. *K. Schwabe* and *F. Lohmann*, Z. physik. Chem. *215*, 158 (1960/61).

tion (p) than they pass into solution. (The simplifying assumption is made that all parts of the metal surface react in the same way or have the same coverage).

According to *Kolotyrkin*[96], the increased adsorption can lead to a further increase in the activating action of the anions with increasing anodic polarization. According to *Müller*[54b, 100], the area not covered by the oxide film, *i.e.* the active area, decreases exponentially with increasing polarization. The Flade potential can therefore be interpreted as the value of the Galvani tension above which the passivating reaction (o) is faster than the active dissolution. The negative current-voltage characteristic is due to the fact that as the voltage is increased, the covering of the metal surface as a result of reaction (o) inhibits both the active dissolution and reaction (o) itself.

The quantitative treatment of this competition between electrode processes is extremely difficult, since the free (active) and covered (passive) fractions of the surface are themselves functions of time, current, and potential, and since the attack on the surface of the electrode may not be uniform. However, the behavior of nickel and iron in alkaline solutions containing halogen ions (in spite of the pitting that occurs in these cases) has been quantitatively explained on the basis of competing electrode reactions[89b, 101]. The difficulties connected with the conditions at the metal/corrosive medium interface cannot be overcome by impulse methods in the study of the passivation and reactivation processes, since these processes proceed slowly. Thus even for the most widely studied metals, *i.e.* iron, nickel, and aluminum, a quantiative kinetic treatment has not yet been achieved.

The situation is further complicated, however, by the fact that the primary monomolecular passive layer is not ideal; its structure is abnormal or it is less stable at various parts of the surface, owing to grain boundaries, dislocations, and impurities. More metal atoms will react with the water or the anions in these regions, with the result that the passive layers become thicker and the course of the attack may be largely determined by the transport processes in these layers. In the primary layer, the transport of the metal atoms in the metal lattice and the bond energy in the chemisorbed layer will be the main factors controlling further passage through the layer (except at faults in the layer)[102]. In the base metals (Al, Ti, Zr, *etc.*), each fault will lead to further oxide formation in accordance with Equation (p). The passive layer will therefore become steadily thicker, but the rate of growth will decrease owing to the increasing diffusion path. This may ultimately lead to a steady state in which the thickening of the layer with increasing potential compensates for the increased rate of transport, so that the current is found to be independent of the voltage[103]. Studies on alloys are therefore much more difficult to interpret[104].

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[104] *H. H. Uhlig*: Corrosion and Corrosion Control. Wiley, New York-London 1963; Corrosion Handbook. Wiley, New York 1948, p. 617; *F. Tödt*: Korrosion und Korrosionsschutz. W. de Gruyter, Berlin 1961; *N. D. Tomashov* and *R. M. Altovskij*: Corrosion and Inhibition of Corrosion of Titanium (in Russian), Mašgiz, Moscow 1963; *G. P. Cernova* and *N. D. Tomashov*, Z. physik. Chem. *226*, 136 (1964).

# The Significance of Enterobacterial Mutants for the Chemical Investigation of their Cell-Wall Polysaccharides

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*Dedicated to Professor Karl Freudenberg on the occasion of his 80th birthday*

*The outer cell surface of Enterobacteriaceae, i.e. the cell wall, consists of a rigid structure (murein) on which additional proteins, lipids, and polysaccharides are deposited. In the bacterial wild types (S forms) the polysaccharide is species-specific and carries the serologically determinant groups of the respective O antigen. These specific polysaccharides often consist of a large number of monosaccharides; up to eight different monosaccharides may be involved. Bound to lipid A, the cell-wall lipopolysaccharides represent the endotoxins of the bacteria. During the past few years the structures of the enterobacterial cell-wall polysaccharides have been elucidated by chemical, immunochemical, biochemical, and genetic investigations, particularly in the Salmonella. Here the polysaccharides consist of a basal polysaccharide common to all species, to which (in the S form) are bound longer species-specific side chains, consisting of repeating oligosaccharide units. Spontaneous S → R mutation leads to R forms which are deficient mutants of the wild types in regard to the biosynthesis of the complete cell-wall polysaccharide. In contrast to the multiplicity of the serological specificities of the somatic antigens of the S forms, only a few serological types were found among the R forms (R I, R II, etc.). These R polysaccharides correspond to intermediates in the biosynthesis of the wild-type polysaccharides. The S → R mutation leads to the loss (or block) of an enzyme (transferase, synthetase) participating in the synthesis of the S polysaccharides. Recently many deficient mutants have been isolated and analysed, and in this way numerous stages in the biosynthesis of the cell-wall polysaccharides, for example, of Salmonella minnesota, have been made accessible to direct analysis. According to these investigations, the cell-wall polysaccharides of Salmonella consist of a basic polyheptose phosphate core which is bound to lipid A via ketodeoxyoctonic acid. To the basic core are linked pentasaccharide units of*

*N-acetylglucosaminyl→glucosyl→galactosyl→glucosyl→galactosyl*

*(R II structure). All other R forms are structurally deficient mutants of R II. In the complete polysaccharides of Salmonella S forms (wild types), the repeating oligosaccharide units of the specific side chain are bound to the terminal N-acetylglucosamine of the R II structure.*

## Introduction

Enterobacteriaceae form a large group of microorganisms which is subdivided into several genera comprising *Salmonella*, *Shigella*, *Coli* bacteria, and others[1]. On the basis of serological reactions, these genera consist of several species or serotypes. The genus *Salmonella*, for example, comprises more than 700 species which are classified serologically in the Kauffmann-White scheme[2,3]. They include pathogenic and hence clinically important organisms, *e.g.* typhoid and paratyphoid bacteria, but also many non-pathogenic representatives. Similarly, several hundred *Coli* species have been discovered and new ones are constantly being isolated and characterized serologically.

Much work has been carried out on the morphological cell structure of Enterobacteriaceae[4]. Particular interest has been devoted to the cell wall which forms the outer structured surface of the cell[5]. It is superposed on the cytoplasmic membrane which encloses the cytoplasm and consists principally of two main parts, a rigid structure and filling material. The rigid structure, which imparts stability to the bacterial cell, has been investigated by *Weidel*[6] and his group and others. Each cell forms a giant bag-shaped molecule or sacculus, the murein, which consists of chains of alternating *N*-acetylglucosamine and *N*-acetylmuraminic acid units

[1] *F. Kauffmann*: Enterobacteriaceae. 2nd edit., Munksgaard, Copenhagen 1954.

[2] *F. Kauffmann* in *E. van Oye*: The world problem of Salmonellosis. Uitgeverij Dr. W. Junk, The Hague 1964, p. 21.

[3] *F. Kauffmann*: Die Bakteriologie der Salmonella-Species. Munksgaard, Copenhagen 1961.

[4] *M. R. J. Salton*: The bacterial cell wall. Elsevier, Amsterdam 1964.

[5] *H. R. Perkins*, Bacteriol. Rev. *27*, 18 (1963).

[6] *W. Weidel*, Angew. Chem. *76*, 801 (1964); *W. Weidel* and *H. Pelzer*, Adv. Enzymol. *26*, 193 (1964).

with peptide cross-linkages [7,8]. In these muramyl peptides, which have a similar composition in all bacteria investigated so far, D-amino acids (D-alanine, D-glutamic acid) are regularly encountered in addition to L-amino acids (L-alanine, L-lysine, *etc*). The chemical elucidation of the rigid structure has provided an interpretation of the effect of enzymes such as lysozyme and of antibiotics such as cycloserine and penicillin on bacteria.

Characteristic higher-molecular cell-wall building units are superimposed on the rigid structure [4]: protein, lipid, and polysaccharide (Fig. 1).

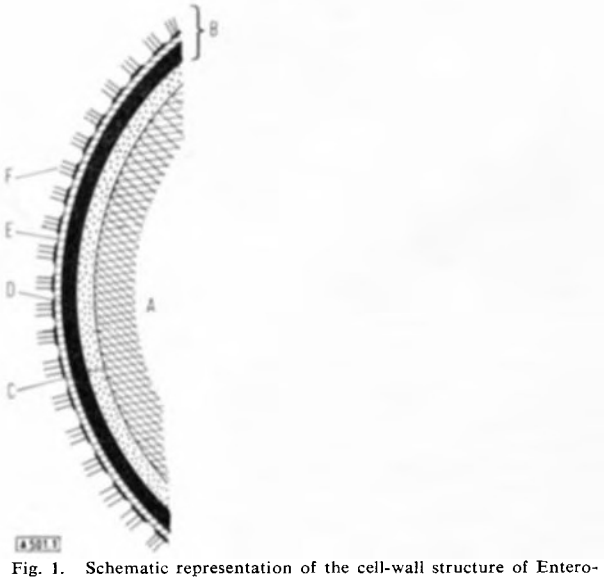


Fig. 1. Schematic representation of the cell-wall structure of Enterobacteriaceae.
A: Cytoplasm. B: Cell wall. C: Cytoplasmic membrane. D: Rigid structure (muramyl peptide). E: Protein, lipid. F: Polysaccharide.

Of these building units, proteins and lipids seem to have a similar composition in many, if not all, species, and the same holds for the rigid structure of the cell wall [9,10]. In contrast, Enterobacteriaceae exhibit an extraordinary multiplicity in regard to the polysaccharide, which is largely responsible for the serological species- or group specificity. When rabbits are immunized with killed bacteria, they form antisera which cause agglutination of the bacteria and of serologically cross-reacting types. Of the somatic antigens on the surface of the bacteria, which are responsible for this agglutination, the polysaccharide antigen (or O antigen in wild types) plays an important part, *i.e.* specific determinant structures of the cell-wall polysaccharides react with corresponding antibodies. These determinant oligosaccharidic structures (see *e.g.* [11]) form the basis for the understanding of the serological diagnosis of enterobacterial serotypes, *e.g.* as established in the Kauffmann-White scheme of the *Salmonella* [3]. The immunochemical elucidation of the determinant regions in these polysaccharide antigens was made possible only by the use of monospecific antisera (factor sera), the preparation of which has been described by *Kauffmann* [3].

In the cell wall, the polysaccharide antigens are firmly bound to a lipid component, the so-called lipid A [12], and to protein. Depending on the extraction method used [9–11,13], these antigens can be transferred into aqueous solution in more or less complex form. It has been found that particularly the lipopolysaccharides (lipid A-polysaccharides) of Enterobacteriaceae act not only as O antigens but also as endotoxins, *i.e.* substances of extreme biological activity (pyrogens *etc.* [14]). In this way, the non-specific endotoxic and the specific antigenic properties of these bacteria reside in the same complex molecule, the lipopolysaccharide. While the lipid A component is essential for the endotoxic activity, the polysaccharide component is responsible for the antigenic (serological) specificity (see [15,16]). The bacterial lipopolysaccharides can be extracted directly from the bacteria with phenol/water [17], and are then obtained together with nucleic acid, from which they must be subsequently separated. Otherwise, purified cell walls can be initially prepared [18] and subsequently extracted with phenol/water.

## The Specific Polysaccharides of the Enterobacterial Wild Types (S Forms)

The general principle of the structure of the enterobacterial cell-wall polysaccharides has been largely elucidated. The results show that the polysaccharides of the wild-types (smooth or S forms) consist of a polyheptose phosphate core (a), to which side chains are bound. These, in turn, consist of a substantially ubiquitous inner oligosaccharide chain (b), to which longer chains (c) are bound consisting of periodically repeating species-specific oligosaccharide units. The repeating units themselves can be straight chains or may carry short side chains of several monosaccharides. *Staub et al.* [11,19–23] at the Pasteur Institute in Paris have

[7] *J. M. Ghuysen, D. J. Tipper,* and *J. L. Strominger,* Biochemistry *4,* 474 (1965).

[8] *J. L. Strominger,* Ann. N.Y. Acad. Sci. *128,* 59 (1965).

[9] *W. T. J. Morgan* and *S. M. Partridge,* Biochem. J. *35,* 1140 (1941).

[10] *F. Binkley, W. F. Goebel,* and *E. Perlman,* J. exp. Med. *81,* 331 (1945).

[11] *O. Lüderitz, A. M. Staub,* and *O. Westphal,* Bacteriol. Rev. 1966, in the press.

[12] *O. Westphal* and *O. Lüderitz,* Angew. Chem. *66,* 407 (1954).

[13] *A. Boivin, I. Mesrobeanu,* and *L. Mesrobeanu,* C. R. Séances Soc. Biol. Filiales Associées *113,* 490 (1933).

[14] *M. Landy* and *W. Braun* in: Bacterial Endotoxins. Rutgers, The State University, New Brunswick 1964.

[15] *O. Westphal, A. Novotny, O. Lüderitz, H. Hurni,* and *E. Eichenberger,* Pharmac. Acta Helvetiae *33,* 401 (1958).

[16] *O. Westphal,* Ann. Inst. Pasteur *98,* 789 (1960).

[17] *O. Westphal, O. Lüderitz,* and *F. Bister,* Z. Naturforsch. *7b,* 148 (1952); *O. Westphal* and *K. Jann,* Methods of Carbohydrate Chem. *5,* 83 (1965).

[18] *M. J. Osborn,* Proc. nat. Acad. Sci. *50,* 499 (1963); *E. Ribi et al.* in: Bacterial Endotoxins. Rutgers, The State University, New Brunswick 1964, p. 16; see also *E. Kröger et al.,* Naturwissenschaften *46,* 428 (1959).

[19] *A. M. Staub* and *R. Tinelli,* Bull. Soc. Chim. Biol. *42,* 1537 (1960).

[20] *A. M. Staub* and *N. Forest,* Ann. Inst. Pasteur *104,* 371, (1963).

[21] *A. M. Staub* in: Bacterial Endotoxins. Rutgers, The State University, New Brunswick 1964, p. 38.

pioneered the investigation of the chemistry and immunochemistry of these side chains. The sugars involved in the repeating units, the type of their glycosidic linkage, and the bond between the units determine the specificity of the polysaccharide and hence the serotype.

Because of this structure, the enterobacterial S forms contain comb-shaped polysaccharide molecules (see Fig. 1), which consist of a basic heptose phosphate chain and an inner ubiquitous side chain, to which the specific repeating units are linked (Fig. 2).

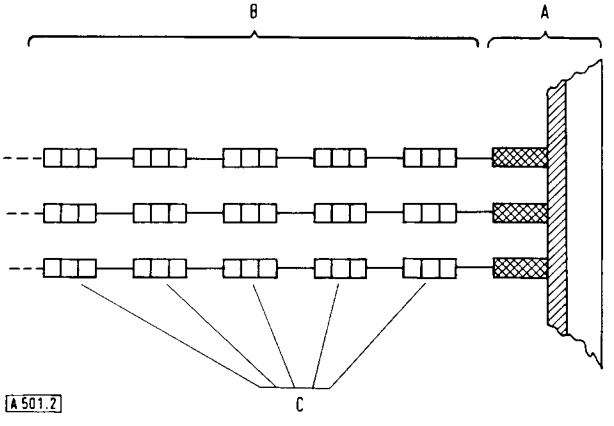


Fig. 2. Schematic representation of the specific and non-specific regions in the polysaccharide of *Salmonella* O antigens.

A: Basal structure. B: O-specific side chain. C: Repeating units.

*Osborn*[18] and *Heath*[24] have demonstrated that the heptose phosphate core in the lipopolysaccharides is bound to lipid A *via* ketodeoxyoctonic acid (KDO). This latter compound was discovered by *Heath* and *Galambor*[25] who also elucidated its structure. Lipid A is a derivative of poly-*N*-β-hydroxymyristinoyl-D-glucosamine phosphate esterified with long-chain fatty acids[15,26,27]. The analysis of enterobacterial lipopolysaccharides therefore always reveals D-glucosamine and KDO, and it is necessary to determine whether, and in which position, glucosamine occurs in the polysaccharide as well as in the lipid A.

For several years we have concerned ourselves with chemical and immunochemical analyses of the O-specific polysaccharides from enterobacterial S forms. Together with *Kauffmann* (Copenhagen), who worked out the serological classification of the *Salmonella* over a period of several decades (Kauffmann-White scheme), we have isolated the lipopolysaccharides from the S forms of over a hundred *Salmonella* species and indified the sugars contained in their polysaccharide components[28,29]. Figure 3 shows the results and is intended merely to convey an indication of the multiplicity of the sugar combinations (chemotypes)[28]. Some polysaccharides contain as many as eight different monosaccharides.

| Chemotype | Hexosamines: D-Galactosamine | Hexosamines: D-Glucosamine | KDO: 2-Keto-3deoxyoctonate | Heptose: L-Glycero-D-manno- | Hexosens: D-Galactose | Hexosens: D-Glucose | Hexosens: D-Mannose | 6-Deoxyhexosens: L-Fucose | 6-Deoxyhexosens: L-Rhamnose | Pentosens: Ribose | 3,6-Bisdeoxyhexosens: Colitose | 3,6-Bisdeoxyhexosens: Abequose | 3,6-Bisdeoxyhexosens: Paratose | 3,6-Bisdeoxyhexosens: Tyvelose | O serogroups |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | | ◪ | ◪ | ◪ | ◪ | ◪ | | | | | | | | | 1,V,X,Y,58 |
| II | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | | | | | | | | | L,P,51,55 |
| III | | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | | | | | | | | $C_1$,$C_4$,H,S |
| IV | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | | | | | | | | K,R |
| V | | ◪ | ◪ | ◪ | ◪ | ◪ | | ○ | | | | | | | W |
| VI | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | | ○ | | | | | | | G,N,U |
| VII | | ◪ | ◪ | ◪ | ◪ | ◪ | | | ○ | | | | | | T,59 |
| VIII | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | | | ○ | | | | | | M,[$28_1$,$28_3$]53,57 |
| XXV | | ◪ | ◪ | ◪ | ◪ | ◪ | | | | ○ | | | | | 52 |
| IX | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | | | | ○ | | | | | M,[$28_1$,$28_2$]56 |
| X | | ◪ | ◪ | ◪ | ◪ | ◪ | | | | | ○ | | | | 0 |
| XI | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | | | | | ○ | | | | Z |
| XII | ○ | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | ○ | | | | | | | 1,Q |
| XIII | | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | | ○ | | | | | | E,F,54 |
| XIV | | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | | ○ | | | ○ | | | B,C2,C3 |
| XV | | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | | ○ | | | | ○ | | A |
| XVI | | ◪ | ◪ | ◪ | ◪ | ◪ | ○ | | ○ | | | | | ○ | 01,02 |

A 501.3

Fig. 3. Sugar constituents of *Salmonella* lipopolysaccharides (classification into chemotypes) [28,29].

Empty circles: Specific sugars. Hatched circles: Basal sugars.

It is noteworthy that all investigated *Salmonella* lipopolysaccharides contain KDO, heptose, galactose, glucose, and glucosamine, which we have termed "basal sugars" (hatched circles in Fig. 3). In addition to these basal sugars different combinations of the specific sugars, *e.g.* galactosamine, mannose, fucose, or rhamnose and the 3,6-dideoxyhexoses[30] (paratose, abequose, tyvelose, or colitose), may be present. The combination of the basal sugars without specific sugars corresponds to chemotype I. In *Salmonella* O antigens, the 17 different sugar combinations (chemotypes I–XVI and XXV) compiled in Figure 3 have so far been found. Approximately 25 different chemotypes are obtained when the specific polysaccharides from the S forms of *E. coli* analysed to date are added[31,32]. The variety of heteropolysaccharides is even greater when one considers that, for the same qualitative composition,

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[23] *A. M. Staub* and *O. Westphal*, Bull. Soc. Chim. Biol. *46*, 1647 (1964).

[24] *R. D. Edstrom* and *E. C. Heath*, Biochem. biophysic. Res. Commun. *16*, 576 (1964).

[25] *E. C. Heath* and *M. A. Ghalambor*, Biochem. biophysic. Res. Coummun. *10*, 340 (1963).

[26] *A. Nowotny*, J. Amer. chem. Soc. *83*, 501 (1961).

[27] *A. J. Burton* and *H. E. Carter*, Biochemistry *3*, 411 (1964).

[28] *F. Kauffmann*, *O. Lüderitz*, *H. Stierlin*, and *O. Westphal*, Zbl. Bakteriol., Parasitenkunde Infektionskrankh., Abt. I, Orig. *178*, 442 (1960).

[29] *F. Kauffmann*, *B. Jann*, *L. Krüger*, *O. Lüderitz*, and *O. Westphal*, Zbl. Bakteriol., Parasitenkunde Infektionskrankh., Abt. I, Orig. *186*, 509 (1962).

[30] *O. Westphal* and *O. Lüderitz*, Angew. Chem. *72*, 881 (1960).

[31] *B. Jann*, Dissertation, Universität Freiburg 1965.

[32] *F. Ørskov*, *I. Ørskov*, *K. Jann*, and *B. Jann*, Acta pathol. microbiol. scand. 1966, in the press.

the sugars in dieffrent O antigens can occur in different sequences and also with different linkages between them.

The multiplicity of the serological specificities of *Salmonella* O antigens, expressed by the Kauffmann-White scheme, is matched by a corresponding multiplicity of the structures of the polysaccharide side chains (Figures 4 and 5). The oligosaccharides listed in Fig. 4 were elucidated by analysis of partial hydrolysates from the side chains of the polysaccharides of several *Salmonella* species. Their constitutions were determined by *Staub et al.* [19–23, 33] for *Salmonella* groups B, D, and $E_4$, and by *Robbins*, *Uchida*, and *Luria* [34] for groups $E_1$, $E_2$, and $E_3$. The side chains of all these polysaccharides contain the same sugar sequence, *i.e.* galactose→mannose→rhamnose (Gal→Man→Rha), while the linkages may be different and short side chains may be present or absent.

| Sero-group | O factors | Structures of the repeating units |
|---|---|---|
| $E_1$ | 3, 10 | →α-Ac-GAL-(1→6)-α-MAN-(1→4)-RHA→ |
| $E_2$ | 3, 15 | →β-GAL-(1→6)-α-MAN-(1→4)-RHA→ |
| $E_3$ | (3), (15), 34 | α-Glc ↓1,4 →β-GAL-(1→6)-α-MAN-(1→4)-RHA→ |
| $E_4$ | 1, 3, 19 | α-Glc ↓1,6 →α-GAL-(1→6)-α-MAN-(1→4)-RHA→ |
| $D_2$ | 3, (9), 46 | α-Tyv ↓ →GAL-(1→6)-MAN-(1→x)-RHA→ (hypothetical) |
| B | $4_1$, $12_1$, 27, 27B | α-Abe ↓1,3 →GAL-(1→6)-β-MAN-(1→4)-RHA→ |
| | $4_1$, $4_2$, $12_1$ | α-Abe ↓1,3 →GAL-(1→4)-β-MAN-(1→4)-RHA→ |
| | $4_1$, $4_2$, 5, $12_1$, $12_2$ | α-Glc ↓1,4 α-Abe ↓1,4 →α-Ac-GAL-(1→4)-β-MAN-(1→4)-RHA→ |
| $D_1$ | $9_1$, $12_1$, $12_3$ | α-Tyv ↓ →GAL-(1→4)-MAN-(1→x)-RHA→ |
| | 9, $12_1$, $12_2$, $12_3$ | α-Glc ↓1,4 α-Tyv ↓ →α-GAL-(1→4)-MAN-(1→x)-RHA→ |

Fig. 4. Structurally related O-specific oligosaccharides (repeating units) in lipopolysaccharides of various *Salmonella* species of serogroups B, D, and E [11, 33, 34, 36, 80].

Any alteration in the structure of these repeating units is expressed by a new partial serological specificity, on the basis of which the bacterial genus can be characterized and which corresponds to an individual antigen formula which had its place in the Kauffmann-White scheme long before these structures were recognized.

Several of the side-chain structures shown in Fig. 4 are interconvertible by lysogenic conversion and are therefore often closely related genetically, although they may belong to different, sometimes serologically little related, serogroups. For example, infection of *Salmonella uganda* (O antigen factors 3, 10) with the lysogenic phage $\varepsilon_{15}$ converts the former into *Salmonella newington* [3, 15]. In turn, this strain is converted into *S. illinois* (O factors 3, 15) after infection with phage $\varepsilon_{34}$. The structural changes in the corresponding polysaccharides, which were elucidated by *Robbins et al.* [34], can be seen in Figure 4. A further example of lysogenic conversion was investigated by *Le Minor* and *Staub* [33, 35]. *Salmonella* of groups A, B, and D were transformed into new serological types after infection with phage $\varphi_{27}$, *i.e.*

Group A: 2,12 $\xrightarrow{\varphi 27}$ 2, 12, 27A, 27

Group B: 4,12 $\xrightarrow{\varphi 27}$ 4, 12, 27B, 27

Group C: 9,12 $\xrightarrow{\varphi 27}$ 9, 12, 27D, 27

In all three antigens the glycosidic linkage between galactose and mannose is altered throughout the entire chain:

α-galactose(1→4)mannose→α-galactose(1→6)mannose. This change gives rise to new specificities. *Staub* and her group have also elucidated the chemical changes leading to the appearance of specificity 1 after infection with phage P22 [36].

The biological information contained in the phage nucleic acid provides a genetic link between several of the *Salmonella* serotypes shown in Figure 4. They may form a family of species which has emerged during the evolution of the *Salmonella* from an original form containing (Gal → Man → Rha) chains.

Figure 5 shows that the specific chains of polysaccharides of other *Salmonella* groups (*e.g.* G, N, and U) may consist of other sugars, for example, galactosamine, glucosamine, galactose, glucose, and fucose. The constitution of the corresponding lipopolysaccharides has been investigated by *A. R. Simmons* in our laboratory [37]. Their sugar compositions resemble those of the human blood-group substances. *Springer et al.* [38] have shown that *S. milwaukee* has a strong blood-group B specificity. The last formula in Figure 5 indicates that this cross-reaction is presumably due to the α-galactosyl-(1→3)galactose grouping, which, according to *Morgan* [39], is also involved in the structure of the blood-group B substance.

Figures 4 and 5 show oligosaccharide units isolated from partial hydrolysates of the lipopolysaccharides.

Glc-(1→2)-β-Gal-(1→3)-GalNAc-(1→3)-GalNAc→Fuc
*S. friedenau*

Glc ↓1,4
β-Glc-(1→3)-GalNAc→Fuc
*S. godesberg*

α-Gal ↓1,3
β-Gal-(1→3)-GalNAc-(1→3)-GlcNAc-(1→4)-Fuc
*S. milwaukee*

Fig. 5. O-specific oligosaccharides in lipoplysaccharides of groups G (*S. friedenau*), N (*S. godesberg*), and U (*S. milwaukee*) [37].

[33] *G. Bagdian, O. Lüderitz*, and *A. M. Staub*, Ann. N.Y. Acad. Sci. 1966, in the press.

[34] *T. Uchida, P. W. Robbins*, and *S. E. Luria*, Biochemistry *2*, 663 (1963); *P. W. Robbins* and *T. Uchida*, J. biol. Chemistry *240*, 375 (1965).

[35] *L. le Minor*, Ann. Inst. Pasteur *103*, 684 (1962); *A. M. Staub* and *N. Forest*, *ibid. 104*, 371 (1963).

[36] *B. A. D. Stocker, A. M. Staub, R. Tinelli*, and *B. Kopacka*, Ann. Inst. Pasteur *98*, 505 (1960).

[37] *D. A. R. Simmons, O. Lüderitz*, and *O. Westphal*, Biochem. J. *97*, 807, 815, 820 (1965).

[38] *G. F. Springer, P. Williamson*, and *W. C. Brandes*, J. exp. Med. *113*, 1077 (1961).

[39] *V. P. Rege, T. J. Painter, W. M. Watkins*, and *W. T. J. Morgan*, Nature (London) *200*, 532 (1963).

It is still unknown in which sequence the oligosaccharides of Figure 5 are linked within the chain, which sugar starts the chain, and how long the chain is.

The oligosaccharides shown in Figure 4 are linked in the manner indicated. Glucose and the 3,6-dideoxyhexoses form short side chains. The first sugar in the O-specific chain is galactose. The isolated units Gal→Man→Rha are therefore different from the biological units (Man→Rha→Gal)[40].

It should be interesting to obtain information about the structure of the repeating oligosaccharide units of as many O antigens of *Salmonella* S forms and other genera as possible. During comparative analyses of numerous *E. coli* species, *Jann et al.*[31,32] have found that 14 non-cross-reacting *Coli* strains form O antigens of chemotype I (only basal sugars), while 17 strains form O antigens of chemotype VII (basal sugars plus L-rhamnose). All these strains, with chemotypically the same polysaccharide antigen, must therefore have structurally different side chains.

## The S→R Mutation

It has been known for a long time that the wild types of Enterobacteriaceae can undergo spontaneous mutation. The mutated strains are easily recognized because, in general, they form rough shallow colonies (R forms) on agar, while the parent strains grow in smooth, shiny colonies (S forms)[3]. With this morphological change is connected a loss of certain biological properties. R mutants have lost the serological O specificity of the original strain and generally do not agglutinate in the related O antiserum. The R forms frequently exhibit spontaneous agglutination in liquid nutrient media. In comparison with the wild types (S forms), R mutants are less pathogenic; rapid phagocytosis and intracellular destruction occurs in higher organisms. R mutants also synthesize a cell-wall lipopolysaccharide which can be extracted with phenol/water[41,42] and which, in the animal, is generally as effective an endotoxin as the lipopolysaccharide from the related S forms.

Because of the loss of the serological O specificity during S→R mutation, it was to be expected that R lipopolysaccharides differ in constitution from the corresponding O-specific S lipopolysaccharides. Starting from about 25 different *Salmonella* S forms with O antigens of nearly all chemotypes (cf. Fig. 3) *Kauffmann* has isolated R mutants from which we extracted the corresponding lipopolysaccharides[42]. The results of the sugar analyses of these R lipopolysaccharides can be seen in Figure 3. In contrast to the multiplicity of the sugar combinations (chemotypes) in the lipopolysaccharides of the S forms, the lipopolysaccharides of the R mutants contain only the basal sugars (shaded in Fig. 3), irrespective of which chemotype the S form belonged to. The specific sugars of the wild-type lipopolysaccharides have disappeared in the corresponding R lipopolysaccharides. After S→R mutation the multiplicity in the constitution of the O antigens is replaced by a very uniform picture; the investigated R antigens all belong to chemotype I (basal sugars only)[42].

Two facts appear to be significant: (1) the *Salmonella* O antigens always contain the same five basal sugars in addition to the specific sugars, and (2) the same five sugars make up the lipopolysaccharides of the investigated R mutants. This led us to the hypothesis[42,43], which was independently developed by *Nikaido*[44], that the polysaccharides of the R forms are preformed as the nucleus in the polysaccharides of the S forms (see Fig. 2).

According to this scheme, O antigens consist of a basal polysaccharide with the five basal sugars and the O-specific side chains. These side chains form the bulk of the molecule; the basal polysaccharide appears to be the common underlying structure of all O antigens. When the biosynthesis of the O-specific side chains in an enterobacterial wild type has been interrupted by an enzyme block produced as a result of a mutation, only the synthesis of the basal part occurs. Accordingly, this part represents the R-specific polysaccharide of the R mutants. In addition, it is plausible that R form polysaccharides contain no sugars which are not also present in the S form.

This postulate of an ubiquitous basal polysaccharide and of specific side chains has admittedly not yet been finally proved as a general principle, but it is now largely accepted for the *Salmonella*. This hypothesis (Fig. 2) is supported by the findings presented in the following sections.

## RI- and RII-Specific Polysaccharides

As shown above, the lipopolysaccharides from R forms of *Salmonella* are chemically very uniform. All investigated R lipopolysaccharides consist of the five basal sugars KDO, glucosamine, heptose, galactose, and glucose. This chemical uniformity is matched by a great serological uniformity. The R lipopolysaccharides,which have lost the O-specificity of the related wild types, exhibit strong mutual serological cross-reactions[3,45]. In hemagglutination inhibition experiments[45], it was found that R lipopolysaccharides can be be classified into two serological groups on the basis of their serological reactivity with two R antisera (Table 1).

To carry out passive hemagglutination[46,47], lipopolysaccharides pretreated by heating or with weak alkali are fixed on the surface of erythrocytes. When the blood corpuscles sensitized in this way are incubated with antisera prepared by immunization of rabbits against the appropriate bacterium, the erythrocytes undergo agglutination. This reaction is in-

[40] *H. Nikaido, Y. Naide,* and *P. H. Mäkelä,* Ann. N.Y. Acad. Sci. 1966, in the press.

[41] *O. Westphal* and *O. Lüderitz,* 6th Internat. Congr. Microbiol. *2,* 22 (1953).

[42] *F. Kauffmann, L. Krüger, O. Lüderitz,* and *O. Westphal,* Zbl. Bakteriol., Parasitenkunde Infektionskrankh., Abt. I, Orig. *182,* 57 (1961).

[43] *O. Lüderitz, F. Kauffmann, H. Stierlin,* and *O. Westphal,* Zbl. Bakteriol., Parasitenkunde Infektionskrankh., Abt. I, Orig. *179,* 180 (1960).

[44] *H. Nikaido,* Proc. nat. Acad. Sci. USA *48,* 1542 (1962).

[45] *I. Beckmann, O. Lüderitz,* and *O. Westphal,* Biochem. Z. *339,* 401 (1964).

[46] *E. Neter,* Bacteriol. Rev. *20,* 166 (1956).

[47] *E. Neter, O. Westphal, O. Lüderitz,* and *E. A. Gorzynski,* Ann. N.Y. Acad. Sci. *66,* 141 (1956).

hibited when serologically identical or cross-reacting lipopolysaccharides are added to the agglutinating system. These then react with the antiserum, so that hemagglutination fails to take place. This inhibition reaction is highly specific and can be performed with microgram quantities of antigen.

Table 1. Serological classification of *Salmonella* R lipopolysaccharides (hemagglutination inhibition test) [45].

| R serogroup | Lipopolysaccharide from *Salmonella* serotype | | Amount of lipopolysaccharide needed to inhibit antibodies against *S. minnesota* RI | Amount of lipopolysaccharide needed to inhibit antibodies against *S. inverness* RII |
|---|---|---|---|---|
| I | *S. berlin* | R | 1–8 μg/ml | > 250 μg/ml |
| | *S. bergen* | R | | |
| | *S. minnesota* | R | | |
| | *S. worthington* | R | | |
| | *S. monschaui* | R | | |
| II | *S. typhimurium* | R | > 250 μg/ml | 0,5–4 μg/ml |
| | *S. hvittingfoss* | R | | |
| | *S. inverness* | R | | |
| | *S. typhi* | R | | |
| | *S. minnesota* | R | | |
| | *S. binza* | R | | |
| | *S. tel-aviv* | R | | |
| | *S. weslaco* | R | | |
| | *S. poona* | R | | |
| | *S. bareilly* | R | | |
| | *S. parathyphi C* | R | | |
| | *S. paratyphi A* | R | | |
| | *S. newport* | R | | |
| | *S. aberdeen* | R | | |
| | *S. greenside* | R | | |
| | *S. deversoir* | R | | |
| | *S. dugbe* | R | | |
| | *S. cerro* | R | | |
| | *S. dahlem* | R | | |
| | *S. djakarta* | R | | |

Kauffmann-White scheme by numerous antigen factors (specificities of S forms) and their combinations, is therefore reduced to a few R specificities.

We had initially assumed that the S→R mutation would, for unknown reasons, lead to RI mutants in some species and to RII mutants in others, *i.e.* that the result of mutation is determined by properties of the wild type. However, *Kauffmann* then isolated a second *S. minnesota* R mutant which differs serologically from the RI type; the analysis of its lipopolysaccharide showed that it belongs to the RII group. At the same time, *Stocker* [48,50] isolated RI and RII mutants of *S. typhimurium*, and we now assume that each *Salmonella* species can undergo mutation to RI as well as to RII.

In recombination experiments with colicinogenic strains, *Subbaiah* and *Stocker* [48] found that for *S. typhimurium* the mutation to RI mutants occurs at the gene locus rou A, while during mutation to RII mutants gene locus rou B is involved. Further experiments showed that locus rou A is responsible for the biosynthesis of the basal polysaccharide and locus rou B for the biosynthesis of the O-specific side chains [49].

An attempt to elucidate the chemical structure and the biosynthesis of RI and RII-specific (lipo)polysaccharides, their mutual relationship, and that to the (lipo)polysaccharide of the S form has meanwhile been undertaken by several groups of workers. We have been concerned primarily with the comparative analysis of

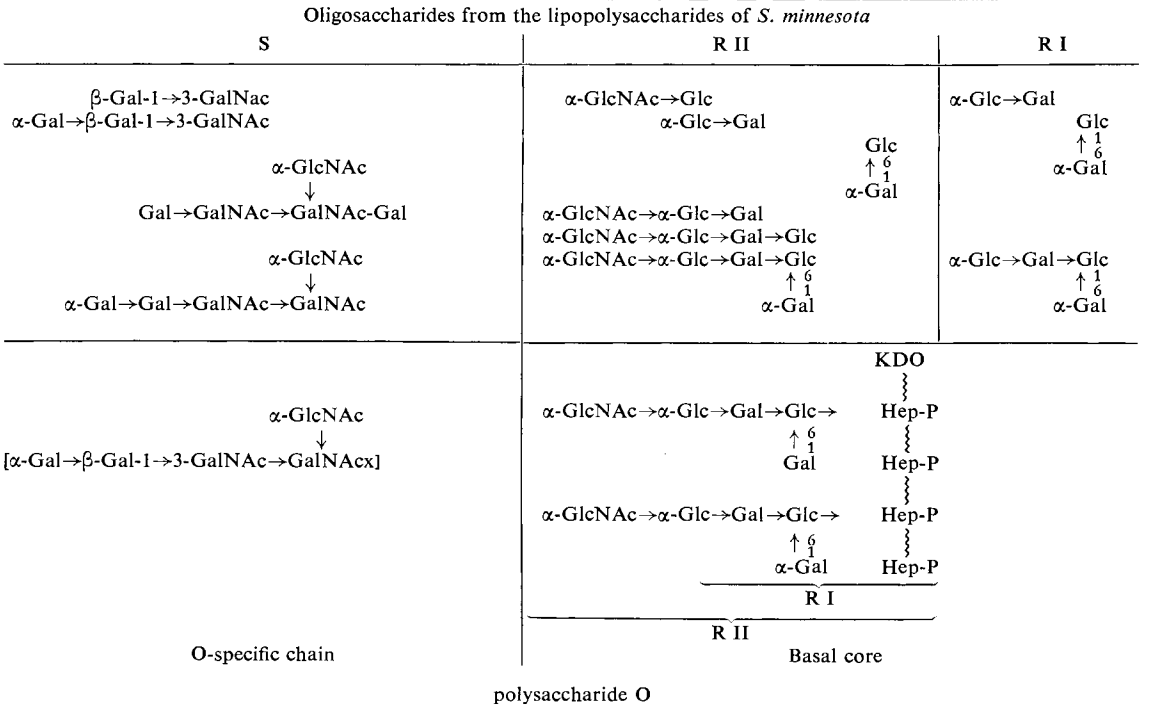


Fig. 6. Possible structures of the oligosaccharides of *S. minnesota* S, RI, and RII lipopolysaccharides (top) and a hypothetical formula of the O-specific polysaccharide (bottom) [51, 53].

The first group of R lipopolysaccharides inhibits the antiserum obtained with an R mutant of *Salmonella minnesota* (system I), and the second group inhibits a *Salmonella inverness* R antiserum (system II). Because of their serological specificities, the R lipopolysaccharides can be assigned to the serological groups RI or RII.

In the *Salmonella* R mutants, the great serological diversity of the S forms, which is expressed in the

[48] *T. V. Subbaiah* and *B. A. D. Stocker*, Nature (London) *201*, 1298 (1964).

[49] *P. H. Mäkelä*, J. gen. Microbiol. *41*, 57 (1965).

[50] *I. Beckmann*, *T. V. Subbaiah*, and *B. A. D. Stocker*, Nature (London) *201*, 1299 (1964).

[51] *I. W. Sutherland*, *O. Lüderitz*, and *O. Westphal*, Biochem. J. *96*, 439 (1965).

the S form of *S. minnesota* and the mutants *S. minnesota* RI and RII. *Salmonella minnesota* belongs to the O serogroup L. In addition to the main antigen 21, it contains the weakly established factor 26[3], which was introduced, because of a cross-reaction with species of group $E_1$ *(e.g. S. london)* with the factors 3, 10. The formulae are therefore: *S. minnesota* 21, 26 and *S. london* 3, 10, 26. Factor 26 was not included in the Kauffmann-White scheme. In addition to the basal sugars, the *S. minnesota* lipopolysaccharide contains galactosamine as the specific sugar[28].

To elucidate the chemical structure of the O antigen and the R antigens of *S. minnesota*, partial hydrolyses were carried out. The oligosaccharides thus obtained from the RI, RII, and S lipopolysaccharides are listed in Figure 6[51].

### The RII Polysaccharide

Of the listed RII oligosaccharides, five fragments can be recombined to form a pentasaccharide. This pentasaccharide has the structure of an *N*-acetylglucosaminyl→glucosyl→galactosyl→glucose with an α(1→6)-linked galactosyl residue in the side chain and glucose as the reducing end-group. The provisional formula for the RII polysaccharide (Fig. 6, bottom) contains this pentasaccharide linked to heptose. The formula is based partly on investigations on other mutants by *Nikaido*[52], who isolated a glucose-heptose oligosaccharide. *Kuriki* and *Kurahashi*[52a] recently isolated oligosaccharides from a UDP-glucose deficient mutant, which consist of 10 heptose units and one (reduced) KDO unit. This proves that part of the heptose units is linked glycosidically (probably 1→2).

### The RI Polysaccharide

A similar set of oligosaccharides, but without the terminal *N*-acetylglucosamine, was obtained by partial hydrolysis of the *S. minnesota* RI lipopolysaccharide (Fig. 6). This leads to the formula of the RI polysaccharide which is shown at the bottom of Figure 6 as part of the RII formula.

Thus the RI polysaccharide of *S. minnesota* differs from the RII polysaccharide merely by the absence of the terminal non-reducing glucosamine unit, or, alternatively, the RII polysaccharide is obtained from the RI polysaccharide when the glucosamine unit is added onto the non-reducing terminal glucose residue (Fig. 6). The RI polysaccharide therefore behaves as a precursor of the RII polysaccharide.

We have also investigated the lipopolysaccharides of the RII mutants of *S. typhimurium*, *S. inverness*, and *S. poona*. Their partial hydrolysates contained the same oligosaccharides as the *S. minnesota* RII lipopolysaccharide. It follows that RII lipopolysaccharides of different origin are not only serologically identical but also have the same chemical composition.

### The O-Specific Polysaccharide of the Wild Type

*Schulte-Holthausen*[33] in our laboratory isolated 15 basic or neutral oligosaccharides from the lipopolysaccharide of the S form of *S. minnesota*. So far, only the four compounds shown on the left-hand side of Figure 6 have been purified sufficiently for analyses to be carried out (sugar determinations before and after borohydride reduction, Morgan-Elson reaction, attempts to split the molecule with glycosidases). The formulae shown have not yet been finally confirmed. α-Linked *N*-acetylglucosamine very likely acts as a specificity-determining immunodominant sugar[11] in antigen factor 21[54], while α-linked galactose may be important for the specificity of antigen factor 26[34]. The formula reconstructed in the lower left-hand part of Figure 6 from the structures of the oligosaccharide fragments is a provisional one. However, it can be assumed that these or similar oligosaccharides form the repeating units of the long chains of the O antigen of *S. minnesota*.

If the RI structure is a precursor of the RII structure, and if the RII structure is the same in all *Salmonella*, it may be assumed that the RII lipopolysaccharide represents the ubiquitous basal structure to which the specific side chains with their repeating oligosaccharide units are bound, and which carry the O-antigenic specificity of the S forms. It should then be possible to obtain at least small amounts of oligosaccharidic RI and RII fragments by partial hydrolysis of wild-type O-antigenic lipopolysaccharides. *Schulte-Holthausen*[53] was indeed able to isolate three glucose-containing oligosaccharides from partial hydrolysates of the lipopolysaccharide of *S. minnesota* O antigen (together with O-specific galactosamine-containing oligosaccharides), and these proved to be identical with the glucosamine-containing di-, tri-, and tetrasaccharides from the RII lipopolysaccharide shown in Figure 6. Analogously, *Simmons* was able to isolate R-specific oligosaccharides from three further *Salmonella* O antigens[37].

In a further series of experiments, we subjected different lipopolysaccharides of *Salmonella* S forms to mild acid hydrolysis and tested the partial hydrolysates for their activity as inhibitors towards RI and RII antisera in hemagglutination tests[55]. It was found that even the lipopolysaccharides of higher chemotypes give rise to RI-specific structures during hydrolysis. No RII structures could be detected in this way, presumably because the RII structure is more sensitive to acid.

It is noteworthy that, during partial hydrolysis of a serologically cross-reacting *E. coli* strain (comparison of *S. adelaide* with *E. coli* 0111, whose O antigens are of the identical chemo-

[52] *H. Nikaido*, Biochemistry *4*, 1550 (1965).

[52a] *Y. Kuriki* and *K. Kurahashi*, J. Biochem. (Tokyo) *58*, 308 (1965).

[53] *H. Schulte-Holthausen*, Dissertation, Universität Freiburg, in preparation.

[54] *O. Lüderitz, H. R. Risse, H. Schulte-Holthausen, J. L. Strominger, I. W. Sutherland*, and *O. Westphal*, J. Bacteriol. *89*, 343 (1965).

[55] *O. Lüderitz, I. Beckmann*, and *O. Westphal*, Biochem. Z. *339*, 416 (1964).

type, *i.e.* basal sugars plus colitose[56]), RI or RII structures could at no time be detected serologically[55]. Whether the constitution of the *Coli* polysaccharide differs fundamentally from that of the *Salmonella* polysaccharide can be established only by a study of further *Coli* strains. However, there are *Coli* O antigens which contain no galactose[31,32], and also some *Shigella* strains without glucose[57], which in *Salmonella* are basal sugars participating in the RI and RII structures (Figs. 2 and 6).

The above results support the postulate that in *Salmonella* the RII (and RI) polysaccharide is a fundamental structure and an inner part of the O-antigenic lipopolysaccharide of the wild type (S form).

## Biochemical Investigations of R Mutants

On the basis of the investigations on deficient mutants of *Salmonella*, which have been carried out particularly by *Nikaido et al.*[44,58] in Boston, it was postulated that, during S→R mutation, enzyme defects arise in the resulting RII- and RI-specific *Salmonella* strains. A first insight into the mechanism of the S→RII and S→RI mutations in *S. minnesota* was obtained when we tested three strains, *viz.* S, RII, and RI, in regard to their content of enzymes necessary for the biosynthesis of the O antigen of the S form.

From results deduced so far, the biosynthesis of the O-specific polysaccharides proceeds in two stages. In the first stage, the activated monosaccharides are synthesized in the form of their nucleoside diphosphate derivatives. The enzymes involved are termed synthetases. In the second stage, the sugar residues are transferred to the growing polysaccharide by specific transferases[59-61].

In addition to the basal sugars, the *S. minnesota* O antigen contains galactosamine, and this sugar is the only one which is absent from the lipopolysaccharide of the R mutants.

In the bacteria, galactosamine is formed from glucosamine under the action of a 4-epimerase, which converts UDP-*N*-acetylglucosamine into UDP-*N*-acetylgalactosamine. We have determined this enzyme in the S form and in both R types (RI and RII) of *S. minnesota*[54] (Fig. 7). For this purpose, [$^{14}$C]-UDP-*N*-acetylglucosamine was prepared and incubated with cell-free extracts from S and R cells. After hydrolysis, the three *N*-acetylhexosamines were separated chromatographically on borate-treated paper, and the distribution of the radioactivity was determined. It was found that incubation of radioactive UDP-*N*-acetylglucsoamine with S and RI extracts leads to the formation of galactosamine, whereas in the case of an RII extract no galactosamine is formed. The RII species is therefore a mutant, from which the UDP-acetylglucosamine 4-epimerase is missing, and we assume that the inability to synthesize UDP-*N*-acetylgalactosamine is the cause for the block in the biosynthesis of the cell-wall polysaccharide, so that it stops at the stage of the RII structure.

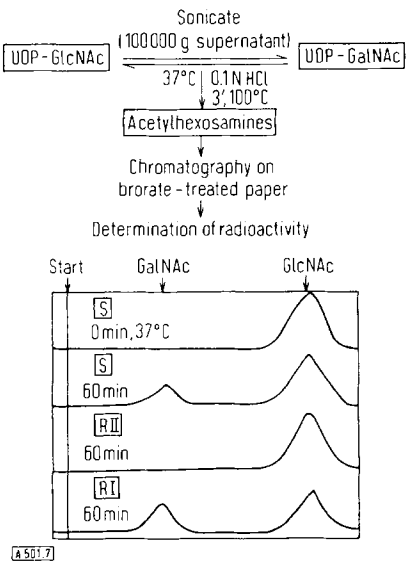


Fig. 7. Detection of UDP-*N*-acetylglucosamine 4-epimerase in S, RI, and RII forms of *S. minnesota* [54].

Other RII mutants which are likewise characterized by a defect in the synthesis of a specific sugar (which is a constituent of the side chain of the O antigen) can be isolated from *S. typhimurium* cultures. Examples are a mutant which is unable to form TDP-rhamnose[58], and another mutant which forms no GDP-mannose[61,62]. In contrast, the RI mutant of *S. minnesota* contains UDP-acetylglucosamine epimerase, and is therefore capable of forming galactosamine. However, the galactosamine is not incorporated into the cell-wall lipopolysaccharide, because a block in the biosynthesis (RI appears as the precursor of RII) prevents complete synthesis of the substrate for galactosamine incorporation.

### The O-Specific Polysaccharide Hapten in RI Mutants

A further important discovery was that of an O-specific polysaccharide in RI mutants by *I. Beckmann*[50] in our laboratory.

To obtain the lipopolysaccharides the cells are generally extracted with phenol/water[17] (Figure 8), and the crude aqueous extract is subsequently centrifuged at 100000 g. The lipopolysaccharide is obtained as a sediment, while the supernatant contains chiefly nucleic acid. During fractionation of the supernatant from an extract of *S. typhimurium* RI, *Beckmann*[50] found a polysaccharide containing the sugars mannose, rhamnose, and abequose, characteristic for the related O-antigenic wild-type lipopolysaccharide (see Figure 3, chemotype XIV), but no heptose, and which precipitates specifically with *S. typhimurium* O antiserum. While the RI bacterium serologically exhibits only RI specificity it forms in addition a relatively low-molecular polysaccharide with the O specificity of the wild type.

[56] *O. Westphal, F. Kauffmann, O. Lüderitz*, and *H. Stierlin*, Zbl. Bakteriol., Parasitenkunde Infektionskrankh., Abt. I. Orig. *179*, 336 (1960).

[57] *W. T. J. Morgan*, Helv. chim. Acta *21*, 469 (1938; *D. A. L. Davies, W. T. J. Morgan*, and *R. R. Record*, Biochem. J. *60*, 290 (1955).

[58] *H. Nikaido, K. Nikaido, T. V. Subbaiah*, and *B. A. D. Stocker*, Nature (London) *201*, 1301 (1964).

[59] *L. F. Leloir*, Biochem. J. *91*, 1 (1964).

[60] *V. Ginsburg*, Adv. Enzymology *26*, 35 (1964).

[61] *M. J. Osborn, S. M. Rosen, L. Rothfield, L. D. Zeleznick*, and *B. L. Horecker*, Science (Washington) *145*, 783 (1964).

[62] *L. D. Zeleznick, S. M. Rosen, M. Saltmarsh-Andrew, M. J. Osborn*, and *B. L. Horecker*, VI. Internat. Congr. Biochem., New York 1964, Abstr. VI/Y 125.

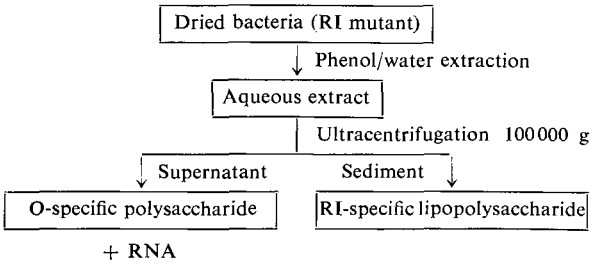


Fig. 8. Scheme illustrating the phenol/water extraction of RI mutants [17,50].

After phenol/water extraction of *S. minnesota* RI cells appreciable quantities of non-dialysable galactosamine were found in the supernatant obtained on ultracentrifugation. This sugar is completely absent from the lipopolysaccharide of the RI mutant and is characteristic for the side chain of the lipopolysaccharide of the O-antigenic wild type. It was shown [54] that in *S. minnesota* RI cells galactosamine is the constituent of a polysaccharide with the O specificity of the *S. minnesota* wild type which is precipitated by *S. minnesota* O-antiserum.

In RI mutants of *Salmonella* of different serological groups (B and L), R lipopolysaccharides are found in the cell wall, while the polysaccharide specific for the wild type is found in the cell interior. This polysaccharide, which presumably represents the isolated side chain of the O antigen, is not antigenic for rabbits, *i.e.* it is a hapten. In contrast, no O-specific polysaccharide hapten has ever been found in RII cells.

The conclusion is that RI mutants have a defect in the biosynthesis of the complete RII structure. The latter appears to be the substrate for the incorporation of the O-specific side chains, *i.e.* the repeating O-specific oligosaccharide units. RII mutants, on the other hand, have a block in the biosynthesis of one of the sugars in the side chain (or in its transfer). Thus RI mutants retain the ability to form the specific side chain, but the necessary substrate, *i.e.* the complete RII structure (Figure 6) with terminal *N*-acetylglucosamine, is missing, so that the side chain cannot be incorporated in the cell-wall lipopolysaccharide, whose biosynthesis stops after the RI structure has been formed.

## Further R Forms

If the concepts concerning the S→R mutation in Enterobacteriaceae are correct, then the existence of mutants other than RII and RI must be anticipated. These would differ from the ones described by an even less complete R antigen (R lipopolysaccharide), *i.e.* by a block at an even earlier stage of the polysaccharide biosynthesis. The complete bacterial cell-wall lipopolysaccharide is built up in a sequence of many steps, in which numerous synthetases and transferases participate. The formation of each of these enzymes is controlled genetically and each enzyme can in principle be affected by a mutation. It should therefore be possible to detect each stage of the (lipo)polysaccharide biosynthesis by isolation of a mutant which has an enzyme defect at precisely this stage. Deficient mutants of *S. typhimurium* of this type have indeed been described some years ago, particularly by Japanese workers.

*Nikaido* [44,63,64] was the first to describe a mutant (M mutant) lacking UDP-galactose 4-epimerase, *i.e.* which cannot form galactose on a glucose nutrient because the reaction

$$\text{UDP-Glu} \overset{\text{4-epimerase}}{\rightleftharpoons} \text{UDP-Gal}$$

is blocked [44,63,64]. *Nikaido*'s work was based on investigations of *Kalckar et al.* [65,66]. In this M mutant, the biosynthesis of the cell-wall lipopolysaccharide ceases where (in the wild type) the first incorporation of galactose takes place. The lipopolysaccharide of the M mutant contains only (lipid)glucosamine, KDO, heptose, and glucose. Subsequently, *Fukasawa et al.* [67] described a mutant in which the conversion of glucose 1-phosphate into UDP-glucose is blocked by the absence of the enzyme UDP-glucose pyrophosphorylase. This mutant forms only the polyheptose phosphate core with KDO and lipid A, and even the incorporation of glucose is blocked because the cell is unable to synthesize activated glucose.

Mutants without UDP-galactose 4-epimerase (M mutants) or without UDP-glucose pyrophosphorylase were later isolated from cultures of other *Salmonella* (and *E. coli*) species, so that it can be assumed that, like the RII and RI mutants, they can arise from any *Salmonella* species.

In collaboration with *J. Schlosshardt* [68], we have attempted in recent years to isolate and analyse a great number of R mutants from *S. minnesota*, in order to obtain as many intermediate stages of the biosynthesis of the O antigen (wild-type lipopolysaccharide) as possible. *S. ruiru* (antigen factor 21) was included in the investigation; it belongs to the same chemotype and serotype as *S. minnesota*.

To isolate the mutants, a synthetic medium of pH 8.2, which contained citrate and ammonia, was inoculated with *S. minnesota* or *S. ruiru* and incubated at 37 °C. After various periods of time, samples were transferred to agar and rough colonies were selected for further single-cell culturing. After five days, almost all colonies were rough. During the bacteriological investigations, the principal difficulty was to isolate new mutants with as yet unknown properties. *Schlosshardt* has used the sensitivity of the R strains to phages in order to differentiate between the various R mutants. She attempted to isolate as many R strains of different phage-sensitivity as possible, in the hope that some of the phages would require structurally different R lipopolysaccharides on the cell surface as the receptor and in this way would permit the differentiation of R classes.

Approximately 30 mutated strains were isolated [68], all of which possessed the flagella antigens (H antigens) and

[63] *T. Fukasawa* and *H. Nikaido*, Nature (London) *184*, 1168 (1959).

[64] *H. Nikaido*, Proc. nat. Acad. Sci. USA *48*, 1337 (1962).

[65] *T. A. Sundararajan, A. M. C. Rapin*, and *H. M. Kalckar*, Proc. nat. Acad. Sci. USA *48*, 2187 (1962).

[66] *H. M. Kalckar*, Science (Washington) *150*, 305 (1965).

[67] *T. Fukasawa, K. Jokura*, and *K. Kurahashi*, Biochem. biophysic. Res. Commun. *7*, 121 (1962).

[68] *O. Lüderitz, C. Galanos, H. J. Risse, E. Ruschmann, S. Schlecht, G. Schmidt, H. Schulte-Holthausen, R. Wheat, O. Westphal*, and *J. Schlosshardt*, Ann. N.Y. Acad. Sci. 1966, in the press.

the fermentation properties of the parent strain. The lipopolysaccharides were extracted with phenol/water and their sugars were identified and determined quantitatively. The mutants were then classified into different chemotypes on the basis of the composition of their lipopolysaccharide sugars (Figure 9).

Injection of the heat-killed bacteria into rabbits led to the formation of antisera. Hemagglutination inhibition tests (cf. Figure 6) were again employed to detect serological cross-reactions of the R lipopolysaccharides. The results are shown in the right-hand part of Figure 9.

| Chemotype | Strain | % of lipopolysaccharide: Lipid A | KDO | Heptose | Glucose | Galactose | GNAc(PS)[*] | GalNAc | Hemagglutinating system: S | S• | 1 | RII | RI | 2 | 2• | 62 | 1• | 3 | 4 | 3• | 7 | 595 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| II | S | + | 5 | 3 | 4 | 13 | 10 | 17 | ⊗ | ○ | | ○ | | | | | | | | | | |
| | S• | + | 4 | 4 | 3 | 15 | 10 | 17 | ○ | ⊗ | | | | | | | | | | | | |
| II | 1 | + | 10 | 5 | 1 | 5 | 10 | 14 | ○ | ○ | ⊗ | | ○ | ○ | | | | | | | | ○ |
| | 608 | + | 8 | 7 | 2 | 18 | n.d. | 14 | ○ | ○ | | | ○ | ○ | | | | | | | | |
| | 46 | + | 4 | 9 | 3 | 15 | 10 | 16 | ○ | ○ | | | | | | | | | | | | |
| | 1001 | + | 5 | 12 | 4 | 11 | n.d. | 8 | ○ | ○ | | | | | | | | | | | | |
| | 61 | 50 | 8 | 10 | 3 | 6 | 3 | 4 | ○ | ○ | | ○ | | | | ○ | ○ | ○ | | | | |
| | 2• | + | 10 | 17 | 2 | 2 | n.d. | 4 | ○ | ○ | | | | | | ⊗ | | | | | | ○ |
| Ra | RII | + | 5 | 7 | 6 | 8 | 6 | | | | | ⊗ | | | | | | | | | | |
| | 555 | 45 | 9 | 11 | 3 | 6 | 2 | | | | | ○ | ○ | ○ | | | | | | | | ○ |
| | 708 | 47 | 10 | 11 | 4 | 6 | 2 | | | | | ○ | ○ | ○ | | | | | | | | |
| Rb | RI | + | 5 | 10 | 4 | 9 | | | ○ | ○ | | | ⊗ | | | | | | | | | |
| | 2 | 50 | 7 | 14 | 3 | 4 | | | | | ○ | | ○ | ⊗ | | | | | | | | |
| | 592 | 53 | 9 | 10 | 5 | 4 | | | | | | | | ○ | ○ | ○ | | | | | | |
| Rc | 5 | + | 8 | 11 | 5 | | | | | | | ○ | ○ | ○ | ○ | ○ | ○ | | | | | |
| | 8 | + | 10 | 6 | 4 | | | | | | | | ○ | ○ | ○ | ○ | ○ | | | | | ○ |
| | 62 | 52 | 9 | 10 | 4 | | | | | | | | ○ | ○ | ○ | ⊗ | ○ | | | | ○ | |
| | 1• | + | 8 | 15 | 2 | | | | | | | | | | ○ | ○ | ⊗ | | | | ○ | |
| Rd | 541• | 52 | + | 17 | | | | | | | | | | | ○ | ○ | ○ | | | | ○ | |
| | 3 | 63 | 9 | 7 | | | | | | | | | | | | | | ⊗ | ○ | ○ | | |
| | 4 | + | 8 | 7 | | | | | | | | | | | | | | ○ | ⊗ | ○ | | |
| | 3• | + | 9 | 6 | | | | | | | | | | | | | | ○ | ○ | ⊗ | | |
| | 597 | + | 11 | 5 | | | | | | | | | | | | | | ○ | ○ | ○ | | |
| | 7 | 58 | 9 | 13 | | | | | | | | | | | | | | | | | ⊗ | |
| Re | 1000 | + | 16 | | | | | | | | | | | | | | | ○ | ○ | ○ | ○ | |
| | 128• | 64 | 16 | | | | | | | | | | | | | | | | | | ○ | ○ |
| | 595 | + | 16 | | | | | | | | | | | | | | | | | | ⊗ | |
| | 613 | 65 | 17 | | | | | | | | | | | | | | | | | | ○ | |

A 501.9

Fig. 9. Chemical and serological classification of R-mutants of *S minnesota* and *S. ruiru* [68].

Strain numbers followed by a dot are genetically related to *S. ruiru*; the others were isolated from *S. minnesota*.

+ : present but not determined quantitatively.
n.d. : not determined.

[*] Glucosamine was determined after separation of lipid A from the polysaccharide.
Hemagglutinating system: Alkali-treated lipopolysaccharide fixed on erythrocytes) and homologous serum.
Circles denote inhibition of the hemagglutinating system by the lipopolysaccharide isolated from the strain shown on the left. Example: *S. minnesota* R3 lipopolysaccharide (group Rd, line 2) inhibits the hemagglutinating system with *S. minnesota* R3 (homologous system, indicated by a cross), *S. minnesota* R4, and *S. ruiru* R3.

It is seen that mutants of numerous chemotypes were found (Ra–Re) [11]. In Figure 9, the lipopolysaccharides of these mutants become progressively poorer in sugars from top to bottom. In each succeeding group (chemotype) a further sugar is missing. At the bottom of Figure 9, the R antigens of chemotype Re contain no hexoses and no heptose, and the only identifiable building units are lipid A and ketodeoxyoctonic acid (KDO), which together comprise at least 80 to 90% of the substance.

It is further seen from Figure 9 that the chemically classified mutants also form serological groups, and groups of different phage sensitivity [68]. This parallelism of chemical composition, serological specificity, and phage sensitivity may indicate that the lipopolysaccharides of these mutants can function as determinant groups during antibody formation and as phage receptors, although they are partly rather incomplete. With these R mutants a large number of steps in the biosynthesis of the *S. minnesota* O antigen has been verified.

This is illustrated by Figure 10, showing lipopolysaccharide structures which – provided our concept is correct – are all traversed in the course of O antigen biosynthesis. Details of these structures, which represent the innermost part of the core polysaccharide, will have to be determined. We trust that the newly discovered R strains and their R lipopolysaccharides will facilitate the structural analysis.

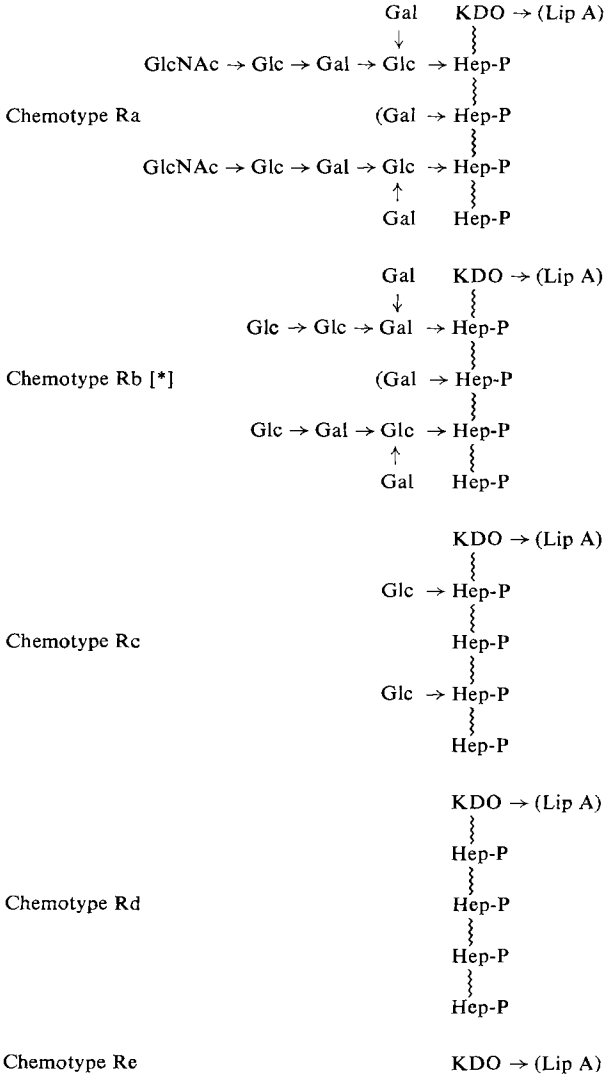


Fig. 10. Possible structures of polysaccharides isolated from R mutants (intermediates in the biosynthesis of O-specific polysaccharides).

[*] This structure follows from the analysis of the RI polysaccharide of *S. minnesota*. Structures intermediate between the Rb and Rc structures shown are probable. All belong to chemotype Rb (*i.e.* they consist of lipid A, glucosamine, KDO, heptose, galactose, and glucose); see *e.g. I. W. Sutherland et al.* [51].

The heptose-containing (but hexose-free) and the heptose-free lipopolysaccharides are of particular interest. It is possible that heptose is a serologically determinant sugar in Ra mutants. We do not know which groups are the carriers of serological specificity in the heptose-free mutants, and the same is true of the phage receptors. Furthermore, heptose-free mutants will be particularly suitable for investigations on the anabolism and the activation of heptose, about which little is known. The heptose in the basal chain of *Salmonella* lipopolysaccharides has been identified as L-glycero-D-manno-heptose[69, 70].

### The Chemical Nature of the Endotoxins

The mutants described are of considerable interest in the study of the biological effects of bacterial lipopolysaccharides (endotoxins) and especially in the search for active structures. In the lipopolysaccharides of Enterobacteriaceae, the polysaccharide part is responsible for the serological specificity. In addition, it may serve as a water-soluble carrier and consequently be of indirect significance for non-specific, endotoxic effects. However, we assume that lipid A, present in all lipopolysaccharides, is the factor determining endotoxic properties. *Nakano*[71] showed recently that lipopolysaccharides from M mutants (cf. Figure 10), containing only lipid A, KDO, heptose, and glucose, exhibit the same toxicity as the lipopolysaccharides of the related wild type with the complete O-specific polysaccharide. Lipid A can be obtained only by acid hydrolysis from the lipopolysaccharides, and a greater or smaller loss in activity is inevitable. Hydrolysis under very mild conditions, on the other hand, provides no guarantee

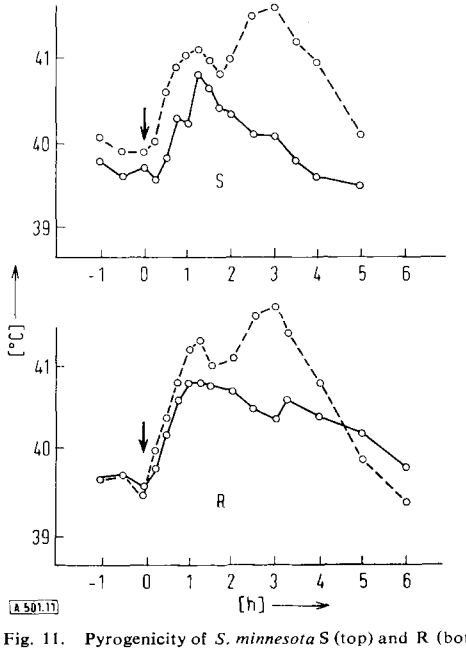


Fig. 11. Pyrogenicity of *S. minnesota* S (top) and R (bottom) lipopolysaccharides in rabbits *(Eichenberger)*.
o—o 0.1 μg/kg. o - - - o 1 μg/kg.
Ordinate: body temperature [°C].
Abscissa: time after application [hours].
Arrows denote the time of application.

[69] *G. Bagadian, W. Dröge, K. Kotelko, O. Lüderitz*, and *O. Westphal*, Biochem. Z. 1966, in the press.

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that all residual polysaccharide components have been split from the lipid. Extracts from Re mutants (Figure 10) which contain only lipid A and KDO – with a lipid A content of more than 70% – and are free from heptose and hexoses, seem suitable for a renewed study of the significance of the lipid A and of the polysaccharide components in bringing about endotoxic effects.

In collaboration with *E. Eichenberger* of the Wander laboratories in Berne, Switzerland, we have tested the pyrogenic activity of two extreme lipopolysaccharides: the polysaccharide of the S form and of the Re mutant of *S. minnesota*. Figure 11 shows that both preparations exert approximately equal pyrogenicity in rabbits after intravenous injection.

Table 2 shows the results of toxicity determinations after intraperitoneal application to mice. The $LD_{50}$ value for the lipopolysaccharide of the S form of *S. minnesota* is about 250 μg per mouse. The lipid A-KDO complex from the R mutant has a weaker effect (about one-quarter of that of the wild-type lipopolysaccharide), but here also the "polysaccharide-free" lipid A is endotoxically active, and allowance must be made for the fact that the preparation has only moderate solubility in water. Similar results were obtained by *Tripodi* and *Nowotny*[79] with our R lipopolysaccharides.

Table 2. Lethal toxicity of *S. minnesota* S and R lipopolysaccharide in mice [68]. The numbers in the table denote the proportion of deaths.

| Lipopolysaccharides from | Quantity injected per mouse 125 μg | 250 μg | 500 μg | 1000 μg | 2000 μg |
|---|---|---|---|---|---|
| *S. minnesota* S | 0/16 | 11/20 | 19/26 | 16/16 | |
| *S. ruiru* S | 1/10 | 7/10 | 7/10 | 7/10 | |
| *S. minnesota* RII | | | 7/10 | 7/10 | 10/10 |
| *S. minnesota* RI | | | 8/10 | 10/10 | 10/10 |
| *S. minnesota* R3 | | | 1/10 | 3/10 | 10/10 |
| *S. minnesota* R4 | | | 2/10 | 8/10 | 8/10 |
| *S. minnesota* R595 | 0/6 | | 2/26 | 9/26 | 11/20 |
| *S. minnesota* R613 | | | 0/10 | 2/10 | 9/10 |

These experiments demonstrate that the polysaccharide component of bacterial lipopolysaccharides has little or no effect on the endotoxic action produced in the animal, except possibly as a solubilizing agent. Instead, lipid A appears to be the factor decisive for at least some endotoxic effects.

## Intermediate Forms

### Semi-R Mutants

If the hypothesis that in the lipopolysaccharides of *Salmonella* S forms the repeating oligosaccharide units of the specific side chains are bound to the terminal *N*-acetylglucosamine of the RII structure (basal polysaccharide) (Figures 6 and 12) is correct, then the type of linkage of the first specific oligosaccharide unit is different from that of all the following ones. The repeating units of many *Salmonella* lipopolysaccharides are (mannose→rhamnose→galactose→) oligosaccharides (Figures 4 and 12), with the galactose of the first unit (denoted by Gal I in Figure 12) bound to the *N*-acetylglucosamine of the RII structure, while the galactose of

the second unit (Gal II), like all further galactose groups, is bound to the mannose of the preceding unit. Therefore, the Gal I transferase, which leads to the incorporation of the galactose in the first unit, differs from Gal II transferase, which participates in the incorporation of the galactose residues in all further units. The existence of *Salmonella* mutants in which the Gal II transferase is blocked is therefore indicated.

Such mutants have indeed been isolated recently from *S. typhimurium* cultures by *Naide*, *Nikaido*, *Mäkelä*, *Wilkinson*, and *Stocker*[72]. They were designated as semi-rough or SR mutants. The colonies of the SR strain of *S. typhimurium* are morphologically intermediate between rough and smooth. The cells are agglutinated by O antisera but not as strongly as the wild type; however, O phages do not cause lysis. In contrast to the wild form, the lipopolysaccharide contains small quantities of mannose, rhamnose, and abequose. A characteristic result is also found on partial hydrolysis, during which, in contrast to the wild type, the SR lipopolysaccharide forms only a single disaccharide with reducing rhamnose, namely mannosyl-rhamnose[40].

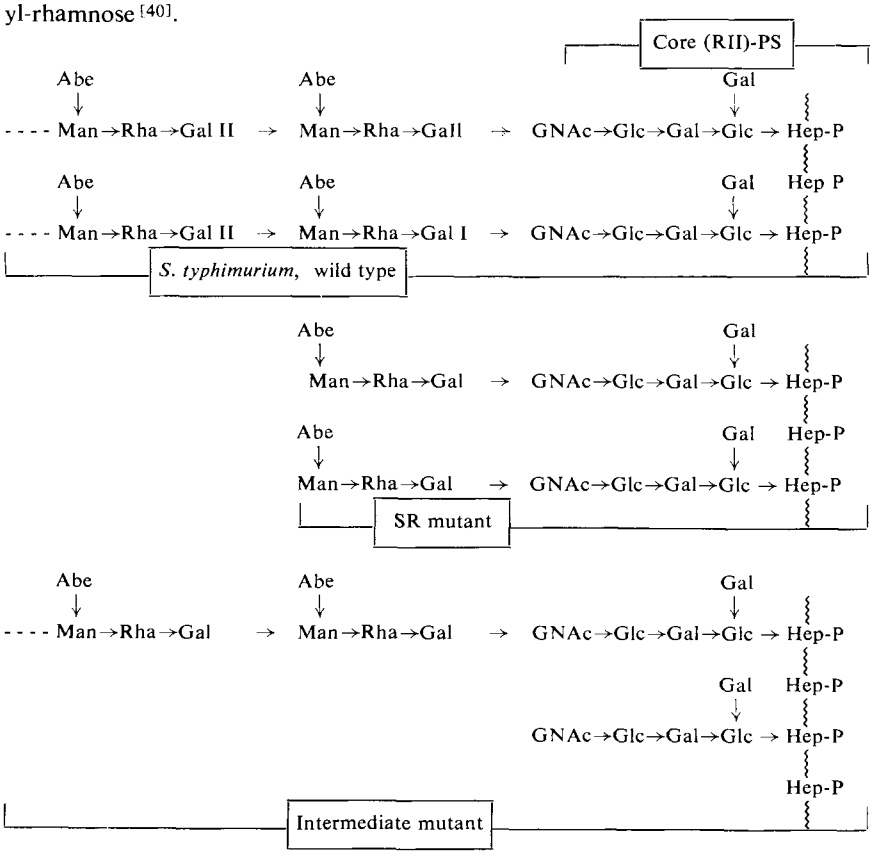


Fig. 12. Proposed structures of the polysaccharides from *S. typhimurium* wild type, SR mutant, and intermediate mutants [72].

### Other Intermediate Mutants

The same authors have discovered a different class of mutants of *S. typhimurium*[42,72], the lipopolysaccharides of which have the same composition as those of the SR-mutants, *i.e.* they contain little mannose, rhamnose, and abequose. In contrast to the SR mutants, these mutants are lysed by O phages and agglutinated by O and R antisera, while partial hydrolysis of the lipopolysaccharides leads to the same oligosaccharide (with reducing rhamnose) as is obtained from the wild-type lipopolysaccharide. These properties suggest the formula shown in the lower part of Figure 12 for this antigen: few, but complete, O-specific chains are bound to the RII core. The enzyme defect which leads to such mutants has not yet been identified.

### T Forms

We have been engaged for some time in a study of a third class of intermediate *Salmonella* mutants, which were discovered by *Kauffmann*[3,73] about 10 years ago and termed "transient" or T forms. Like the R forms they have lost the O specificity of the wild type and do not contain the specific sugars of the side chain, but, like the wild type, they grow in smooth colonies (S form). Serologically, they are characterized by T specificity, *i.e.* they react specifically with T antisera. These T mutants deserve particular interest; we have found[29, 68,74] that their lipopolysaccharides contain a sugar which is not present in the polysaccharide of either the wild type (S form) or the R forms. While all *Salmonella* mutants investigated so far have been shown to be deficient mutants, and their lipopolysaccharides contain fewer sugar units than the lipopolysaccharide of the wild type, it has been demonstrated that T forms contain large quantities of ribose in their lipopolysaccharide. Table 3 shows the analyses of different T lipopolysac-

[72] *Y. Naide*, *H. Nikaido*, *P. H. Mäkelä*, *R. G. Wilkinson*, and *B. A. Stocker*, Proc. nat Acad. Sci. USA *53*, 147 (1965).

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charides. All contain the basic sugars; in addition, there is 14–22% of ribose, and the same quantity of galactose [74]. Ribose is not present as a nucleoside (no absorption at 260 mμ). Ribose and galactose do not form a separate polysaccharide but appear to be incorporated into the T polysaccharide. This was indicated by specific precipitation [74]. When T lipopolysaccharide is precipitated by specific T antiserum, the ribose is obtained quantitatively in the precipitate. After treatment with alkali, the same antiserum precipitates a polysaccharide without ribose. We are at present engaged in carrying out partial hydrolysis with the aim of isolating and analysing the oligosaccharides and, above all, of studying the relationship of T antigens to S and R antigens. T forms mutate relatively easily into R forms. In addition to T forms, there are also *Salmonella* serogroups (M, 52, 56; see Figure 3) which form O-antigenic lipopolysaccharides and contain ribose as the building unit of the specific side chain [28,29].

Table 3. Composition of lipopolysaccharides isolated from various *Salmonella* T1 mutants [74].

| | KDO % | Hep % | Glc % | GlcN % | Gal % | Rib % |
|---|---|---|---|---|---|---|
| *S. typhimurium* T 1 | 4.0 | 7.1 | 4.8 | 5.9 | 20.8 | 14.9 |
| *S. paratyphi* B T 1 | 4.1 | 4.2 | 6.9 | 5.7 | 13.6 | 16.4 |
| *S. dessau* T 1 | 3.8 | 7.3 | 4.6 | 5.7 | 20.8 | 13.8 |
| *S. friedenau* T 1 | 3.6 | 5.3 | 4.4 | 6.3 | 18.4 | 22.2 |
| | 4.2 | 7.5 | 4.6 | 6.2 | 18.0 | 17.1 |

## Concluding Remarks

The analysis of lipopolysaccharides from enterobacterial wild forms (S forms) and their numerous deficient mutants (SR and R forms) has made it possible to determine the structure of the complex heteropolysaccharide components. Detailed results have so far been obtained for *Salmonella*. Since the analysed deficient mutants form intermediates occurring in the biosynthesis of the complete wild-type polysaccharide, it is possible to reconstruct the steps of this synthesis. In agreement with structural analyses, *Horecker, Osborn, et al.* [61,75,76], *Nikaido et al.* [40,52,77], and also *Heath et al.* (in *E. coli* [24]) were able to study in detail many stages of the polysaccharide biosynthesis in isolated systems, using radioactively labelled nucleoside diphosphate hexoses.

In lipopolysaccharides of M mutants, containing a polyheptose phosphate core plus glucose, the incorporation of galactose could be verified experimentally [6,24,44]. Starting from mutants which contain no UDP-glucose pyrophosphorylase (and have only a polyheptose phosphate chain), successful incorporation of glucose, *i.e.* biosynthesis of the M polysaccharide, was achieved. Ultimately, all stages in the biosynthesis of the oligosaccharide chain of the RII structure (cf. Figure 6) could be verified by stepwise incorporation of glucose, galactose, again glucose, and *N*-acetylglucosamine [24,61]. Cell-wall preparations containing RII lipopolysaccharides were found to act as the substrate for the transfer of the specific sugars of the side-chains [76,78], again in agreement with the chemical and immunochemical analyses of the polysaccharides. Here, it was found that the rate of incorporation of each sugar is increased when all sugars participating in the repeating oligosaccharide unit are added in the form of their nucleoside diphosphate derivatives. It is now assumed that in the biosynthesis of the specific side chains, the repeating oligosaccharide units, or at least their main chains (*e.g.* Man→Rha→Gal in *Salmonella* of groups A, B, D, and E; Figure 4) are preformed as lipid-bound oligosaccharides and are then transferred as a whole to the growing chain [76,78].

In this way the two parts of the *Salmonella* polysaccharides, *i.e.* the core polysaccharide up to the RII structure and the specific side chains (Figure 2), are matched by two biosynthetic reaction sequences: the ubiquitous basal polysaccharide is built up as far as the RII structure by transfer of monosaccharides, while the specific side chains present in wild types (S forms) are attached by the transfer of activated species-specific oligosaccharides. Three classes of cell-wall lipids can be distinguished on the basis of their biological activity and chemical constitution. Lipid A, bound to the O-specific polysaccharide, is a part of the O antigen and is responsible for its endotoxic effects. A phosphatidylethanolamine isolated by *Rothfield* and *Horecker* [81] from the cell wall of *Salmonella* acts as a cofactor in the biosynthesis of the basal structure of the O antigens. A further lipid, whose chemical composition is as yet unknown, has recently been recognized as an activator of the oligosaccharide 1-phosphate which is used by the cell to synthesize the specific chains of the O antigens [76,78].

It is reasonable that, in the R mutants, many different genotypes can lead to the same phenotype. For example, defects in the enzymes necessary for the formation and transfer of a specific sugar of the repeating oligosaccharide unit of a specific side chain will generally lead to phenotypic R forms with RII polysaccharide. The same is true of other mutants.

Recent chemical, immunochemical, biochemical, and genetic investigations, are in accord with the present postulates about the structure and biosynthesis of enterobacterial cell-wall polysaccharides. It will be of great interest to analyse many more Enterobacteriaceae from as many genera as possible, in order to obtain a comprehensive picture of the extraordinary multiplicity of the polysaccharides of the bacterial cell surfaces and of their effects on the biological behavior of the cell.

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# Diels-Alder-Reactions
# Part I: New Preparative Aspects[*]

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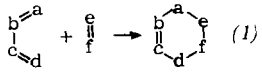
*Cycloadditions of conjugated dienes, named after their discoverers, have claimed preparative and mechanistic interest for nearly 40 years. The almost inexhaustible variability of the components of these one-stage reactions offers entry to important classes of compounds. The systematization of the preparative uses of these reactions which is offered in this paper relates predominantly to recent results. The mechanistic aspects of the Diels-Alder reactions will be discussed later in the second part of this contribution.*

A. Definition and History
B. The Diene Components
1. Acyclic Dienes
2. Acyclic Dienes with Heteroatoms
3. Polyenes
4. 1,2-Dimethylenecycloalkanes
5. Alicyclic Dienes
6. Cyclopentadienones
7. *o*-Quinones and *o*-Quinonoid Systems
8. Aromatic Compounds
9. Heterocyclic Compounds
10. Olefins and Non-Conjugated Dienes
C. The Dienophilic Components
1. Acyclic Alkenes and Alkynes
2. Allenes
3. Cyclic Dienophiles
4. Cyclic Azo Compounds
5. Other Dienophiles with Heteroatoms
D. Retro-Diels-Alder Reactions
E. Future Prospects

## A. Definition and History

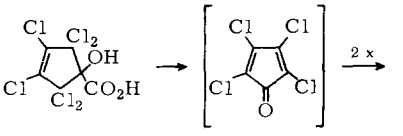
The combination of conjugated dienes with olefins is only a special case of the more general reaction of cycloaddition[1]; in the formation of the six-membered ring *(1)*, two new σ-bonds are formed at the expense of two π-bonds.

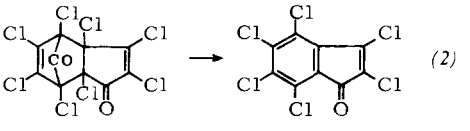


*(1)*

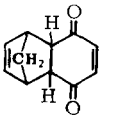
Other examples of cycloadditions are epoxidations and carbene additions, dimerizations of olefins to cyclobutane derivatives, and 1,3-dipolar addition reactions[1,2].

Individual examples of diene additions according to the Diels-Alder scheme are found in the literature as early as the turn of the century. Although *Zincke*[3] correctly explained the dimerization to perchloroindenone *(2)* of the tetrachlorocyclopentadienone occurring as an intermediate in the pyrolysis of 1-hydroxyperchlorocyclopent-3-enecarboxylic acid, an elucidation of the structure of the 1:1 adduct *(3)* of *p*-benzoquinone and cyclopentadiene was first given by *Diels* and *Alder*[4]; structures proposed earlier by *Staudinger* (with a cyclobutane ring) and *Albrecht* proved to require revision.



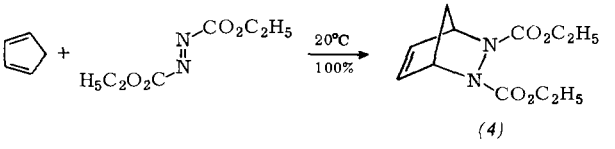


*(2)*

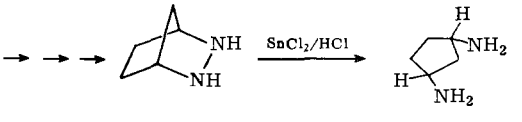


*(3)*

The structure of the 1:1 addition compound *(4)* from cyclopentadiene and diethyl azodicarboxylate[5] first indicated that these addition reactions of dienes were cases



*(4)*



[*] Part II will appear shortly in this Journal.

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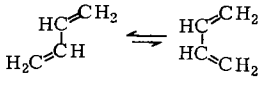
of a more general reaction principle. The classical paper of *Diels* and *Alder* [4a] provided the mental breakthrough and introduced the fruitful preparative and mechanistic investigations of these authors.

Complete treatment of the extensive experimental material is possible only within the scope of a monograph. In this survey, the reviews that appeared before 1955 [6–13b] and a recent article [1] will be supplemented by newer examples from the literature.

## B. The Diene Components

### 1. Acyclic Dienes

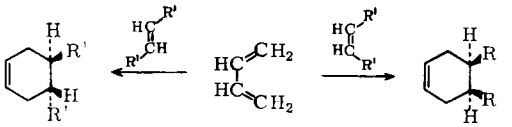
Owing to the possibility of rotation about the single bond between the two conjugated double bonds, open-chain dienes can occur in two conformations. With butadiene and its simple alkyl derivatives, the *transoid* form *(5)* frequently predominates in the conformer equilibrium [14]. However, only the *cisoid* conformer *(6)* is capable of taking part in the Diels-Alder reaction.



transoid *(5)* cisoid *(6)*

Substituents in butadiene influence the rate of cycloaddition to form six-membered rings, both through their electronic nature and by displacing the conformational equilibrium.

By combining butadiene with dimethyl maleate or fumarate in toluene at 155 °C the *cis*- *(7)* and the *trans*-form *(8)*, respectively, of the cyclohexene-4,5-dicarboxylic ester are readily accessible *via* a stereospecific *cis*-addition [15].

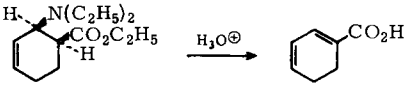


*(8)* 84% R' = $CO_2CH_3$ *(7)* 68%

1-Substituted butadienes can be used [16] almost without exception provided the substituent R is in the *trans*-arrangement *(9)*, while the *cis*-form *(10)* generally undergoes a Diels-Alder reaction only with poor yield.

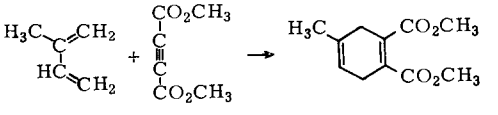
*(9)* *(10)*

The extremely acid-sensitive 1-diethylaminobutadiene *(9)*, R = $N(C_2H_5)_2$, adds to ethyl acrylate in benzene at 20 °C to form the 1:1 *cis*-adduct *(11)*, which changes readily into 2,3-dihydrobenzoic acid [17]. In the analogous reactions of 1,4-bis(dialkylamino)butadiene the two-fold elimination of amine from the Diels-Alder adduct yields the aromatic system [18].



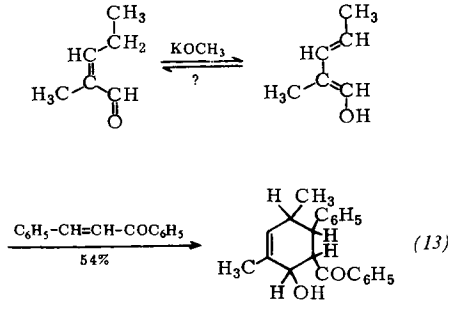
*(11)* 94%

1,4-Dihydroaromatic compounds, *e.g. (12)*, are obtained in excellent yields when butadienes react with dienophiles containing triple bonds [19] (at about 150 °C in toluene in the example illustrated).



*(12)* 87%

1-Hydroxybuta-1,3-dienes can be regarded as tautomers of the α,β-unsaturated aldehydes and ketones. As an example, we select a reaction of 2-methylpent-2-enal (2-ethyl-1-methylacrolein) [7]; here the primary adduct *(13)* can be isolated [20].



*(13)*

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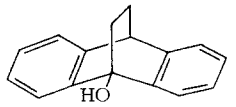
[17] *S. Hünig* and *H. Kahanek*, Chem. Ber. *90*, 238 (1957).

[18] *M. F. Fegley, N. M. Bortnick,* and *C. H. McKeever*, J. Amer. chem. Soc. *79*, 4736 (1957).

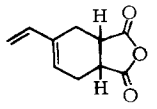
[19] See, *e.g., N. P. Sopov* and *V. S. Miklashevskaya*, Zh. obshch. Khim. *26*, 1914 (1956); Chem. Abstr. *51*, 4968 (1957).

[20] *H. Meerwein*, Ber. dtsch. chem. Ges. *77*, 227 (1944).

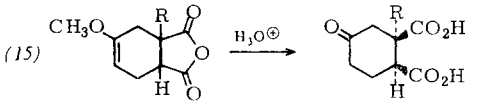
The mechanistic relationship of this sequence of reactions to the Diels-Alder scheme has not, however, been shown. Recently, anthrone has been made to react with ethylene in the presence of bases according to the same scheme to give *(14)* in 60 % yield [21].



*(14)*



*(16)*



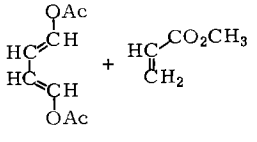
*(15)*

*a* R = H, 93%
*b* R = $CH_3$, 94%

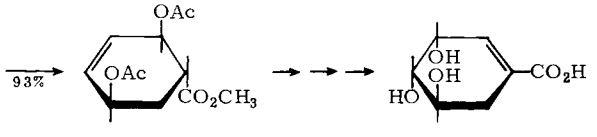
R = H, 96%

The adducts *(15)* of 2-alkoxybutadienes with maleic anhydride and its derivatives, which are obtained in high yields, can, as enol ethers, easily be hydrolysed to cyclohexanone derivatives [22]. In the case of 2-methylene-1,4-pentadiene (2-vinylbutadiene), the reaction with maleic anhydride does not stop at the stage of the 1:1 adduct *(16)*; the new diene system adds on a second molecule of the dienophile to give the 1:2 adduct [23].

Disubstituted dienes have been used very frequently; 2,3-diphenylbutadiene, for example, gives *o*-terphenyl derivatives [24]. The reaction of *trans,trans*-1,4-diacetoxybutadiene *(18)* with methyl acrylate forms the first step of a total synthesis of shikimic acid *(17)* [25]; a second

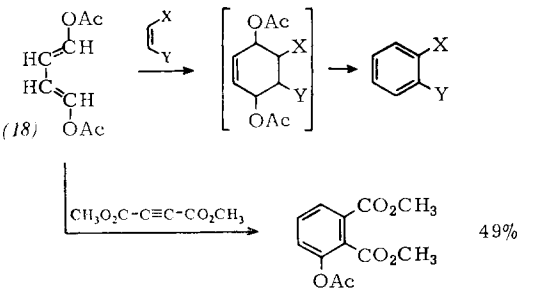


*(18)*



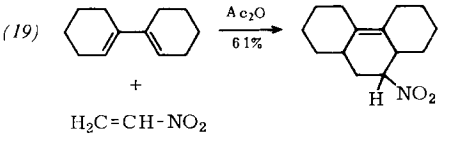
*(17)*

route to this compound begins with the Diels-Alder reaction between butadiene and propiolic acid (yield 85 %) [26]. Diacetoxybutadiene *(18)* has very recently been recognized as a suitable diene component for the synthesis of benzene derivatives without isolation of intermediate products [27].



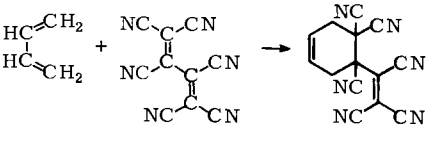
49%

Tetraalkylbutadienes are eminently suitable for diene additions provided they do not exhibit the structural element *(10)* of *cis*-1-substituted butadienes; 1,1'-bicyclopentenyl and 1,1'-bicyclohexenyl *(19)* [28] lead to polycyclic compounds [29], as illustrated here for nitroethylene as the dienophile.



*(19)*

Hexacyanobutadiene *(20)* [30] acts not as a diene but as a dienophile with respect to butadiene, *i.e.* it behaves as a derivative of the very reactive tetracyanoethylene (see Section C 1).



*(20)*

## 2. Acyclic Dienes with Heteroatoms

Whereas one or both carbon atoms in the dienophile component can be replaced by heteroatoms (see Sections C. 4 and C. 5), there are fewer analogous examples in the case of the dienes [31]. Replacement of carbon atom 1 in 1,3-dienes by oxygen yields α,β-unsaturated aldehydes and ketones which combine preferentially with electron-rich double bonds, enol ethers, olefins [32], enamines [33], *N*-vinylcarbamic esters, and *N*-vinylureas [34] to form 1:1-adducts; these addition compounds arise formally from a Diels-Alder reaction. Hydrolysis of the enamine adducts *(21)* and the enol ether adducts yield 1,5-dicarbonyl compounds, which are valuable starting compounds for syntheses of alkaloids [35]. With acrolein *(22)* as the diene component,

[21] *J. S. Meek, W. Brice, V. Evans Godefroi, W. R. Benson, M. F. Wilcox, W. G. Clark,* and *T. Tiedeman,* J. org. Chemistry *26,* 4281 (1960).

[22] *M. S. Newman* and *H. A. Lloyd,* J. org. Chemistry *17,* 577 (1952).

[23] *A. T. Blomquist* and *J. A. Verdol,* J. Amer. chem. Soc. *77,* 81 (1955).

[24] *K. Alder* and *J. Haydn,* Liebigs Ann. Chem. *570,* 201 (1950).

[25] *E. E. Smissman, J. T. Suh, M. Oxman,* and *R. Daniels,* J. Amer. chem. Soc. *84,* 1040 (1962).

[26] *R. Grewe* and *I. Hinrich,* Chem. Ber. *97,* 443 (1964).

[27] *R. K. Hill* and *R. M. Carlson,* Tetrahedron Letters *1964,* 1157; J. org. Chemistry *30,* 2414 (1965).

[28] For example: *E. D. Bergmann, H. Davies,* and *R. Pappo,* J. org. Chemistry *17,* 1331 (1952).

[29] *N. L. Drake* and *C. M. Kraebel,* J. org. Chemistry *26,* 41 (1961).

[30] *O. W. Webster,* J. Amer. chem. Soc. *86,* 2898 (1964).

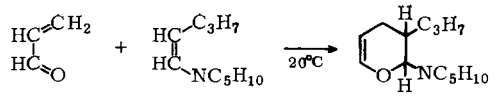
[31] A review of heterodienes and heterodienophiles is given by *S. B. Needleman* and *M. C. Chang Kuo,* Chem. Reviews *62,* 405 (1962).

[32] *C. W. Smith, D. G. Norton,* and *S. A. Ballard,* J. Amer. chem. Soc. *73,* 5267, 5273 (1951).

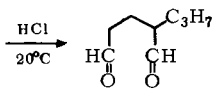
[33] *G. Opitz* and *I. Löschmann,* Angew. Chem. *72,* 523 (1960).

[34] *R. C. Schulz* and *H. Hartmann,* Chem. Ber. *95,* 2735 (1962).

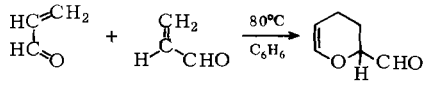
[35] *K. Alder, H. Betzing, R. Kuth,* and *H. A. Dortmann,* Liebigs Ann. Chem. *620,* 73 (1959).



(22) (21) 79%

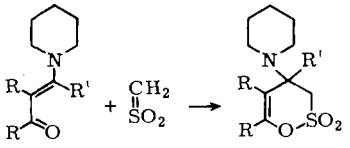


the use for less reactive dienophiles is limited by the competing dimerization of the unsaturated aldehyde, which formally is also a Diels-Alder reaction [36].



(22) (22) 40-45%

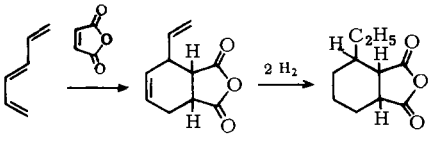
The reaction of compound *(23)*, prepared *in situ* from methanesulfonyl chloride and triethylamine, with vinylogous amides can also be regarded as a Diels-Alder reaction [37].



(23) R = $CH_3$, R' = H, 80%

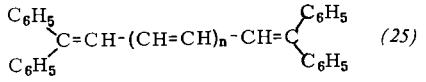
### 3. Polyenes

The mode of reaction of conjugated polyenes in diene addition can be understood by regarding them as substituted butadienes. The case of 2-vinylbutadiene has already been mentioned in Section B. 1. *trans*-Hexa-1,3,5-triene reacts as 1-vinylbutadiene; the hydrogenation product *(24)* of the Diels-Alder adduct with maleic anhydride can also be obtained from *trans*-hexa-1,3-diene [38].



*(24)*

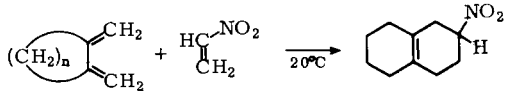
*cis*-Hexa-1,3,5-triene, as a *cis*-1-substituted butadiene *(10)*, R = $CH{=}CH_2$, does not react with dienophiles, so that it can be separated from the *trans* isomer by the Diels-Alder reaction [39]. Of the *trans*-ω,ω,ω'ω'-tetraphenylpolyenes *(25)*, only the representatives with n > 1 are capable of adding dienes; with large values of n, *Alder* and *Schumacher* observed a relationship between the chain length and the position of addition of the dienophile [40].



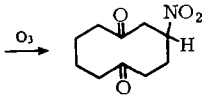
*(25)*

### 4. 1,2-Dimethylenecycloalkanes

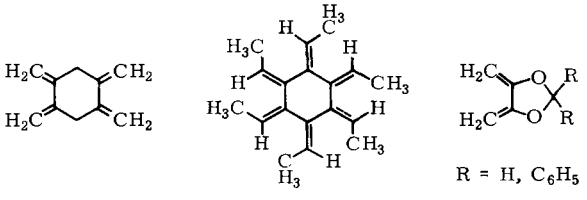
1,2-Dimethylenecycloalkanes *(26)*, in which the *cisoid* conformation *(6)* necessary for reaction is fixed by the linkage of the 2,3-positions of the diene through a ring, are characterized by high reactivity [41]. This, and the ready accessibility of this class of compounds by the pyrolysis of esters or the Hofman elimination of suitable bifunctional quaternary ammonium salts [42], make the 1,2-dimethylenecycloalkanes *(26)* the favorite dienes for the synthesis of polycyclic compounds, *e.g. (27)*; the reaction of 1,2-dimethylenecyclohexane [*(26)*, n = 4] may serve as an example [43].



*(26)* *(27)* 85%



With *(28)*, the Diels-Alder addition goes as far as the 1:2-adduct [44]; with *(29)* only two of the three diene systems are



*(28)* *(29)* *(30)*

R = H, $C_6H_5$

used for the addition of the dienophile [45]. The dioxolane derivatives *(30)* react only with the "record" dienophile tetracyanoethylene [46].

The four-membered cyclic diene *(26)*, n = 2, adds to one equivalent of maleic anhydride at 20–80 °C; for the formation of the 1:2-adduct an opening of the four-mem-

[36] *K. Alder* and *E. Rüden*, Ber. dtsch. chem. Ges. *74*, 920 (1941); *K. Alder, H. Offermanns*, and *E. Rüden, ibid. 74*, 905 (1941).

[37] *G. Opitz* and *E. Tempel*, Angew. Chem. *76*, 921 (1964); Angew. Chem. internat. Edit. *3*, 754 (1964).

[38] *K. Alder* and *H. von Brachel*, Liebigs Ann. Chem. *608*, 195 (1957).

[39] *J. C. H. Hwa, P. L. De Benneville*, and *H. J. Sims*, J. Amer. chem. Soc. *82*, 2537 (1960).

[40] *K. Alder* and *M. Schumacher*, Liebigs Ann. Chem. *570*, 178 (1950). For further examples of polyene addition, see [8].

[41] Kinetic measurements: *J. Sauer, D. Lang*, and *A. Mielert*, Angew. Chem. *74*, 352 (1962); Angew. Chem. internat. Edit. *1*, 268 (1962); *D. Lang*, Dissertation, Universität München 1963.

[42] Review: *Y. A. Titov*, Russ. chem. Rev. (Engl. transl. of Usp. Khim.) *30*, 327 (1961).

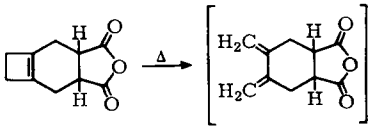
[43] *W. J. Bailey* and *H. R. Golden*, J. Amer. chem. Soc. *79*, 6516 (1957).

[44] *W. J. Bailey, E. J. Fetter*, and *J. Economy*, J. org. Chemistry *27*, 3479 (1962).

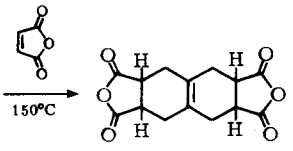
[45] *H. Hopff* and *G. Kormany*, Helv. chim. Acta *46*, 2533 (1963).

[46] *J. B. Miller*, J. org. Chemistry *25*, 1279 (1960).

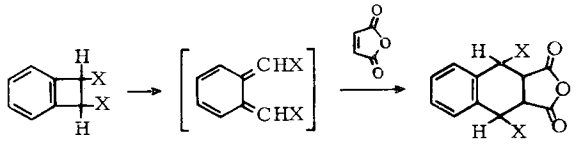
bered ring of the 1:1-addition compound *(31)* has been discussed [47]. In the reactions of benzocyclobutene derivatives *(32)* with dienophiles (see Table 1), a primary



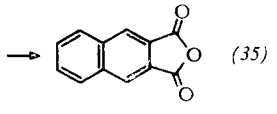
*(31)*



ring opening to the 1,2-dimethylene derivative *(33)*, which here has an *o*-quinonoid structure, is also assumed [48,49]. The diiodo compound *(32)* (X = I) reacts similarly with *N*-phenylmaleimide [49] to give 35 % of the naphthalenedicarboxylic derivative.



*(32)* *(33)* *(34)*



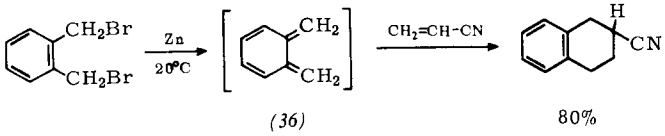
*(35)*

Table 1. Reaction of benzocyclobutene derivatives *(32)* with maleic anhydride.

| *(32)*, X | Temp. [°C] | Yield of *(34)* [%] | Yield of *(35)* [%] |
|---|---|---|---|
| $C_6H_5$ | 25 | 100 | |
| Br | 100 | | 32 |
| H | 200 | 98 | |

*Huisgen* and *Seidl* [50] have recently shown that a valence-tautomeric equilibrium *(32)* ⇌ *(33)*, in which the four-membered ring opens stereospecifically, precedes the Diels-Alder reactions of *cis*- and *trans*-2,3-diphenylbenzocyclobutenes [*(32)*, X = $C_6H_5$].

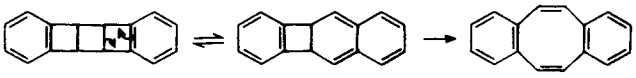
"*o*-Quinonoid" 1,2-dimethylenecycloalkenes have been postulated as intermediates in other reaction sequences. Thus the highly reactive 5,6-dimethylenecyclohexa-1,3-diene (*o*-quinodimethane) *(36)*, which cannot be isolated, can be trapped in solution with maleic anhydride, *N*-phenylmaleimide, or acrylonitrile [51,52]. The "*in situ*" occurrence of 2,3-dihydronaphthalene and 2,2-dimethyl-2*H*-indene has been shown similarly



*(36)* 80%

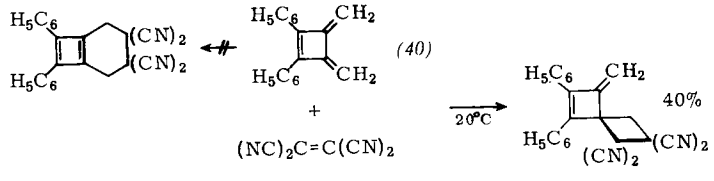
by means of trapping reactions [53,51]. Both compounds, like *(36)*, were obtained by dehalogenation of dibromo compounds.

An intermediate *(39)* with the dihydronaphthalene unit occurs also in the two-stage valence isomerization of the benzocyclobutadiene dimer *(37)* to dibenzocyclooctatetraene *(38)*. Compound *(39)* can be detected by a Diels-Alder reaction with *N*-phenylmaleimide [54].



*(37)* *(39)* *(38)*

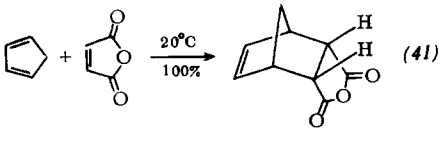
The expectation that the Diels-Alder reaction of *(40)* with tetracyanoethylene would lead to a derivative of cyclobutadiene proved incorrect; instead an adduct with spiro structure [55] is formed.



*(40)* 40%

## 5. Alicyclic Dienes

The Diels-Alder reactions of alicyclic dienes claim both historic and preparative interest. *Diels* and *Alder* recognized the general validity of the reaction scheme with cyclopentadiene [4]. For example, with maleic anhydride, the 1:1-adduct *(41)* arises stereospecifically in quantitative yield.



*(41)*

The preferred *endo*-orientation in the addition is observed with many reactions of cyclic dienes, and is a characteristic of this type of reaction [56]. Thus *endo*-di-

[47] *A. T. Blomquist* and *J. A. Verdol*, J. Amer. chem. Soc. *77*, 1806 (1955); *78*, 109 (1956); *K. Alder* and *O. Ackermann*, Chem. Ber. *87*, 1567 (1954).

[48] *F. R. Jensen*, *W. E. Coleman*, and *A. J. Berlin*, Tetrahedron Letters *1962*, 15.

[49] *M. P. Cava* and *M. J. Mitchell*, J. Amer. chem. Soc. *81*, 5409 (1959); *M. P. Cava*, *A. A. Deana*, and *K. Muth*, *ibid.* *81*, 6458 (1959); *M. P. Cava*, *R. L. Shirley*, and *B. W. Erickson*, J. org. Chemistry *27*, 755 (1962).

[50] *R. Huisgen* and *H. Seidl*, Tetrahedron Letters *1964*, 3381; cf. also *G. Quinkert*, *K. Opitz*, *W. W. Wiersdorff*, and *M. Finke*, Tetrahedron Letters *1965*, 3009; *G. Quinkert*, Pure appl. Chem. *9*, 607 (1964).

[51] *K. Alder* and *M. Fremery*, Tetrahedron *14*, 190 (1961).

[52] *M. P. Cava*, *A. A. Deana*, and *K. Muth*, J. Amer. chem. Soc. *81*, 6458 (1959).

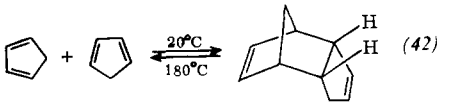
[53] *I. G. Dinulescu*, *M. Avram*, and *C. D. Nenitzescu*, Chem. Ber. *93*, 1795 (1960); *M. Avram*, *I. G. Dinulescu*, *D. Dinu*, and *C. D. Nenitzescu*, Chem. and Ind. *1962*, 555.

[54] *M. Avram*, *I. G. Dinuslescu*, *D. Dinu*, *G. Mateescu*, and *C. D. Nenitzescu*, Tetrahedron *19*, 309 (1963).

[55] *A. T. Blomquist* and *Y. C. Meinwald*, J. Amer. chem. Soc. *81*, 667 (1959); the reaction of the corresponding dimethyl compound is described by *R. Criegee*, Angew. Chem. *74*, 703 (1962); Angew. Chem. internat. Edit. *1*, 519 (1962).

[56] Review of the stereochemistry of *Diels-Alder* reactions: *J. G. Martin* and *R. K. Hill*, Chem. Reviews *61*, 537 (1961).

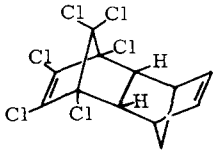
cyclopentadiene *(42)* is formed in high purity from the monomer; in this reaction, cyclopentadiene acts both as a diene and as a dienophile. This phenomenon, already



*(42)*

observed with acrolein, will be encountered again with cyclopentadienones (see Section B.6), *o*-quinones (see Section B.7), and thiophene 1,1-dioxide (see Section B.9). Compound *(42)* serves as a source of cyclopentadiene, which can be obtained from it at 180 °C in a retro-Diels-Alder reaction.

The combination of cyclopentadiene with alkenes and alkynes leads in single-stage syntheses and in high yields to derivatives of the angularly strained bicyclo[2.2.1]hept-2-ene and bicyclo[2.2.1]hepta-2,5-diene. Substituted cyclopentadienes yield camphor derivatives in a few reaction steps[8]. Bicyclo-



*(43)*

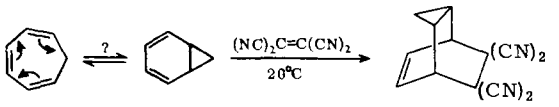
*(43a)*

heptadiene itself is made industrially from cyclopentadiene and acetylene in 60 to 65 % yield[57]; with hexachlorocyclopentadiene[58] it gives quantitatively compound *(43)*, which has become known as an insecticide under the name Aldrin; many other insecticides and heat-resistant polymers are derived from the Diels-Alder adducts of hexachlorocyclopentadiene.

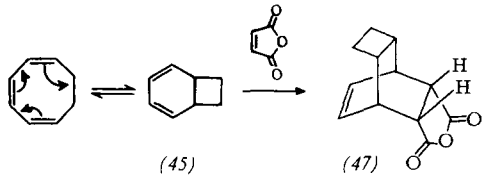
Like cyclopentadiene itself, hexafluorocyclopentadiene *(43a)*, which has been synthesized only very recently, tends to undergo dimerization[58a], while hexachlorocyclopentadiene is stable as a monomer. The reactions of *(43a)* with dienophiles such as ethylene, maleic anhydride, or bicyclo[2.2.1]hepta-2,5-diene take place smoothly; on the other hand, no reaction is obtained with tetrafluoroethylene or tetracyanoethylene. With respect to dienes (*e.g.* cyclopentadiene or anthracene), *(43a)* behaves sometimes as a diene and sometimes as a dienophile.

The reactivity decreases on passing to higher monocyclic conjugated dienes; cyclooctadiene has almost no ability for addition[9]; dienes with 14- and 15-membered rings again react with dienophiles, although under relatively severe conditions.

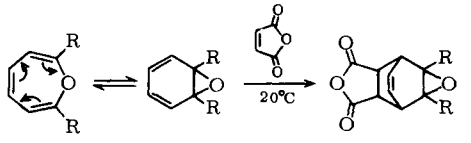
The Diels-Alder adducts of cycloheptatriene and cyclooctatriene are derived from the valence-bond tautomers *(44)* and *(45)*, respectively[59–62]. Whereas the tautomeric equilibrium between the monocyclic and the bicyclic compound can be detected in the eight-membered cyclic triene[62] (15 % of the bicyclic tautomer is present in the equilibrium mixture at 100 °C), the existence of such an equilibrium for the seven-membered cyclic triene is still uncertain; it seems likely, however, from the recent investigations of *Vogel et al.*[63] on oxepin [*(48)*, R = H] and its dimethyl derivative [*(48)*, R = $CH_3$].



*(44)* *(46)* 77%



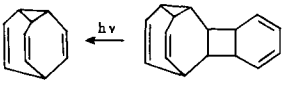
*(45)* *(47)*



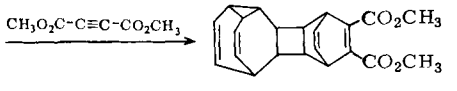
*(48)* *(49)* *(50)* R = $CH_3$: 100%

The Diels-Alder adducts are again derived from the bicyclic compound *(49)*; spectroscopic investigations have shown a valence-tautomeric equilibrium *(48)* ⇌ *(49)* (in each case R = H), which is established very rapidly. However, spectroscopic detection fails with bicyclo-[4.2.0]octa-2,5,7-triene, a valence-bond isomer of cyclooctatetraene. Nevertheless, *Huisgen* and *Mietzsch* demonstrated a small equilibrium concentration (*ca.* 0.01 %) by kinetic studies[64]. At 165–170 °C, a product analogous to *(47)* but poorer by 2 H is formed in 87 % yield with maleic anhydride.

Heating of cyclooctatetraene gives several dimers[65]. *G. Schröder* recently revised the structure proposed for one of them, and assigned to it the constitution *(51)*[66]; he used this compound for his elegant synthesis of bullvalene *(52)*[67]. The typical Diels-Alder additions of the



*(52)* ≈ 80% *(51)*




[57] US.-Pat. 2875256 (Feb. 24th, 1959), *J. Hyman, E. Freireich,* and *R. E. Lidov*; Chem. Abstr. *53*, 13082 (1959).

[58] Reviews of the reactions of hexachlorocyclopentadiene: *H. E. Ungnade* and *E. T. McBee*, Chem. Reviews *58*, 249 (1958); *C. W. Roberts*, Chem. and Ind. *1958*, 110.

[58a] *R. E. Banks, A. C. Harrison, R. N. Haszeldine,* and *K. G. Orrell*, Chem. Commun. (London) *1965*, 41.

[59] *K. Alder* and *G. Jacobs*, Chem. Ber. *86*, 1528 (1953).

[60] *R. Huisgen* and *W. D. Wirth*, unpublished work.

[61] *W. Reppe, O. Schlichting, K. Klager,* and *T. Toepel*, Liebigs Ann. Chem. *560*, 1 (1948).

[62] *A. C. Cope, A. C. Haven, F. L. Ramp,* and *E. R. Trumbull*, J. Amer. chem. Soc. *74*, 4867 (1952).

[63] *E. Vogel, R. Schubart,* and *W. A. Böll*, Angew. Chem. *76*, 535 (1964); Angew. Chem. internat. Edit. *3*, 510 (1964); *E. Vogel, W. A. Böll,* and *H. Günther*, Tetrahedron Letters *1965*, 609.

[64] *R. Huisgen* and *F. Mietzsch*, Angew. Chem. *76*, 36 (1964); Angew. Chem. Internat. Edit. *3*, 83 (1964).

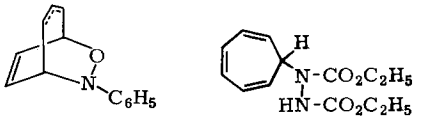
[65] *W. O. Jones*, Chem. and Ind. *1955*, 16.

[66] *G. Schröder*, Chem. Ber. *97*, 3131 (1964).

[67] *G. Schröder*, Chem. Ber. *97*, 3140 (1964).

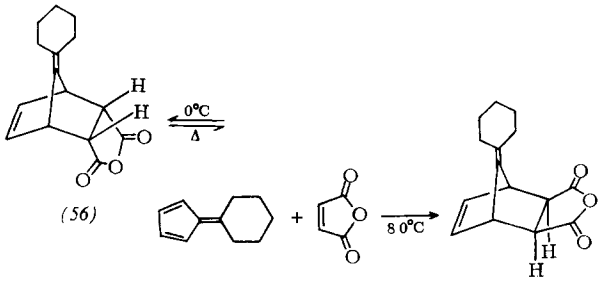
cyclohexadiene system in *(51)* with dienophiles have facilitated the elucidation of the structure of the dimer *(51)*.

It may be recalled that cycloheptatriene reacts with nitrosobenzene [68] or azodicarboxylic ester [69] to give 1:1-adducts *(53)* and *(54)* respectively, which are not derived from the valence tautomer *(44)*. Compound *(54)* opens up a productive route to tropylium salts [69].



*(53)* *(54)*

Fulvenes can be regarded as derivatives of the alicyclic cyclopentadiene; dienophiles add onto the *cisoid* diene system of the ring [70,71]. The splitting into the starting materials, which takes place with the Diels-Alder adducts of the fulvenes even under mild conditions, makes it difficult in many cases to elucidate the configuration of the products; a critical study by *Woodward* and *Baer* has clarified the situation with the pentamethylenefulvene *(55)* maleic anhydride system [72]. The reaction leading to the *endo*-adduct *(56)* at low temperatures is reversible; this enables the formation of the thermodynamically more stable *exo*-adduct *(57)* at 80°C.

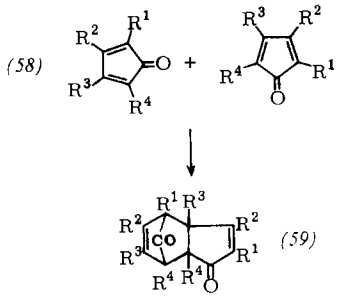


*(56)* *(55)* *(57)*

The position of the adduct ⇌ components equilibrium and the rate of the Diels-Alder addition have been measured in the diarylfulvene-tetracyanoethylene and diarylfulvene-acetylenedicarboxylic ester systems [73].

## 6. Cyclopentadienones

The diene activity of cyclopentadiene is retained in cyclopentadienone and its derivatives *(58)*. Depending on the substituents (see Table 2), cyclopentadienones exist as monomers *(58)* or dimers *(59)* [74]. Like cyclopentadiene, cyclopentadienones may act as diene and dienophile components.

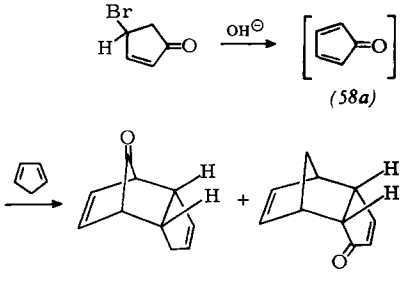


*(58)* *(59)*

Table 2. Reaction 2 *(58)* ⇌ *(59)* as a function of the substituents.

| *(58)*, $R^1$ | $R^2$ | $R^3$ | $R^4$ | Forms present |
|---|---|---|---|---|
| H | H | H | H | *(59)* |
| Cl | Cl | Cl | Cl | |
| H | $C_6H_5$ | $C_6H_5$ | H | 2 *(58)* ⇌ *(59)* |
| $CH_3$ | $C_6H_5$ | $C_6H_5$ | $CH_3$ | |
| $C_2H_5$ | $C_6H_5$ | $C_6H_5$ | $C_2H_5$ | *(58)* |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | |

The tendency towards dimerization is particularly pronounced with the unsubstituted compound *(58a)*. All attempts to prepare this compound – *e.g.* by a retro-Diels-Alder reaction – gave only the dimer [75]. However, the brief occurrence of cyclopentadienone *(58a)* – *i.e.* a finite lifetime for this compound – is suggested by a trapping experiment [76,77]; *(58a)* again exhibits diene and dienophile properties, in this case in the reaction with cyclopentadiene. The *N,N*-dimethylhydrazone of



*(58a)*

*(58a)*, on the other hand, exists in the monomeric form [78]. The tendency of *(58a)* to dimerize can be deduced from its electron distribution [79]. Tetrachlorocyclopentadienone could be trapped as a monomer with cyclopentadiene and norbornadiene [79a].

All cyclopentadienone derivatives existing in the monomeric form and the dimers which dissociate can take part

[68] *G. Kresze* and *G. Schulz*, Tetrahedron *12*, 7 (1961).

[69] *J. M. Cinnamon* and *K. Weiss*, J. org. Chemistry *26*, 2644 (1961).

[70] Review on fulvenes: *J. H. Day*, Chem. Reviews *53*, 167 (1953).

[71] Examples: *K. Alder* and *R. Rühmann*, Liebigs Ann. Chem. *566*, 1 (1950); *D. Craig, J. J. Shipman, J. Kiehl, F. Widmer, R. Fowler*, and *A. Hawthorne*, J. Amer. chem. Soc. *76*, 4573 (1954); *C. H. DePuy* and *P. R. Story*, *ibid. 82*, 627 (1960).

[72] *R. B. Woodward* and *H. Baer*, J. Amer. chem. Soc. *66*, 645 (1944).

[73] *G. Kresze, S. Rau, G. Sabelus*, and *H. Goetz*, Liebigs Ann. Chem. *648*, 57 (1961).

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[75] *K. Alder* and *F. H. Flock*, Chem. Ber. *87*, 1916 (1954); *C. H. DePuy* and *C. E. Lyons*, J. Amer. chem. Soc. *82*, 631 (1960).

[76] *K. Hafner* and *K. Goliasch*, Chem. Ber. *94*, 2909 (1961).

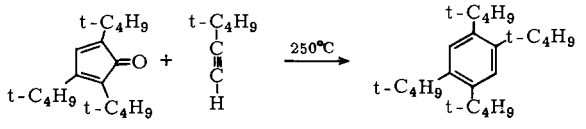
[77] *C. H. DePuy, M. Isaks*, and *K. L. Eilers*, Chem. and Ind. *1961*, 429; *C. H. DePuy, M. Isaks, K. L. Eilers*, and *G. F. Morris*, J. org. Chemistry *29*, 3503 (1964).

[78] *K. Hafner* and *K. Wagner*, Angew. Chem. *75*, 1104 (1963); Angew. Chem. internat. Edit. *2*, 740 (1963).

[79] *R. D. Brown*, J. chem. Soc. (London) *1951*, 2670; *E. D. Bergmann, G. Berthier, D. Ginsburg, Y. Hirshberg, D. Lavie, S. Pinchas, P. Pullman*, and *A. Pullman*, Bull. Soc. chim. France (5) *18*, 661 (1951).

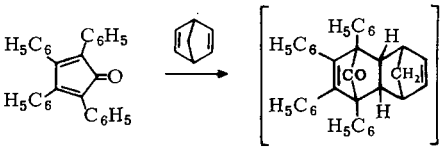
[79a] *W. H. Dietsche*, Tetrahedron Letters *1966*, 201.

in Diels-Alder reactions as diene components. With double-bond dienophiles as co-reactants, the 1:1-adducts occurring as primary products can as a rule be isolated; when the temperature is raised, the CO bridges break [74]. The primary adducts with alkynes can be isolated only in exceptional cases; the tendency towards aromatization possibly brings about the spontaneous elimination of CO [74,80]. Even the highly strained 1,2,4,5-tetra-t-butylbenzene can be obtained in good yield in this way from *(60)* [81].

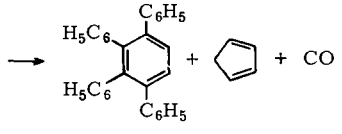


*(60)*

An interesting complication occurs in the reaction of tetraphenylcyclopentadienone with bicyclo[2.2.1]heptadiene (in $CHCl_3$ under reflux) [82]. The angulary strained 1:1-adduct *(61)* undergoes a retro-Diels-Alder reaction under astonishingly mild conditions; here the tendency towards aromatization is an additional driving force.

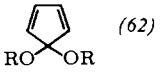


*(61)*



92% 32%

It is not only cyclopentadienone *(58a)* that is characterized by an extraordinary tendency to undergo dimerization, but also the ketals *(62)* derived from it. Earlier attempts to obtain the monomers *(62d)* gave only the dimers [82a].



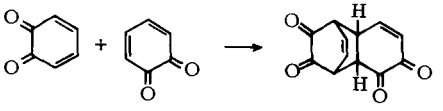
*(62)*

*a* R = $CH_3$ *c* R–R = $-(CH_2)_3-$
*b* R = $C_2H_5$ *d* R–R = $-(CH_2)_2-$

*Eaton* and *Hudson* [82b] recently showed that the ketals *(62a)–(62d)* have finite lifetimes. Trapping experiments with some dienophiles gave the expected Diels-Alder adducts in good yields. The rate of dimerization of compounds *(62)* depends on the group R; *(62d)* dimerizes about 1100 times faster than *(62a)*, and *(62b)* almost 500 times faster than cyclopentadiene.

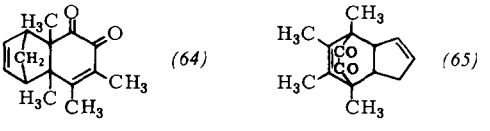
### 7. *o*-Quinones and *o*-Quinonoid Systems

The dimerization observed with many *o*-quinones shows that these compounds are in principle capable of reacting as dienes and dienophiles, *e.g.* to give *(63)* [83,84]; however, as a rule, their capacity for acting as dienes predominates [85]. Thus the structure *(64)* of the 1:1-adduct



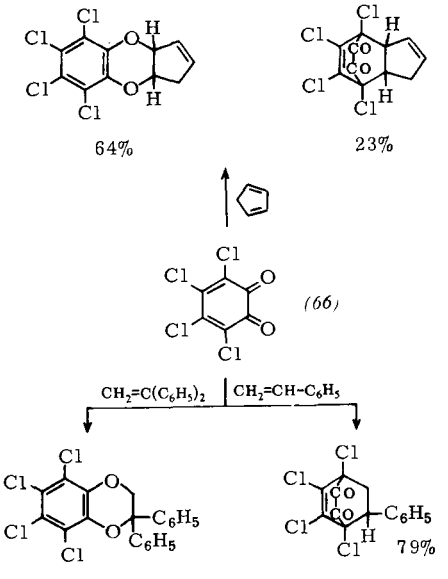
*(63)* 30-50%

from cyclopentadiene and tetramethyl-*o*-benzoquinone [86] proved to require revision: cyclopentadiene takes part in the reaction as the dienophile and *(65)* is formed [87].



*(64)* *(65)*

*o*-Quinones contain two diene systems – the carbocyclic system of the six-membered ring and that of the 1,2-diketo grouping with two heteroatoms. *Horner* and *Merz* [88] observed an interesting competition of these two



64% 23%

*(66)*

$CH_2=C(C_6H_5)_2$ | $CH_2=CH-C_6H_5$

79%

[80] *J. J. Dudkowski* and *E. I. Becker*, J. org. Chemistry *17*, 201 (1952).

[81] *C. Hoogzand* and *W. Hübel*, Tetrahedron Letters *1961*, 637.

[82] *K. Mackenzie*, J. chem. Soc. (London) *1960*, 473.

[82a] *E. Vogel* and *E. G. Wyes*, Angew. Chem. *74*, 489 (1962); Angew. Chem. internat. Edit. *1*, 404 (1962); *C. H. DePuy*, *B. W. Ponder*, and *J. D. Fitzpatrick*, J. org. Chemistry *29*, 3508 (1964).

[82b] *P. E. Eaton* and *R. A. Hudson*, J. Amer. chem. Soc. *87*, 2769 (1965).

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[85] *L. W. Butz* and *A. W. Rytina*, Org. Reactions *5*, 136 (1949); *J. A. Barltrop* and *J. A. D. Jeffreys*, J. chem. Soc. (London) *1954*, 154.

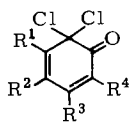
[86] *L. I. Smith* and *L. R. Hac*, J. Amer. chem. Soc. *58*, 229 (1936).

[87] *L. Horner* and *W. Spietschka*, Liebigs Ann. Chem. *579*, 159 (1953).

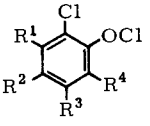
[88] *L. Horner* and *H. Merz*, Liebigs Ann. Chem. *570*, 89 (1950).

diene systems in tetrachloro-*o*-benzoquinone *(66)*. Addition to the cyclohexadiene system or to the heterodiene system takes place depending on the nature of the dienophile (styrene, 1,1-diphenylethylene); with cyclopentadiene as the dienophile (all reactions at 80 °C in benzene) both reactions occur to comparable extents. Tetrachloro-*o*-benzoquinone is, however, inert to typical dienophiles such as acrylonitrile and maleic anhydride.

On the basis of the addition reactions with cyclopentadiene and maleic anhydride as dienophiles, it has been found that the chlorination products of phenol and some methylphenols possess the *o*-quinonoid structure *(67)* and not the hypohalite structure *(68)* ($R^1$–$R^4$ = Cl or $CH_3$) [89].

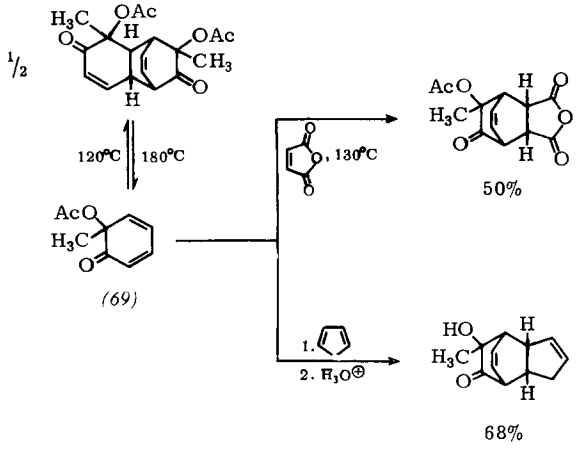


*(67)*



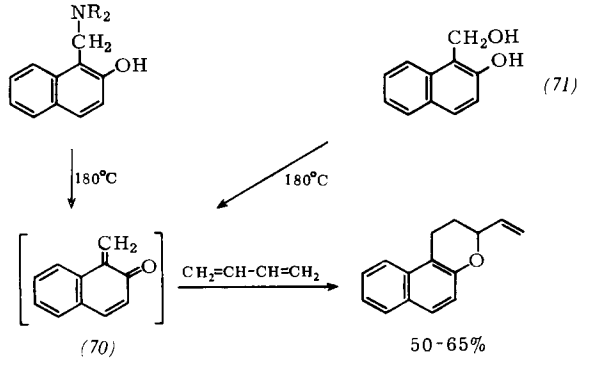
*(68)*

The tendency of the *o*-quinones to dimerize is retained even in 6,6-disubstituted cyclohexadienones [90,91], as can be seen from the example of methyl-*o*-quinol acetate *(69)* [92].




*(69)*

It is also reasonable to assume an *o*-quinonoid intermediate *(70)* for reactions of certain Mannich bases




*(71)*

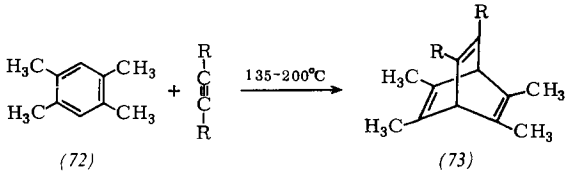
*(70)*

with dienophiles [93]. The reaction again takes place preferentially with electron-rich dienophiles such as butadiene, styrene (55 %), isobutylene (45 %), and 1,1-diphenylethylene (87 %). The intermediate *(70)* is also accessible *in situ* by intramolecular elimination of water from *(71)*.

Analogous reactions are possible in the benzene series with *o*-dialkyl(aryl)aminomethylphenols or *o*-hydroxymethylphenol as sources of dienes, although the yields are only moderate [93].

### 8. Aromatic Compounds

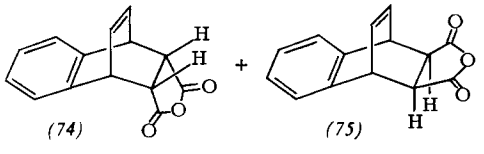
In the adducts from aromatic compounds and dienophiles, the low-energy state of cyclic conjugation is completely destroyed. Since the loss of aromatic resonance may already be quite considerable in the transition state of cycloaddition, high activation energies, *i.e.* low reactivities, are to be expected for the Diels-Alder additions of this class of compounds. In agreement with theoretical considerations [94], the diene properties increase in the sequence benzene < naphthalene < anthracene. As expected, benzene itself takes part in Diels-Alder reactions only very sluggishly, and no 1:1-adducts have yet been isolated; the formation of 1,2-bis(trifluoromethyl)benzene in the reaction of benzene with hexafluorobut-2-yne can, however, be rationalized as a normal diene addition with subsequent elimination of acetylene [95]. With durene *(72)* as the diene component, the 1:1-adduct *(73)* is obtained; this is a derivative of the interesting bicyclic compound barrelene [95,96].




*(72)* *(73)*

R = $CF_3$: 41%
R = CN: ≈ 4%

The reactions of naphthalene with dienophiles, *e.g.* maleic anhydride, still require drastic reaction conditions (100 °C) [97,98]; with maleic anhydride a total yield of 5 % of the adducts *(74)* and *(75)*, approximately in a 1:1 ratio, is obtained. 1,2,3,4-Tetramethylnaphthalene



*(74)* *(75)*

[89] *S. Kumamoto*, J. chem. Soc. Japan, ind. Chem. Sect. (Kogyo Kagaku Zasshi) *64*, 188 (1961); Chem. Abstr. *58*, 2391f (1963).

[90] *D. Y. Curtin* and *R. R. Fraser*, J. Amer. chem. Soc. *81*, 662 (1959).

[91] *K. Alder*, *F. H. Flock*, and *H. Lessenich*, Chem. Ber. *90*, 1709 (1957).

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[93] *J. Brugidou* and *H. Cristol*, C. R. hebd. Séances Acad. Sci. *256*, 3149, 3326 (1963).

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[95] *C. G. Krespan*, *B. C. McKusick*, and *T. L. Cairns*, J. Amer. chem. Soc. *83*, 3428 (1961).

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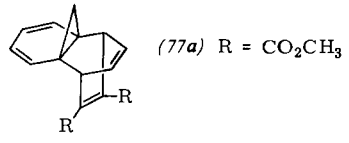
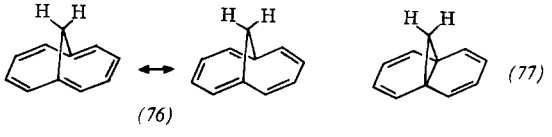
[98] *K. Takeda*, *K. Kitahonoki*, *M. Sugiura*, and *Y. Takano*, Chem. Ber. *95*, 2344 (1962).

reacts substantially faster than naphthalene. Surprisingly an excess of the dienophile is said to slow down the reaction with naphthalene[98]. In contrast to other examples[99a], the reaction is not accelerated by the action of light[99b].

Similarly to naphthalene, the 1,6-methanocyclodecapentaene *(76)* recently synthesized by *Vogel* and *Roth*[100] has a cyclic conjugated 10 $\pi$-electron system with aromatic character. Diene addition with maleic anhydride sets in only at about 150 °C and stops at the 1:1-adduct; here the reaction involves the valence tautomer *(77)* (two cyclohexadiene systems). The 1:1-addition compound *(77a)* from *(76)* and dimethyl acetylenedicarboxylate readily undergo thermolysis to give dimethyl phthalate and benzocyclopropene (see Section D).

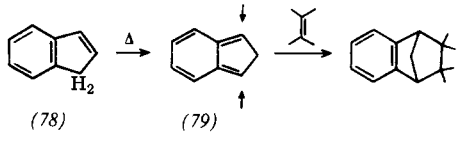


*(77a)* R = $CO_2CH_3$



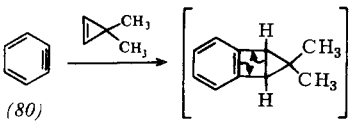
*(76)* *(77)*

On the basis of the structure of the resulting 1:1-adducts, *Alder*, *Pascher*, and *Vagt*[101] postulated for the addition reactions of indene *(78)* a preliminary transition into 2*H*-indene *(79)*, which adds dienophiles in the positions

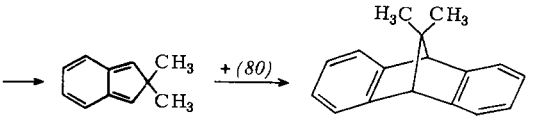


*(78)* *(79)*

indicated. The fact that such an isomerization with a hydrogen shift is possible in the temperature range of diene additions (200 °C) has recently been shown by *Roth* in an elegant NMR study on deuterated indene[102]. *Berson* and *Aspelin*[102a] have come to the same conclusion concerning the reaction mechanism. The formation of *(82)* in small amount in the reaction of benzyne *(80)* with 1,1-dimethylcyclopropene can also be explained readily by a 2*H*-indene intermediate *(81)*[103].

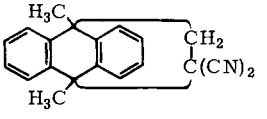


*(80)*

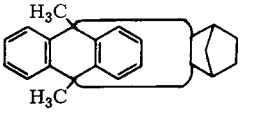


*(81)* *(82)*

As with other additions (*e.g.* halogenations to 9,10-dihalogeno-9,10-dihydroanthracenes), with anthracene and its derivatives the dienophile usually adds in positions 9 and 10. With 1,1-dicyanoethylene, 9,10-dimethylanthracene yields 95 % of *(83)* even at room temperature, while reaction with the angularly strained norbornene to yield 88 % of *(84)* requires heating to 140 °C[104].

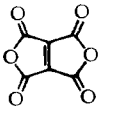


*(83)*



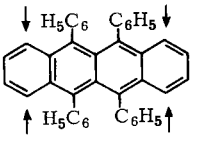
*(84)*

The addition in dioxane of the compound $C_6O_6$ *(85)*, a bis-anhydride of ethylenetetracarboxylic acid, to 9,10-dialkoxyanthracenes in the 9,10-positions is reversible at 20 °C; at 100 °C the dienophile adds irreversibly in the 1,4-positions of the anthracene system[105]. This reaction resembles that of 9,10-diphenylanthracene with maleic anhydride; here a Diels-Alder addition takes place only in the melt, again in the 1,4-position[106].

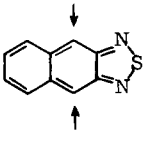


*(85)*

In this case of the naphthacene derivative *(86)*, as with 9,10-diphenylanthracene, steric factors are probably responsible for the fact that the dienophiles add to the "external" diene systems in the positions indicated[107].



*(86)*



*(87)*

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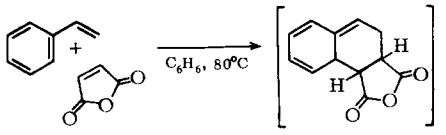
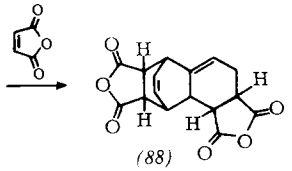
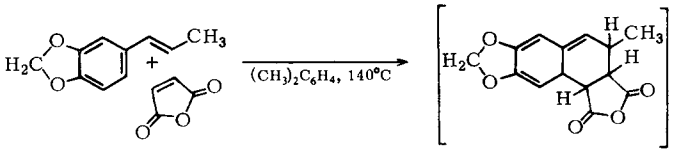
The red-orange naphthothiadiazole *(87)* is less reactive than anthracene, but, like the latter, adds *e.g.* maleic anhydride to the central ring [108].

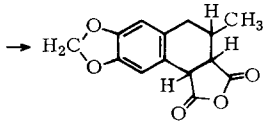
The reactions of styrene and its derivatives, in which only one double bond of the diene system belongs to the aromatic ring, sometimes give yields too low for preparative purposes because of the tendency of styrene to undergo polymerization or copolymerization. As a rule, the 1:1-adduct first produced is not isolated; this can either add a second molecule of the dienophile [*e.g.* to give *(88)*] or can undergo aromatization with a hydrogen shift [*e.g.* to *(89)*] [109,110].



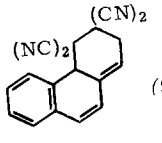
*(88)*



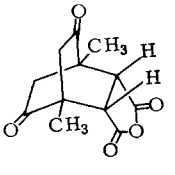



*(89)* 40-50%

In contrast, 2-vinylnaphthalene and tetracyanoethylene give 95 % of the 1:1-adduct *(90)* at room temperature [111]



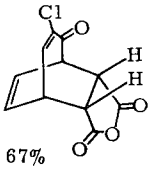
*(90)*



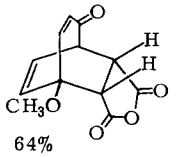
*(91)*

Phenols react with dienophiles only under drastic conditions [112–114]; the adducts are derived from the tautomeric keto forms of the phenols, as in the case of 2,5-dimethylhydroquinone and maleic anhydride: at 200 °C, 21 % of *(91)* is obtained and not the primary adduct [112].

Of the pseudoaromatic compounds azulene and tropolone, only some derivatives of the latter are suitable for the Diels-Alder reaction [115]. 2-Chlorotropolone [116] and γ-tropolone methyl ether [117] react with maleic anhydride to give respectively *(92)* and *(93)*.



*(92)* 67%

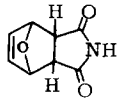


*(93)* 64%

## 9. Heterocyclic Compounds

Since the discovery of the Diels-Alder reaction, the heterocycles furan, pyrrole, and thiophen have been thoroughly investigated with respect to their suitability as diene components; their reactivity decreases in the above sequence.

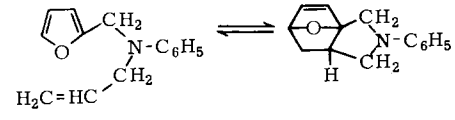
Furan adds maleic acid derivatives even at room temperature [118,119]; oxabicycloheptene derivatives are readily accessible in this way [*e.g. (94)* by reaction with maleimide in ether at 20 °C]. The tendency of the adducts to redissociate is as pronounced as with the fulvene adducts (cf. Section B.5). Like the alkyl derivatives, the derivatives of cyanofuran [120] and chlorofuran [121], are capable of undergoing cycloaddition.



*(94)*

Some intramolecular diene additions of furan derivatives take place particularly readily; thus the non-activated olefinic part of *(95)* adds to the furan nucleus even at room temperature; dissociation takes place on

*(95)*



[108] *M. P. Cava* and *R. H. Schlessinger*, Tetrahedron Letters *1964*, 3815.

[109] *K. Alder* and *R. Schmitz-Josten*, Liebigs Ann. Chem. *595*, 1 (1955); *K. Alder* and *H. Niklas*, *ibid. 585*, 97 (1954).

[110] *B. J. F. Hudson* and *R. Robinson*, J. chem. Soc. (London) *1941*, 715.

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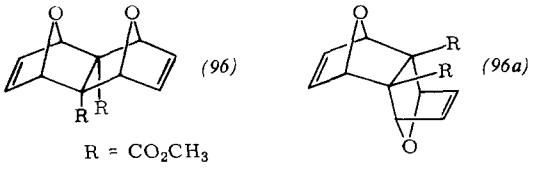
[119] With maleic acid: *J. A. Berson* and *R. Swidler*, J. Amer. chem. Soc. *75*, 1721 (1953).

[120] *C. D. Weis*, J. org. Chemistry *27*, 3514, 3520 (1962).

[121] *H. Krzikalla* and *H. Linge*, Chem. Ber. *96*, 1751 (1963).

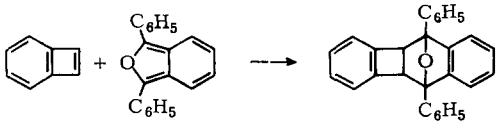
vacuum distillation[122]. Furan itself combines with acetylenedicarboxylic ester to give a 2:1-adduct *(96)* [123].



*(96)* *(96a)*

R = $CO_2CH_3$

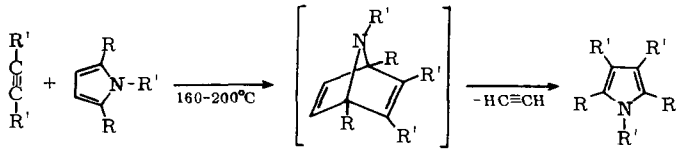
Diphenylisobenzofuran *(97)*, which itself is easy to obtain by a sequence including a Diels-Alder reaction[124], is a valuable diene component; the benzocyclobutadiene *(98)* appearing as an intermediate has recently been



*(98)* *(97)* *(99)*

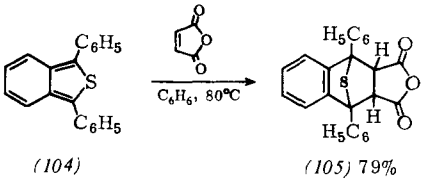
trapped in the form of its diene adduct *(99)* with the aid of this substance[125–127]. The addition of *(98)* to furan itself is possible, but gives a yield of only 5 %[128].

Pyrrole and its derivatives have for many years had the reputation of being unsuitable for Diels-Alder additions; the electrophilic substitution readily occurring in the α-position of the base substance gave rise to side reactions: with maleic anhydride α-pyrrylsuccinic acid was obtained after hydrolysis. Some examples appearing in the last few years show that pyrrole derivatives also possess, in principle, the capacity for taking part in Diels-Alder reactions: *N*-benzylpyrrole[129,130], *N*-methoxycarbonylpyrrole[131], *N*-triphenylmethylpyrrole, and *N*-1-naphthylpyrrole[132] can be converted into Diels-Alder adducts, particularly with acetylenedicarboxylic ester. In the reaction of *N*-methoxycarbonylpyrrole [*(100)*, R = H], the primary adduct *(101)* cannot be isolated because it eliminates acetylene at the high temperature.

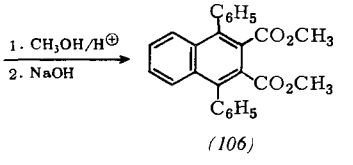


*(100)* *(101)* *(102)* R = H: 43%
*(103)* R = $CH_3$: 51%
R' = $CO_2CH_3$

It has so far been impossible to cause thiophene to react with dienophiles; in fact, with hexachlorocyclopentadiene the heterocycle acts as a dienophile with the formation of a bis-adduct[133]. 2- and 3-vinylthiophenes, in which only one double bond belongs to the diene system of the heterocycle, react in a manner similar to that of styrene[134]. Of a number of benzo[*c*]thiophenes[135], the diphenyl derivative *(104)* may be selected as an example[136].

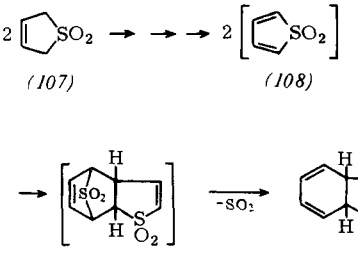


*(104)* *(105)* 79%



*(106)*

Thiophene 1,1-dioxide *(108)* can be prepared "*in situ*" in several stages from the butadiene-sulfur dioxide adduct *(107)*; all attempts to isolate or trap *(108)* have so far failed[137], since dimerization outweighs all competing reactions. In the case of the stable 3,4-dichloro derivative *(109)*, on the other hand, additions are successful, *(109)* taking part in the reaction sometimes as a diene and sometimes as a dienophile. For example, the adducts *(109a)* and *(109b)* are formed in exothermic reactions in 61 and 16 % yields, respectively, based on *(109)*. Dimerization occurs only at a relatively high temperature[138].



*(107)* *(108)*

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[128] *M. P. Cava* and *M. J. Mitchell,* J. Amer. chem. Soc. *81,* 5409 (1959).

[129] *L. Mandell* and *W. A. Blanchard,* J. Amer. chem. Soc. *79,* 6198 (1957).

[130] *R. M. Acheson* and *J. M. Vernon,* J. chem. Soc. (London) *1962,* 1148.

[131] *R. M. Acheson* and *J. M. Vernon,* J. chem. Soc. (London) *1961,* 457; cf. also *N. W. Gabel,* J. org. Chemistry *27,* 301 (1962).

[132] *L. Mandell, J. U. Piper,* and *C. E. Pesterfield,* J. org. Chemistry *28,* 574 (1963).

[133] *H. Hamadait* and *M. Neeman,* Israel. Pat. 9749; Chem. Abstr. *52,* 1263 (1958).

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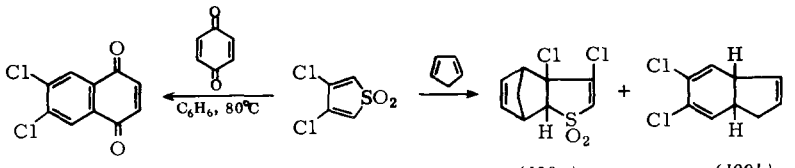
[135] *O. Dann, M. Kokorudz,* and *R. Gropper,* Chem. Ber. *87,* 140 (1954).

[136] *G. Wittig, E. Knauss,* and *K. Niethammer,* Liebigs Ann. Chem. *630,* 10 (1960).

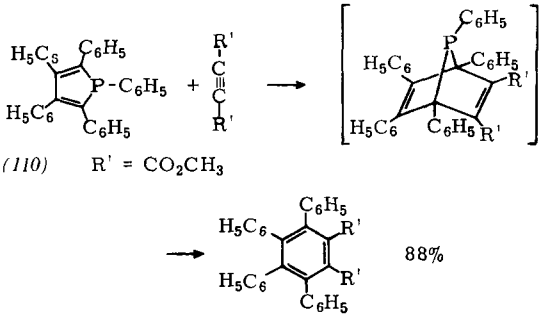
[137] *W. J. Bailey* and *E. W. Cummins,* J. Amer. chem. Soc. *76,* 1936 (1954). An account of the relative rates of addition of $SO_2$ and maleic anhydride to dienes is given by *O. Grummitt* and *A. L. Endrey,* J. Amer. chem. Soc. *82,* 3614 (1960).

[138] *H. Bluestone, R. M. Bimber, R. Berkey,* and *Z. Mandel,* J. org. Chemistry *26,* 346 (1961); US.-Pat. 3110739 (Nov. 12th, 1963), Diamond Alkali Comp., inventor: *R. M. Bimber*; Chem. Abstr. *60,* 2870b (1964).



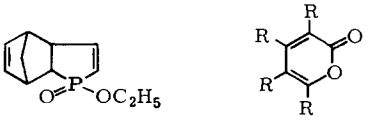
(109) (109a) (109b)

The reaction of arylphospholes with acetylenedicarboxylic ester can be formulated by means of a diene synthesis as the initial reaction step [139]; for example, the pentaphenyl derivative *(110)* forms tetraphenylphthalic ester in 88 % yield; the fate of the P-containing fragment has not been elucidated [140].



*(110)* R' = $CO_2CH_3$

1-Ethoxyphosphole 1-oxide, like thiophene 1,1-dioxide *(108)* and cyclopentadienone *(58a)*, has a pronounced tendency to dimerize and can be trapped in the form of its 1:1-adduct *(111)* only with a 50- to 100-fold excess of cyclopentadiene [141].



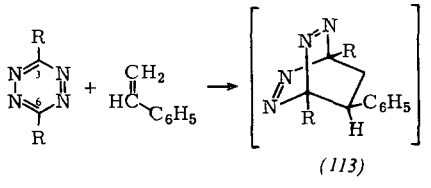
*(111)* *(112)*

Of the five-membered heterocycles with several heteroatoms, only oxazoles [142–145] can be used successfully in Diels-Alder additions, while pyrazoles, thiazoles, imidazoles, and isoxazoles fail [146]. Pyridine derivatives can be obtained in good yields by hydrolytic treatment of the adducts of the oxazoles with dienophiles.

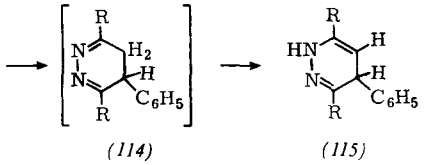
Of the six-membered heterocycles, the α-pyrones *(112)* deserve to be mentioned; they react with olefins to give 1:1-adducts, while the Diels-Alder adducts from *(112)* and acetylenes spontaneously lose $CO_2$ and undergo aromatization [147].

The diene activity is retained in perchloro-α-pyrone [148]. Like anthracene, acridinium bromide adds dienophiles to the central ring [149]. The fact that the addition compounds from 2,3-dimethylquinoxaline and alkenes are not true Diels-Alder adducts has been shown only recently [150].

The reactions of symmetrical tetrazines with simple olefins, discovered by *Carboni* and *Lindsey* [151], deserve interest; *Avram, Dinulescu, Marica*, and *Nenitzescu* [152] have studied some conversions of the very reactive 1,2,4,5-tetrazine-3,6-dicarboxylate. Nitrogen is evolved in an exothermic reaction under surprisingly mild conditions, sometimes at room temperature. 1,4-Dihydropyridazines, whose structures have been established by NMR spectroscopy [153, 154], are produced in high yields. The reaction sequence formulated with a primary dienophile addition in the 3,6-positions of the tetrazines to give



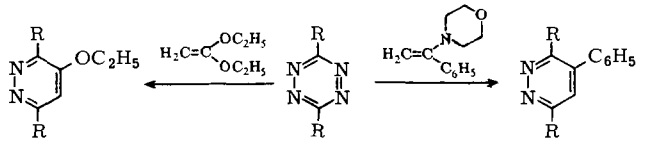
*(113)*



*(114)* *(115)*

R = $CH_3$, $C_6H_5$, $CHF\text{-}CH_3$, $CO_2CH_3$

*(113)* was elucidated on the basis of mechanistic investigations [155]. When enamines, enol ethers, or esters and ketene acetal are used, substituted pyridazines such as *(116)* and *(117)* are obtained directly by single-stage syntheses in excellent yields [154].



*(116)* *(117)*

R = $C_6H_5$, 100% R = $C_6H_5$, 91%
R = $CO_2CH_3$, 100% R = $CO_2CH_3$, 91%

[139] *I. G. M. Campbell, R. C. Cookson*, and *M. B. Hocking*, Chem. and Ind. *1962*, 359.

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[144] An elegant pyridoxine synthesis *via* the diene addition of an oxazole derivative is described by *E. E. Harris, R. A. Firestone, K. Pfister, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson*, and *W. Reuter*, J. org. Chemistry *27*, 2705 (1962).

[145] *G. Y. Kondrat'eva* and *C. H. Huang*, Dokl. Akad. Nauk S.S.S.R. *142*, 593 (1962); Chem. Abstr. *57*, 2204g (1962).

[146] *I. I. Grandberg* and *A. N. Kost*, Zh. obshch. Khim. *29*, 1099 (1959); Chem. Abstr. *54*, 1500g (1960).

[147] *J. D. Bu'Lock* and *H. G. Smith*, J. chem. Soc. (London) *1960*, 502.

[148] *G. Märkl*, Chem. Ber. *96*, 1441 (1963).

[149] *C. K. Bradsher* and *T. W. G. Solomons*, J. Amer. chem. Soc. *80*, 933 (1958).

[150] *C. W. Bird* and *G. W. H. Cheeseman*, J. chem. Soc. (London) *1962*, 3037; *E. C. Taylor* and *E. Smakula-Hand*, J. org. Chemistry *27*, 3734 (1962); Tetrahedron Letters *1962*, 1225.

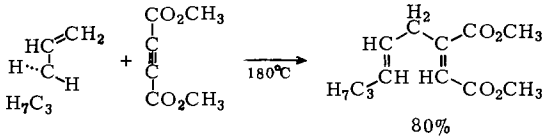
[151] *R. A. Carboni* and *R. V. Lindsey*, J. Amer. chem. Soc. *81*, 4342 (1959).

[152] *M. Avram, I. G. Dinulescu, E. Marica*, and *C. D. Nenitzescu*, Chem. Ber. *95*, 2248 (1962).

[153] *M. Avram G. R. Bedford*, and *A. R. Katritzky*, Recueil Trav. chim. Pays-Bas *82*, 1053 (1963).

Some particularly reactive dienophiles also take part in reactions with simple olefins and non-conjugated dienes, giving 1:1-adducts. The mechanistic relation to Diels-Alder diene additions [1] justifies a brief discussion.

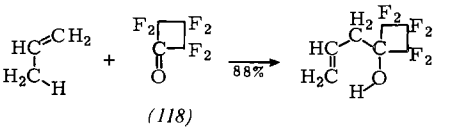
The reaction of 1-hexene with dimethyl acetylenedicarboxylate [156], as an example, includes all the characteristics of this type of reaction which *Alder*, in analogy with "diene synthesis" has called the "ene synthesis", or "indirect substitution addition" [8]: the product of allyl substitution always arises with double displacement in a stereospecific *cis*-addition. The experimental results, together with an elegant study of the asymmetric induction



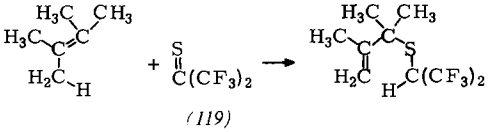

in "ene syntheses" [157], suggest a multi-center mechanism.

"Indirect substitution addition" also takes place with azodicarboxylic ester, as *Huisgen* and *Pohl* [158] have shown with 1,3-diarylpropenes and 1,2- and 1,4-dihydronaphthalenes as the olefinic components; radical and ionic modes of reaction were excluded. The reaction of the azo ester with simple olefins (1-hexene, 1-pentene, cyclopentene, and cyclohexene) also is an "ene synthesis" [159].

The C=O and C=S functions in chloral [160], carbonyl cyanide [161], pyruvic acid [162], perfluorocyclobutanone *(118)* [163], and hexafluorothioacetone *(119)* [164] can



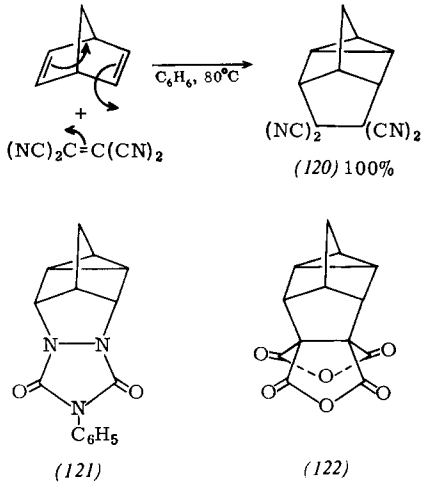

*(118)*



*(119)*

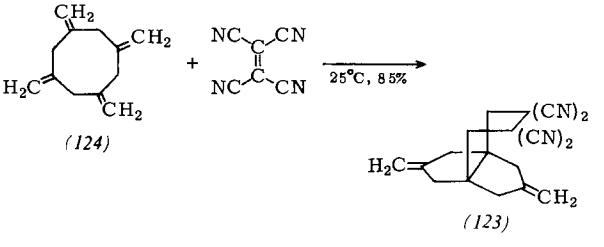
also take part in ene syntheses; however, ketones and thioketones sometimes undergo a change in orientation.

The definition of Diels-Alder additions given in Section A (two π-bonds changing into two σ-bonds) does not apply to the reactions of dienophiles with homodienes, in which the two double bonds are separated by a tetrahedral center. In the homo-Diels-Alder additions of bicycloheptadiene, three new σ-bonds are formed at the expense of three π-bonds in a 1,5-addition. The addition of maleic anhydride, the first example of this type of reaction, takes place in low yield [165]. A substantially higher yield is given by reaction with the "record dienophiles" tetracyanoethylene [166], 4-phenyl-1,2,4-triazoline-3,5-dione [167], and the bis-anhydride *(85)* [105], the products being respectively *(120)*, *(121)*, and *(122)*. Acrylonitrile [168], azodicarboxylic ester [169], dicyanoacetylene [96], and some other highly reactive cyanoethylenes [169a] react similarly.




The combination of barrelene (bicyclo[2.2.2]octa-2,5,7-triene), which has one more double bond, with alkynes also leads to the formation of homo-Diels-Alder adducts [170].

The 1,7-addition of tetracyanoethylene to 1,3,5,7-tetramethylenecyclooctane *(124)* in tetrahydrofuran takes place in accordance with the same structural principle: 3 π-bonds → 3 σ-bonds [171].




*(124)*

*(123)*

[154] *D. Lang*, Dissertation, Universität München 1963; *J. Sauer, A. Mielert, D. Lang*, and *D. Peter*, Chem. Ber. *98*, 1435 (1965).

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[163] *D. C. England*, J. Amer. chem. Soc. *83*, 2205 (1961).

[164] *W. J. Middleton, E. G. Howard*, and *W. H. Sharkey*, J. Amer. chem. Soc. *83*, 2589 (1961); J. org. Chemistry *30*, 1375 (1965); *W. J. Middleton* and *W. H. Sharkey, ibid. 30*, 1384 (1965); *W. J. Middleton, ibid. 30*, 1390, 1395 (1965).

[165] *E. F. Ullman*, Chem. and Ind. *1958*, 1173.

[166] *A. T. Blomquist* and *Y. C. Meinwald*, J. Amer. chem. Soc. *81*, 667 (1959).

[167] *R. C. Cookson, S. S. H. Gilani*, and *I. D. R. Stevens*, Tetrahedron Letters *1962*, 615.

[168] *H. K. Hall*, J. org. Chemistry *25*, 42 (1960). In the presence of the bisacrylonitrile-Ni(O) complex the yield is quantitative: *G. N. Schrauzer* and *S. Eichler*, Chem. Ber. *95*, 2764 (1962).

[169] *S. J. Cristol, E. L. Allred*, and *D. L. Wetzel*, J. org. Chemistry *27*, 4058 (1962); *R. M. Moriarty, ibid. 28*, 2385 (1963).

[169a] *W. J. Middleton*, J. org. Chemistry *30*, 1402 (1965).

[170] *H. E. Zimmerman* and *G. L. Grunewald*, J. Amer. chem. Soc. *86*, 1434 (1964).

[171] *J. K. Williams* and *R. E. Benson*, J. Amer. chem. Soc. *84*, 1257 (1962).

## C. The Dienophilic Components

The enormous preparative importance of Diels-Alder additions is based on the great variability of both the reactants; the discussion above has given a small insight into the variability of the dienes. A short systematization of the dienophiles will now follow. Without going into mechanistic details at this point, it may be mentioned that the reactivity of the dienophiles is a function of the diene component: with electron-rich dienes (*e.g.* cyclopentadiene or 9,10-dimethylanthracene), electron-attracting groups X on the double bond accelerate the reaction [104]; with electron-deficient dienes (*e.g.* hexachlorocyclopentadiene and 1,2,4,5-tetrazines), electron-donating substituents in the dienophile have a promoting effect [154, 155, 172].

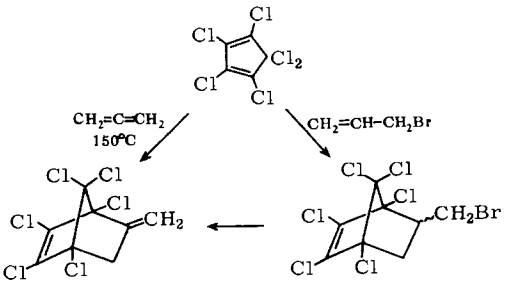
### 1. Acyclic Alkenes and Alkynes

The low reactivity of ethylene and of allylic compounds with respect to electron-rich dienes limits the use of these dienophiles; the necessity of working in autoclaves at high temperatures is also troublesome in the laboratory. Of the monosubstituted ethylenes, acrolein, methyl acrylate and acrylonitrile, styrene derivatives, and nitroolefins [173] enjoy greater favor. 1,1-Disubstituted olefins (*e.g.* dimethyl methylenemalonate and 1,1-dicyanoethylene) are more reactive than their 1,2-disubstituted isomers (dimethyl fumarate and fumaronitrile) [104]. Tri- and tetrasubstituted olefins with several activating substituents increase the preparative possibilities to a considerable extent. The interesting reactions of tri- and tetracyanoethylene, in particular, may be recalled at this point [174, 175].

Acetylene itself reacts with electron-rich dienes only under severe conditions; working with relatively large amounts of acetylene under pressure in the laboratory is not without danger. The reaction of dienes with vinyl bromide and the subsequent elimination of HBr from the Diels-Alder adduct, however, leads to the same product as the direct addition of acetylene. Among the dienophiles derived from mono- and disubstituted alkynes propiolic acid, phenylpropiolic acid, and acetylenedicarboxylic ester may be mentioned in particular. Dicyanoacetylene and hexafluorobut-2-yne have been discussed above in Sections B. 10 and B. 8 [95, 96].

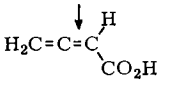
### 2. Allenes

Allene itself exhibits sufficient activity only with respect to electron-deficient dienes – e. g. hexachlorocyclopentadiene [176]. Reference may be made to the addition of allyl bromide with subsequent elimination of HBr, which was used in the example below for establishing the structure of the allene adduct *(125)* [177].

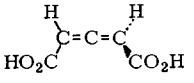



*(125)*

Cyclopentadiene combines with allenecarboxylic acid *(126)* to give a 1:1-adduct in 84 % yield; in this process the dienophile reacts as a derivative of acrylic acid at the double bond indicated [178].



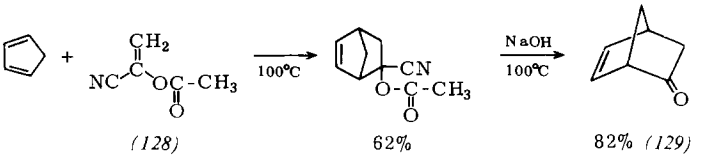
*(126)*



*(127)*

The absolute configuration of allenedicarboxylic acid *(127)* was determined by *Agosta* [179]; a diene addition to cyclopentadiene formed the introductory step of the sequence of reactions.

Extensive investigations by *Staudinger* [180] have shown that for ketenes the four-center cycloaddition to form cyclobutane derivatives is preferred to the formation of a six-membered ring. *Bartlett et al.* pointed out an artifice for the preparation of the Diels-Alder adducts of ketene itself [181]. The diene is treated with 1-cyanovinyl acetate *(128)* to give an adduct which on alkaline hydrolysis yields the desired ketone *(129)*.




*(128)* 62% 82% *(129)*

### 3. Cyclic Dienophiles

Among the cross-conjugated dienophiles, the greatest importance is attached to the derivatives of *p*-benzoquinone [13]. Quinones substituted with electron-attracting groups prove to be particularly reactive with respect

[172] *J. Sauer* and *H. Wiest*, Angew. Chem. *74*, 353 (1962); Angew. Chem. internat. Edit. *1*, 269 (1962); *H. Wiest*, Dissertation, Universität Müchen 1963.

[173] Review of diene syntheses with nitro compounds: *S. S. Novikov*, *G. A. Shvekhgeimer*, and *A. A. Dudinskaya*, Russ. chem. Reviews (Engl. transl.) *29*, 79 (1960).

[174] *C. L. Dickinson*, *D. W. Wiley*, and *B. C. McKusick*, J. Amer. chem. Soc. *82*, 6132 (1960).

[175] *T. L. Cairns* and *B. C. McKusick*, Angew. Chem. *73*, 520 (1961).

[176] *H. Pledger*, J. org. Chemistry *25*, 278 (1960).

[177] *R. Riemschneider*, *F. Herzel*, and *H. J. Koetsch*, Mh. Chem. *92*, 1070 (1961).

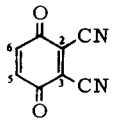
[178] *E. R. H. Jones*, *G. H. Mansfield*, and *M. C. Whiting*, J. chem. Soc. (London) *1956*, 4073.

[179] *W. C. Agosta*, J. Amer. chem. Soc. *84*, 110 (1962); *86*, 2638 (1964).

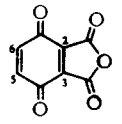
[180] *H. Staudinger*: Die Ketene. F. Enke, Stuttgart 1912; see also *H. L. Dryden*, J. Amer. chem. Soc. *76*, 2841 (1954); *A. T. Blomquist* and *J. Kwiatek*, *ibid. 73*, 2098 (1951); *W. Rellensmann* and *K. Hafner*, Chem. Ber. *95*, 2579 (1962); see also [1].

[181] *P. D. Bartlett* and *B. E. Tate*, J. Amer. chem. Soc. *78*, 2473 (1956); *C. H. DePuy* and *P. R. Story*, *ibid. 82*, 627 (1960).

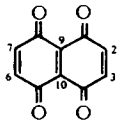
to electron-rich dienes. The dicyanoquinone *(129)* reacts more slowly than tetracyanoethylene, whereas quinonedicarboxylic anhydride *(130)* does so considerably faster [182].



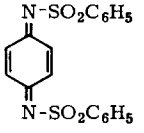
*(129)*



*(130)*



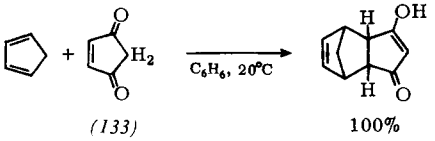
*(131)*



*(132)*

In *(129)*, *(130)*, and 1,4,5,8-naphthodiquinone *(131)* [182], as expected, cyclopentadiene, 2,3-dimethylbutadiene [182], and 1,2-dimethylenecyclobutadiene [183] add to the more highly activated double bond [in the 2,3-position in *(129)* and *(130)* and the 9,10-position in *(131)*] to form the monoadduct. An interesting difference is found with butadiene: *(129)* forms two monoadducts by the reaction of the 5,6- and the 2,3-positions (yields 16 and 62 %, respectively) [184], whereas *(131)* gives a 2:1-adduct (addition in the 2,3- and 6,7-positions) and a 1:1-adduct (reaction of the 9,10-double bond) with comparable yields [182]. On the other hand, *(130)* adds butadiene in the 2,3-position with a yield of about 75 % [182]. There is still no satisfactory explanation for this phenomenon. The dienophilic activity of *p*-benzoquinones is even retained in *N,N'*-disulfonylquinonedi-imines [*e.g. (132)*] [185].

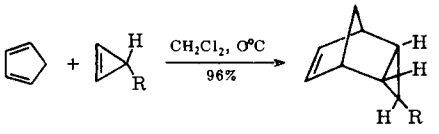
Through its diene additions, cyclopent-1-ene-3,5-dione *(133)*, which exists completely in the diketo form, makes enolized 1,3-dioxocyclopentanes readily accessible [186].



*(133)* 100%

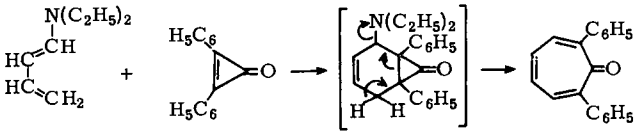
A fairly large number of cyclic olefins and acetylenes with pronounced angular strain have found application as dienophiles in the last few years. Already in the transition state, adduct formation is associated with a reduction in angular deformation; this acts as a driving force in the Diels-Alder addition.

Cyclopropene [*(134)*, R = H] combines with cyclopentadiene even at 0 °C rapidly and stereospecifically to give the *endo* adduct [*(135)*, R = H] [187]. Methylcyclopropene reacts similarly to give *(135)* [R = $CH_3$] [188], but dimethylcyclopropene, probably for steric reasons, does notre act [188]. Triphenylcyclopropene and tetraphenylcyclopentadienone give heptaphenylcycloheptatriene by the elimination of CO from the primary 1:1-adduct [189].



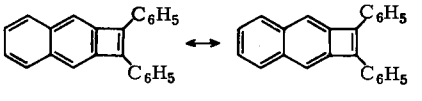
*(134)* *(135)*

Diphenylcyclopropenone and 1-diethylaminobutadiene in boiling benzene give 2,7-diphenylcyclohepta-2,4,6-trienone *(136)* in a single-stage reaction with a yield of almost 70 % [189a]; the adduct *(136a)* probably occurring as an intermediate undergoes elimination and valence-isomerization to *(136)*.



*(136a)* *(136)*

In cyclobutene derivatives, as well, the angular strain has a reaction-promoting effect; 3,3,4,4-tetrafluorocyclobutene reacts with dienes under remarkably mild conditions [190], as do unsaturated four-membered cyclic sulfones [190a]. Trapping reactions with the benzocyclobutadiene probably appearing "*in situ*" (cf. Section B. 9) take place at room temperature. The isolable cyclobutadiene derivative *(137)* also proves to be a very reactive dienophile [191]. The corresponding monobromonaphthocyclobutadiene and the dibromo compound are too short-lived, and could only be detected by trapping [191a].



*(137)*

The sp-hybridization determines the linear structure of acetylene and permits the strain-free incorporation of a triple bond only in rings with nine or more members. The increase in the angular deformation with decreasing ring size in the sequence cyclooctyne → cyclopentyne is shown in an increasing tendency to undergo additions; cyclooctyne exhibits pronounced dienophilic properties. Lower cycloalkynes have not been isolated, but their existence has been proved by trapping reactions [192]; for

[182] *J. Sauer* and *B. Schröder*, unpublished work; *B. Schröder*, Dissertation, Universität München, 1965.

[183] *H. D. Hartzler* and *R. E. Benson*, J. org. Chemistry *26*, 3507 (1961).

[184] *M. F. Ansell, B. W. Nash*, and *D. A. Wilson*, J. chem. Soc. (London) *1963*, 3006, 3012.

[185] Review: *R. Adams* and *W. Reifschneider*, Bull. Soc. chim. France *1958*, 23.

[186] *C. H. DePuy* and *E. F. Zaweski*, J. Amer. chem. Soc. *81*, 4920 (1959); *C. H. DePuy* and *C. E. Lyons*, *ibid. 82*, 631 (1960),

[187] *K. B. Wiberg* and *W. J. Bartley*, J. Amer. chem. Soc. *82*, 6375 (1960).

[188] *G. L. Closs, L. E. Closs*, and *W. A. Böll*, J. Amer. chem. Soc. *85*, 3796 (1963); see also *M. A. Battiste*, Tetrahedron Letters *1964*, 3795.

[189] *M. A. Battiste*, Chem. and Ind. *1961*, 550.

[189a] *J. Cicibattoni* and *G. A. Berchtold*, J. Amer. chem. Soc. *87*, 1404 (1965).

[190] *R. J. Shozda* and *R. E. Putnam*, J. org. Chemistry *27*, 1557 (1962).

[190a] For example, *L. A. Paquette*, J. org. Chemistry *30*, 629 (1965); *D. C. Dittmer* and *N. Takashina*, Tetrahedron Letters *1964*, 3809.

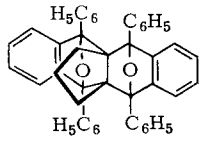
[191] *M. P. Cava, B. Hwang*, and *J. P. van Meter*, J. Amer. chem. Soc. *85*, 4032 (1963).

[191a] *M. P. Cava* and *M. Hwang*, Tetrahedron Letters *1965*, 2297.

[192] *G. Wittig* and *A. Krebs*, Chem. Ber. *94*, 3260 (1961); *G. Wittig* and *R. Pohlke*, *ibid. 94*, 3276 (1961); further studies on cyclic alkynes: *G. Wittig* and *J. Weinlich*, *ibid. 98*, 471 (1965).

example, cyclopentyne gives the bis-adduct *(138)* with diphenylisobenzofuran.

*(138)*

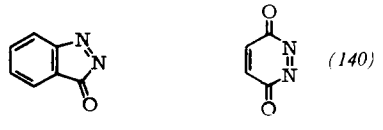


Arynes, *e.g.* dehydrobenzene *(80)* (see also Section B. 8), represent cyclic acetylenes in one resonance form. In brilliant investigations, *Wittig* and his school [193] have demonstrated the Diels-Alder additions of the "dehydroaromatic" intermediates. Cyclopentadiene [193], cyclohexadiene [194], and even benzene and naphthalene [195] add to the highly reactive species $C_6H_4$ *(80)*. The dienophilic activity is also retained in the "dehydroaromatics" of the pyridine series and in quinoline derivatives [196].

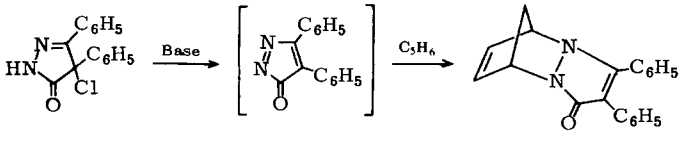
## 4. Cyclic Azo Compounds

Some cyclic azo compounds, which have been synthesized only recently, possess high dienophilic activity; however, only some of them are stable. Thus indazol-3-one *(139)* [197], 2,3-diaza-*p*-benzoquinone *(140)* [198], and 2,3-diaza-1,4-naphthoquinone have been detected by their reactions with dienes at low temperatures; in all cases the azo compounds were prepared by oxidation of the corresponding cyclic hydrazo compounds. The dienes add to the –N=N– bond system of *(139)* and *(140)*. In the dehalogenation of the

*(139)* *(140)*



pyrazolinone *(141)*, it is reasonable to postulate an intermediate with a cyclic azo grouping [199].



*(141)* 70-90%

[193] *G. Wittig*, Angew. Chem. *69*, 245 (1957); *74*, 479 (1962); Angew. Chem. internat. Edit. *1*, 415 (1962); *G. Wittig*, *W. Uhlenbrock*, and *P. Weinhold*, Chem. Ber. *95*, 1692 (1962).

[194] *H. E. Simmons*, J. Amer. chem. Soc. *83*, 1657 (1961).

[195] *R. G. Miller* and *M. Stiles*, J. Amer. chem. Soc. *85*, 1798 (1963).

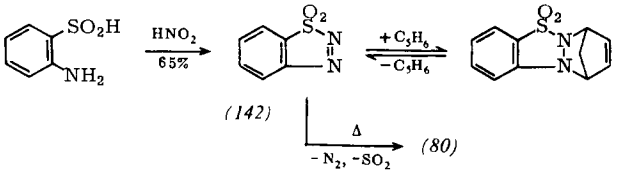
[196] *T. Kauffmann* and *F. P. Boettcher*, Chem. Ber. *95*, 949, 1528 (1962); *R. J. Martens* and *H. J. den Hertog*, Tetrahedron Letters *1962*, 643.

[197] *E. F. Ullman* and *E. A. Bartkus*, Chem. and Ind. *1962*, 93.

[198] *T. J. Kealy*, J. Amer. chem. Soc. *84*, 966 (1962); *R. A. Clement*, J. org. Chemistry *25*, 1724 (1960); *27*, 1115 (1962).

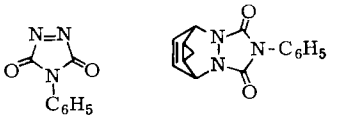
[199] *L. A. Carpino*, *P. H. Terry*, and *S. D. Thatte*, Tetrahedron Letters *1964*, 3329.

The cyclic compounds *(142)* [200] and *(143)* [167], on the other hand, can be isolated. Compound *(142)* adds to cyclopentadiene reversibly; slightly above room temperature *(142)* offers a high-yield route to dehydrobenzene *(80)*.

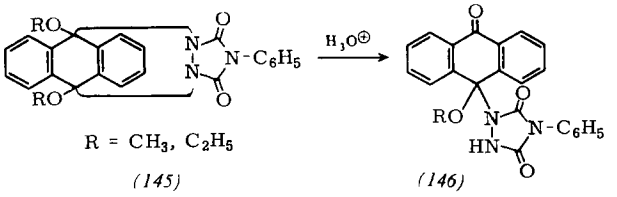


*(142)* *(80)*

4-Phenyl-1,2,4-triazoline-3,5-dione *(143)* was found in kinetic experiments to be a dienophile with extremely good addition properties, many times better than tetracyanoethylene [182]; it combines with cycloheptatriene even at –50 °C to give *(144)* [167]. The Diels-Alder adducts with 9,10-dialkoxyanthracenes undergo an acid-catalysed rearrangement at room temperature to give *(146)* [182].



*(143)* *(144)*



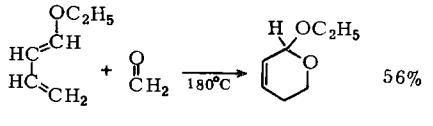
R = $CH_3$, $C_2H_5$

*(145)* *(146)*

## 5. Other Dienophiles with Heteroatoms

The replacement of carbon in the diene chain by heteroatoms is possible only in individual cases, as shown by the examples of the α,β-unsaturated aldehydes and ketones and the 1,2,4,5-tetrazines (cf. Sections B. 2 and B. 9). In contrast, in the dienophiles one or both C atoms of the dienophilic multiple bond can frequently be replaced by heteroatoms without loss of activity. This has already been illustrated by the cyclic azo compounds described in Section C. 4.

Carbonyl functions in aldehydes and ketones add to dienes particularly well if the C=O double bond is deprived of electrons by means of suitable substituents. Formaldehyde reacts slowly [201]; the reactivity increases on passing to chloral [202] and mesoxalic ester or



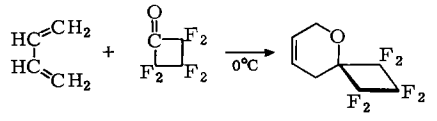
56%

[200] *G. Wittig* and *R. W. Hoffmann*, Chem. Ber. *95*, 2718 (1962).

[201] *D. G. Kubler*, J. org. Chemistry *27*, 1435 (1962); *T. L. Gresham* and *T. R. Steadman*, J. Amer. chem. Soc. *71*, 737 (1949).

[202] *W. J. Dale* and *A. J. Sisti*, J. Amer. chem. Soc. *76*, 81 (1954).

mesoxalonitrile [203], and reaches a maximum with perfluorinated cyclobutanone *(118)* [204, 104]; other fluoroketones *(147)* also react readily [205]. Glyoxylic ester and



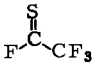
*(118)* 100% *(148)*

*(147)* R = $CF_3$, $CF_2Cl$, $C_2F_5$

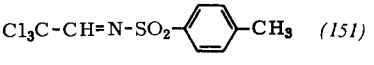
its semiacetals also react with dienes to give partially hydrogenated pyrans [206].

While the C=S bond system has proved to be a highly dipolarophilic grouping [2], only a few examples of a dienophilic activity are known; the dienophilic systems *(119)*, *(149)*, and *(150)* again bear electron-attracting groups [164].

*(149)*



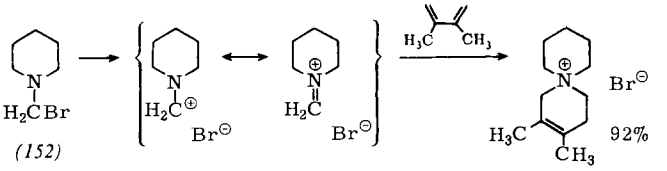
*(150)*



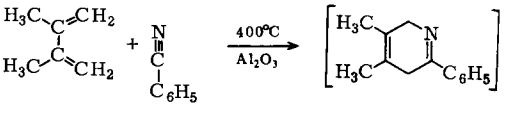
*(151)*

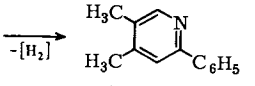
More recent investigations [164, 206a] have shown that simple thioketones – for example, thiofluorenone – react with dienes to give Diels-Alder adducts even at room temperature. Obviously the dienophilic nature of compounds with the C=S double bond has been overlooked, not least because of their unpleasant odor. Here is presumably a wide field of preparative application.

Among Schiff bases [207], immonium salts [208], and nitriles [209] (the latter react only at high temperatures) C=N or C≡N heterodienophiles are occasionally found. *(151)* generally combines with dienes to give Diels-Alder adducts in high yields (> 90 %) [207]. The immonium salts that may be formed as intermediates from α-halogenoamines such as *(152)* make spirocyclic ammonium compounds accessible [208]. Simple nitriles, such as benzonitrile, acetonitrile, and dicyanogen, add to dienes only at about 400 °C; the products of a subsequent dehydrogenation, *e.g. (153)*, are immediately formed [209]. α-Ketonitriles and cyanopyridines react at temperatures as low as about 250 °C [210].



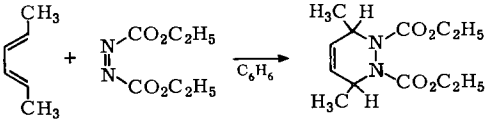
*(152)*



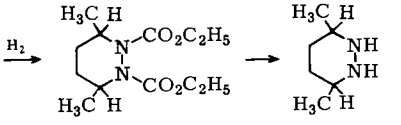


*(153)* 53%

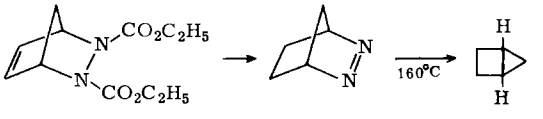
Some of the longest-known addition reactions are those of azodicarboxylic ester [5]. Tetrahydropyridazines such as *(154)* can be isolated, usually in excellent



*(154)* 86%



yields [211, 212], and they can be converted into cyclic hydrazine derivatives. The Diels-Alder adducts, *e.g. (4)*, lead in many cases to new azo compounds, such as *(155)* which, in turn, are capable of undergoing interesting reactions and make new compounds accessible [213, 214].



*(4)* *(155)* 94%

[203] *O. Achmatowicz* and *A. Zamojski*, Bull. Acad. polon. Sci., Cl. III, *5*, 927 (1957); Chem. Abstr. *52*, 6333 (1958).

[204] *D. C. England*, J. Amer. chem. Soc. *83*, 2205 (1961); US.-Pat. 3036091 (May 22nd, 1962); Chem. Abstr. *57*, 16567e (1962).

[205] *W. J. Linn*, J. org. Chemistry *29*, 3111 (1964).

[206] *Y. A. Arbuzov*, *E. M. Klimov*, and *E. I. Klimova*, Dokl. Akad. Nauk S.S.S.R. *142*, 341 (1962); Chem. Abstr. *57*, 765, (1962).

[206a] *A. Schönberg* and *B. König*, Tetrahedron Letters *1965*, 3361.

[207] *G. Kresze* and *R. Albrecht*, Chem. Ber. *97*, 490 (1964); see also *R. Albrecht* and *G. Kresze*, *ibid. 98*, 1431 (1965).

[208] *H. Böhme*, *K. Hartke*, and *A. Müller*, Chem. Ber. *96*, 607 (1963).

[209] *G. J. Janz* and *A. G. Keenan*, Canad. J. Chem. *25 B*, 283 (1947); *G. J. Janz* and *W. J. H. McCulloch*, J. Amer. chem. Soc. *77*, 3143 (1955); *G. J. Janz* and *A. R. Monahan*, J. org. Chemistry *29*, 569 (1964).

[210] Examples: *W. Polaczkowa* and *J. Wolinski*, Roczniki Chem. *26*, 407 (1952); Chem. Abstr. *48*, 11359 (1954); *W. Polaczkowa*, *T. Jaworski*, and *J. Wolinski*, *ibid. 27*, 468 (1953); Chem. Abstr. *49*, 3181 (1955); *T. Jaworski* and *W. Polaczkowa*, *ibid. 34*, 887 (1960); Chem. Abstr. *55*, 8407d (1961); *T. Jaworski*, *ibid. 35*, 1309 (1961); Chem. Abstr. *57*, 5888i (1962).

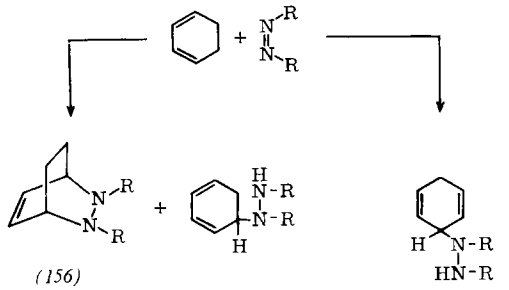
[211] *P. Baranger* and *J. Levisalles*, Bull. Soc. chim. France *1957*, 704; *P. Baranger*, *J. Levisalles*, and *M. Vuidart*, C. R. hebd. Séances Acad. Sci. *236*, 1365 (1953).

[212] *K. Alder* and *H. Niklas*, Liebigs Ann. Chem. *585*, 81, 97 (1954); *J. C. J. McKenzie*, *A. Rodgman*, and *G. F. Wright*, J. org. Chemistry *17*, 1666 (1952); *A. Rodgman* and *G. F. Wright*, *ibid. 18*, 465 (1953); *Y. S. Shabarov*, *N. I. Vasil'ev*, and *R. Y. Levina*, Dokl. Akad. Nauk S.S.S.R. *129*, 600 (1959); Chem. Abstr. *54*, 14259 (1960).

[213] *R. Criegee* and *A. Rimmelin*, Chem. Ber. *90*, 414 (1957).

[214] Experiments with hexachlorocyclopentadiene and azo compounds: *J. G. Kuderna*, *J. W. Sims*, *J. F. Wikstrom*, and *S. B. Soloway*, J. Amer. chem. Soc. *81*, 382 (1959).

The possibility, mentioned in Section B. 10, of a radical allyl substitution [215] or a multi-center reaction with a shift of the double bond in the reaction of azodicarboxylic ester with olefins also exists in principle with dienes, and sometimes makes it difficult to establish the constitution of the Diels-Alder 1:1-adducts. Apparently slight changes in the reaction conditions lead to the formation of different products [216]. Thus azodicarboxylic ester and cyclohexa-1,3-diene at 20 °C in cyclohexane give the compounds *(156)* and *(157)* in an exothermic reaction (total yield 89 %). Without a solvent, between 20 and 80 °C, only *(158)* is formed.



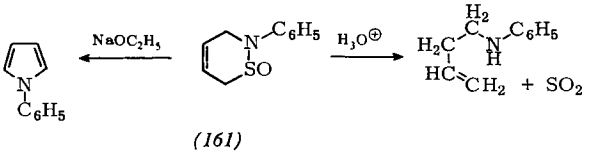
*(156)* *(157)* *(158)*

R = $CO_2C_2H_5$

Possibly the influence of light, recently discovered by *Askani* [216a], offers an explanation of the apparent discrepancy: on irradiation with a high-pressure mercury lamp, cyclohexadiene and azodicarboxylic ester form only the adduct *(156)* in 87 % yield.

Finally, there is also a possibility of replacing the two C atoms of the double bond in the dienophile by two different heteroatoms: nitroso compounds *(159)* and *N*-sulfinyl compounds *(160)*, on addition to dienes, form six-membered heterocycles [31,217]. The adducts of the nitrosoaromatic compounds can easily be converted by hydrogenolysis into *cis*-1,4-aminoalcohols [218], and the diene adducts of *N*-sulfinyl compounds such as *(161)* give rise to a wealth of new reactions [217], two of which are illustrated here.

R–N=O *(159)* R–N=S=O *(160)*



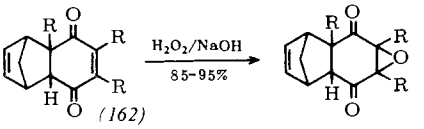
*(161)*

The 1:1-addition compounds from dienes and molecular oxygen, which frequently are formed on irradiation [219], can be regarded formally in some cases as Diels-Alder adducts. These reactions will not be discusssed in this review.

### D. Retro-Diels-Alder Reactions

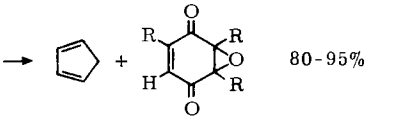
The diene additions are reversible, often under surprisingly mild conditions; for the fulvenes and furans (Sections B. 5 and B. 9) we have already demonstrated this capacity for undergoing the retro-Diels-Alder reaction. Many adducts can be modified chemically and yet still undergo cleavage in a retro-Diels-Alder reaction. In this way a modified diene and/or dienophile are obtained. The fact that the retro-Diels-Alder reactions frequently claim preparative interest may be illustrated by the following example.

The alkali-lability of the simple *p*-benzoquinones interferes with their epoxidation with alkaline $H_2O_2$. On the other hand, the benzoquinone adducts *(162)* with cyclopentadiene can be easily epoxidized; pyrolysis at 420 °C/10 mm smoothly yields the desired quinone epoxides [220].



*(162)*

R = H, $CH_3$



As further examples may be mentioned: the preparation of 6,6-disubstituted cyclohexadienones from dimeric fulvene epoxides [91], the preparations of *o*-quinodimethane [48,49], and of acetylenedicarbonyl dichloride from the anthracene adduct of the free acid [221], and the conversion of 1-vinylcyclohexene into vinylcyclohexane *via* the anthracene adduct [222]. The determination of the position of groups in the cycloheptatriene ring has been carried out through the addition of acetylenedicarboxylic ester and pyrolysis of the adduct to substituted phthalic esters [223]. The transient existence of isobenzo-

[215] *R. Huisgen, F. Jacob, W. Siegel,* and *A. Cadus,* Liebigs Ann. Chem. *590,* 1 (1954); *R. Huisgen* and *F. Jacob, ibid. 590,* 37 (1954).

[216] *S. G. Cohen* and *R. Zand,* J. Amer. chem. Soc. *84,* 586 (1962); *B. T. Gillis* and *B. E. Beck,* J. org. Chemistry *27,* 1947 (1962); *B. Franzus* and *J. H. Surridge, ibid. 27,* 1951 (1962); see also *M. Cais* in *S. Patai*: The Chemistry of Alkenes. Interscience Publishers, New York 1964, p. 739.

[216a] *R. Askani,* Chem. Ber. *98,* 2551 (1965). *cis*-Azodicarbotylate: *G. O. Schenck et al.,* Z. Naturforsch. *20b,* 637 (1965).

[217] *G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla,* and *A. Trede,* Angew. Chem. *74,* 135 (1962); Angew. Chem. internat. Edit. *1,* 89 (1962); *G. Kresze* and *J. Firl,* Angew. Chem. *76,* 439 (1964); Angew. Chem. internat. Edit. *3,* 382 (1964). *E. S. Levchenko, J. G. Bal'on,* and *A. V. Kirsanov,* J. gen. Chem. U.S.S.R. (Engl. transl. of Zh. obshch. Khim.) *33,* 1546 (1963).

[218] *G. Kresze* and *G. Schulz,* Tetrahedron *12,* 7 (1961); Chem. Ber. *96,* 2165 (1963).

[219] *G. O. Schenck,* Naturwissenschaften *35,* 28 (1948); Angew. Chem. *64,* 12 (1952); *A. Schönberg*: Präparative Organische Photochemie. Springer-Verlag, Berlin 1958; see also [8]; *K. Gollnick* and *G. O. Schenck* in: Organic Photochemistry. Internat. IUPAC Symposium, Strasbourg 1964; Butterworths, London 1965.

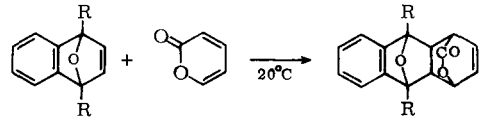
[220] *K. Alder, F. H. Flock,* and *H. Beumling,* Chem. Ber. *93,* 1896 (1960).

[221] *O. Diels* and *W. E. Thiele,* Ber. dtsch. chem. Ges. *71,* 1173 (1938).

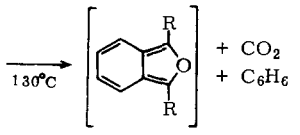
[222] *L. H. Slaugh* and *E. F. Magoon,* J. org. Chemistry *27,* 1037 (1962).

[223] *K. Alder, R. Muders, W. Krane,* and *P. Wirtz,* Liebigs Ann. Chem. *627,* 59 (1959); *K. Alder, H. Jungen,* and *K. Rust, ibid. 602,* 94 (1957); *W. von E. Doering, G. Laber, R. von der Wahl, N. F. Chamberlain,* and *R. B. Williams,* J. Amer. chem. Soc. *78,* 5448 (1956).

furan [*(163)*, R = H] and its dimethyl derivative was also shown for the first time by the retro-Diels-Alder reaction with trapping experiments [224].

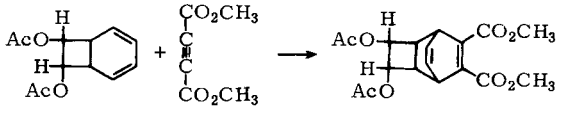


R = H, $CH_3$ 95%

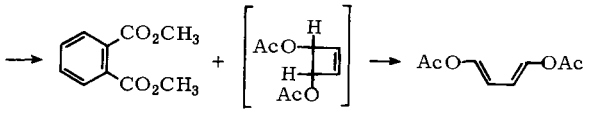


*(163)* R = H: > 92%

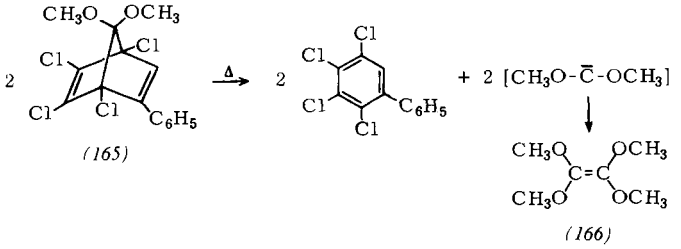
It is not always the bonds formed in the addition that are split on pyrolysis, as can be seen from an example due to *Criegee* [225]. The adduct *(164)* decomposes at about 200 °C/18 mm into dimethyl phthalate and diacetoxybutadiene. Tetramethoxyethylene *(166)* was first obtained by *Hoffmann* and *Häuser* [226] by a retro-diene



*(164)*

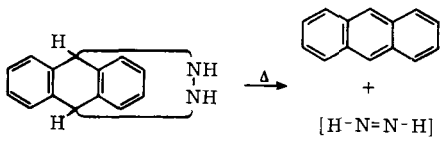


synthesis from the easily accessible adduct *(165)* of 5,5-dimethoxytetrachlorocyclopentadiene and phenylacetylene.



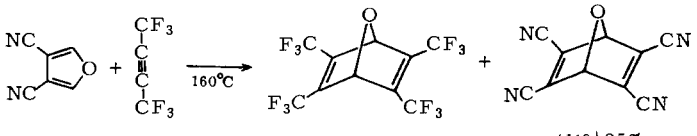
*(165)* *(166)*

The adducts of tri- and tetracyanoethylene, dicyano-*p*-benzoquinone, and dicyanomaleimide with 9,10-dialkoxyanthracenes decompose into the components in solution, even at room temperature, sometimes immeasurably fast [227]; the preparation of the compound $C_6O_6$ *(85)* in solution (Section B. 8) in a similar manner may be recalled. In warm ethanol, the hydrolysis product *(167)* of the adduct from azodicarboxylic ester and anthracene gives the diimide, which is capable of stereospecific *cis*-addition [228].



*(167)*

Compounds *(168)* and *(169)*, which were isolated as the only products, probably arise from many addition and splitting steps: the reversibility of the addition step possibly ensures the establishment of thermodynamic equilibrium [229].



*(168)* 30% *(169)* 35%

A particularly fine example of a retro-Diels-Alder reaction has recently been contributed by *Vogel et al.* [230]. The adduct *(77a)* (see Section B. 8) decomposes at 100 °C/1 mm to give a 45 % yield of benzocyclopropene, which is very interesting in relation to bond theory, and phthalic ester.

## E. Future Prospects

Any short account of the Diels-Alder reaction must necessarily be incomplete. However, the discussion of the modes of reaction of diene and dienophile, possible here only in a sketchy fashion, shows that the preparative possibilities of diene additions are still not exhausted. It has not been possible to discuss Diels-Alder reactions initiated by irradiation.

In addition to preparative investigations, since the discovery of this cycloaddition to form six-membered rings attempts have been made to clarify the reaction mechanism. An account of systematic mechanistic studies with the inclusion of stereochemical and kinetic results and of orientation and catalysis phenomena will be given in the second part of this paper.

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Translated by Express Translation Service, London

[224] *L. F. Fieser* and *M. J. Haddadin*, J. Amer. chem. Soc. *86*, 2081 (1964).

[225] *R. Criegee*, *W. Hörauf*, and *W. D. Schellenberg*, Chem. Ber. *86*, 126 (1953).

[226] *R. W. Hoffmann* and *H. Häuser*, Tetrahedron Letters *1964*, 197.

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# The Quaternary Structure of Proteins

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*Many protein molecules, particularly those with high molecular weights, consist not of a single polypeptide chain, but form a complex made up from several polypeptide chains. This structure, which can be reversibly broken down, is known as the quaternary structure. A number of metabolic phenomena can be explained on a molecular basis by invoking the quaternary structure.*

## I. Introduction [2]

Important advances have been made in recent years in the elucidation of the structure of proteins. One of these advances is the realization that protein molecules very often do not consist of a single polypeptide chain. Although these proteins behave under physiological conditions as monodisperse substances with a defined molecular weight, they actually are complexes of several polypeptide chains not joined to one another by peptide linkages [3]. In an extension of the *Linderstrøm-Lang* terminology [4], *Bernal* (1958) introduced the term "quaternary structure" for this phenomenon [5].

### The Linderstrøm-Lang Terminology [4]

For the description of particular aspects of the structure of a protein molecule *Linderstrøm-Lang* introduced the terms primary, secondary, and tertiary structure (cf. Fig. 1a–1c). The primary structure of a polypeptide chain is given by the number and sequence of the amino-acid residues that are joined together by peptide linkages. Secondary structures (helical and pleated sheet structures) may result from hydrogen bonding between the CO and NH groups of the peptide linkages. Tertiary structure is the spatial arrangement due to interactions between the side-chains of the amino-acid residues. Finally, a protein molecule has a quaternary structure if it consists of a defined number of polypeptide chains (Fig. 1d) [6].

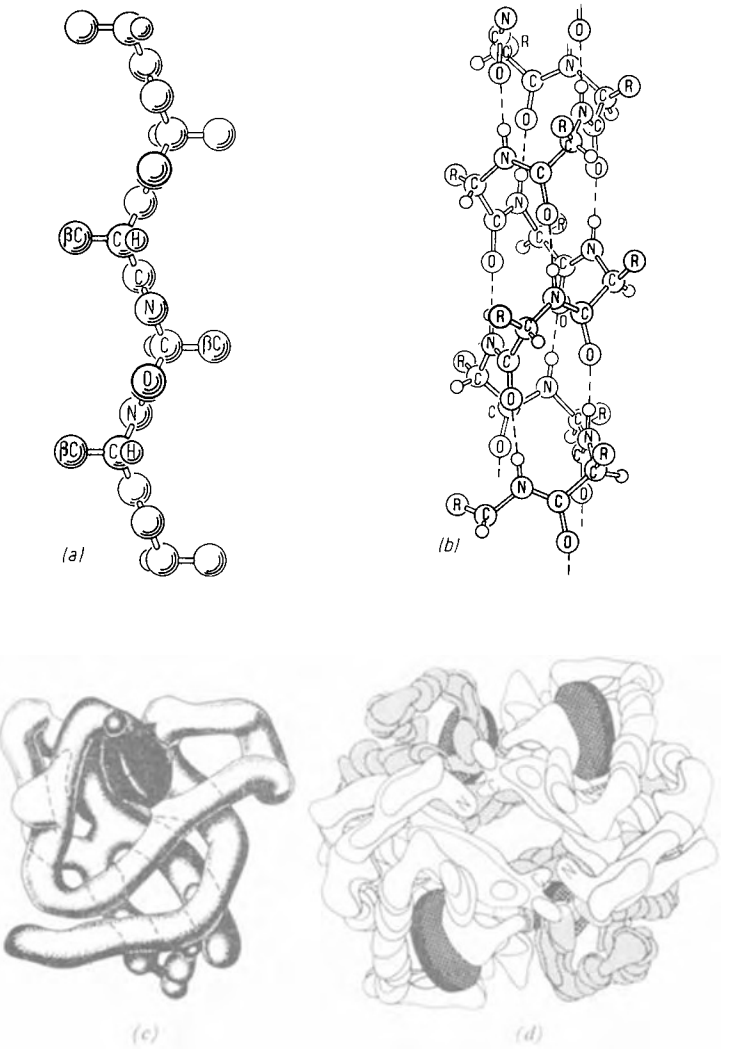


Fig. 1. The principles of protein structure (after *Bernal* [5]).
a) Primary structure (polypeptide chain after [9]).
b) Secondary structure (example: α-helix after *Pauling* and *Corey* [9]).
c) Tertiary structure (example: myoglobin after *Kendrew* [10]).
d) Quaternary structure (example: hemoglobin after *Perutz* [11]). White: polypeptide α-chains, grey: polypeptide β-chains, black disks: heme groups, C and N: C- and N-terminal groups of the two α-chains.

[1a] Based on lectures held during 1964 *(H. S.)*.

[1b] Present address: Biological Laboratories, Harvard University, Cambridge, Massachusetts (USA).

[2] For the historical development of views on the structure, size, and homogeneity of proteins, see *J. T. Edsall*, Arch. Biochem. Biophysics Suppl. *1*, 12 (1962).

[3] Under given conditions the protein molecules, sub-units, and polypeptide chains [cf. Equations (1a)–(1c)] have a characteristic particle weight, which can be measured by physicochemical methods. This weight will be referred to as the molecular weight of the particle.

[4] *K. U. Linderstrøm-Lang* and *J. A. Schellman* in *P. D. Boyer, H. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd edit., Academic Press, New York 1959, Vol. 1, p. 443.

[5] *J. D. Bernal*, Discuss. Faraday Soc. *25*, 7 (1958).

[6] Secondary, tertiary, and quaternary structures are aspects of the conformation of the protein molecule. *Wetlaufer* [7] has suggested that the spatial arrangement of the polypeptide chains and the side-chains of the amino-acid residues should be termed "chain conformation". However, this suggestion has not been adopted. A further proposal concerning the quaternary structure has been made [8].

[7] *D. B. Wetlaufer*, Nature (London) *190*, 1113 (1961).

[8] *J. P. Changeux, A. Ullmann*, and *J. Monod*, quoted by *A. Ullmann, P. R. Vagelos*, and *J. Monod*, Biochem. biophys. Res. Commun. *17*, 86 (1964); *J. P. Changeux*, Brookhaven Symposia Biol. *17*, 182 (1964).

[9] *L. Pauling* and *R. B. Corey*, Fortschr. Chem. org. Naturstoffe *11*, 180 (1954); *L. Pauling*: The Nature of the Chemical Bond, 3rd edit., Cornell University Press, Ithaca 1960. p. 498.

[10] *J. C. Kendrew*, Angew. Chem. *75*, 595 (1963).

[11] *M. F. Perutz*, Angew. Chem. *75*, 589 (1963); Sci. American *211*, No. 5, p. 64 (1964).

### Polypeptide Chains and Sub-Units [3]

A protein molecule consisting of more than two polypeptide chains can dissociate stepwise into these components. A dissociation product that still contains at least two polypeptide chains will be referred to as a sub-unit. The polypeptide chains themselves, on the other hand, consist entirely of amino-acid units joined to one another by peptide linkages. Thus a protein molecule consisting of several polypeptide chains can dissociate in three ways:

(1a) protein molecule $\rightleftharpoons$ *a* polypeptide chains

(1b) protein molecule $\rightleftharpoons$ *a* sub-units $\rightleftharpoons$ *xa* polypeptide chains

(1c) protein molecule $\rightleftharpoons$ *a* sub-units + *b* polypeptide chains

$\Updownarrow$

*xa* polypeptide chains

The polypeptide chains of a protein molecule may all be identical (homogeneous type of quaternary structure) or they may be different (heterogeneous type).

## II. Stabilization of the Protein Structure

### 1. Bond Types

The native conformation of a protein molecule is stabilized by covalent and by non-covalent bonds. These bonds reduce the flexibility of the polypeptide chains, and ensure that they are arranged in an ordered, compact form, instead of as a random coil [12].

Among the covalent bonds, the only type that appears to be of general occurrence is the disulfide bond. This may link different parts of the same polypeptide chain, as in ribonuclease [13,14], or it may join different polypeptide chains, as in insulin [15] and γ-globulin (cf. Section IV.3). No conclusive evidence has yet been found for covalent peptide linkages between different polypeptide chains or between different parts of the same chain (*e.g.* between the ε-amino group of lysine and the γ-carboxyl group of glutamic acid). Ester and phosphate links and linkages *via* carbohydrates or other components are probably peculiar only to a small number of proteins.

Non-covalent bonds include the hydrogen bond, the hydrophobic bond, and the ionic bond [16] (Fig. 2). Recent investigations have shown that the bond energy of a hydrogen bond between a carbonyl oxygen and an amide nitrogen in aqueous solution is at most 1.5 kcal/mole [17,18], *i.e.* much lower than the value of 8 kcal/mole that has previously been accepted [19]. However, the bond energy may be appreciably higher in a non-polar (hydrophobic) medium [16]. Hydrogen bonding may occur not only between peptide groups, but also between suitable donors and acceptors in the amino-acid side-chains (*e.g.* between the OH group of a tyrosine residue and a carboxylate group).

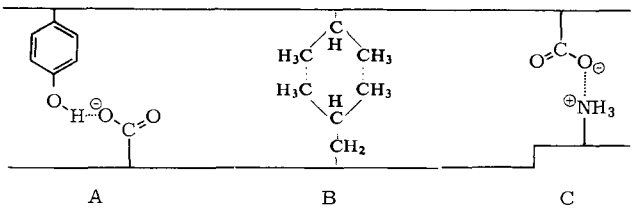


Fig. 2. Examples of non-covalent bonds between amino-acid side-chains, which stabilize the conformation of a protein molecule (cf. also [16a]). A. Hydrogen bond; B. hydrophobic bond; C. ionic bond.

Nowadays it is often considered that the greatest contribution to stabilization of the protein structure is made by hydrophobic bonds. In most proteins, some 40 % of the amino-acid residues have non-polar side-chains. According to *Kauzmann* [12], those protein conformations which bring many of these non-polar groups into contact with one another and thus "remove" them from the aqueous phase are more stable than others. This leads to the formation of "hydrophobic micelles" in the protein molecule. According to *Némethy* and *Scheraga* [16], the hydrophobic bond is not simply a result of van der Waals forces between the non-polar groups, but is due largely to the physical properties of liquid water and its tendency to form hydrogen-bonded clusters (cf. also [16a]).

Coulomb forces between ionic groups in the protein molecule may also have a stabilizing effect, and like hydrogen bonds, these ionic bonds should be stronger in non-polar than in polar media.

The native conformation may in addition be stabilized by metal ions and prosthetic groups, as well as by co-enzyme-substrate interaction.

### 2. Denaturation

A change in the native structure of a protein molecule is referred to as denaturation. This process is generally accompanied by a change in the optical properties and loss of biological activity. Moreover, the unusual reactivity exhibited by functional groups in the native protein molecule is often lost on denaturation. Globular protein molecules are transformed into a less compact structure, and if the changes are sufficiently extensive, the new arrangement may even approximate to the random-coil model. The solubility of the protein often is also affected by denaturation.

Denaturation can be brought about by modification of the solvent (addition of organic solvents, salts, urea, or guanidine hydrochloride) or by a change in pH, by the

[12] *W. Kauzmann*, Advances Protein Chem. *14*, 1 (1959).

[13] *D. H. Spackman, W. H. Stein*, and *S. Moore*, J. biol. Chemistry *235*, 648 (1960).

[14] *R. E. Canfield* and *C. B. Anfinsen* in *H. Neurath*: The Proteins. 2nd edit., Academic Press, New York, London 1963, Vol. 1, p. 311.

[15] *F. Sanger* in *D. E. Green*: Currents in Biochemical Research 1956. Interscience, New York, London 1956, p. 434.

[16] *H. A. Scheraga* in *H. Neurath*: The Proteins. 2nd edit., Academic Press, New York, London 1963, Vol. 1, p. 477.

[16a] *W. Luck*, Fortschr. chem. Forsch. *4*, 653 (1964).

[17] *J. A. Schellman*, C. R. Trav. Lab. Carlsberg, Sér. chim. *29*, 223 (1955).

[18] *I. M. Klotz* and *J. S. Franzen*, J. Amer. chem. Soc. *84*, 3461 (1962).

[19] *L. Pauling, R. B. Corey*, and *H. R. Branson*, Proc. nat. Acad. Sci. U.S.A. *37*, 205 (1951).

addition of detergents, heavy metal ions, or complexing agents, or by a temperature change. Other methods involve the chemical modification of the protein by oxidative or reductive cleavage of disulfide groups, oxidation of thiol groups to sulfonic acid groups, or substitution of functional groups.

Most of the early attempts to convert denatured proteins back into the biologically active forms were unsuccessful. Since there were very few cases of successful renaturation [20], denaturation [*] was generally regarded as irreversible, and the denatured form was assumed to be particularly stable in comparison with the native structure. However, this view has now been abandoned, mainly as a result of many successful reactivations and on the basis of present knowledge of the biosynthesis of proteins. Today, the native conformation of a protein is often regarded simply as a function of the amino-acid sequence of the polypeptide chain *and* the surrounding medium (cf. also Section V).

A considerable conformational entropy has to be overcome during renaturation, and this leads to an increase in free energy of the native conformation. If the native conformation is nevertheless favored relative to the random coil, the formation of hydrogen bonds, hydrophobic bonds, and ionic bonds must make a substantial negative contribution to the free energy in order to make the renaturation possible. The overall change in free energy during the formation of the native compact structure from the random coil should then be small and negative. This is confirmed by the few thermodynamic results available [20]. With regard to attempts to estimate the contribution made by non-covalent bonds to the stabilization of the native structure, the reader is referred to the original publications [16, 21, 22].

## III. Detection of the Quaternary Structure

The quaternary structure can be studied by the following methods [23]:

1. With X-ray analysis, even at relatively low resolutions, the individual sub-units or polypeptide chains can be distinguished, and their arrangement in space recognized.

2. The arrangement of the sub-units can be observed directly by means of the electron microscope, particularly when the technique of negative staining is used.

3. The "classical" technique in protein chemistry is end-group analysis, in which the N-terminal or C-terminal amino-acid of each polypeptide chain is determined with specific reagents or by enzymatic hydrolysis.

4. In "fingerprint analysis", the protein is broken down with trypsin, and the resulting mixture of peptides is separated by chromatography and electrophoresis. The equivalent weight of the polypeptide chain can be found from the lysine and arginine content of the protein and from the number of peptides obtained. The enzymatic degradation may be replaced by reaction of the protein with BrCN; in this case, cleavage of the polypeptide chains occurs at methionine residues [24].

5. A protein molecule consisting of several polypeptide chains often dissociates into sub-units or polypeptide chains on denaturation. The problem of finding the number of sub-units and polypeptide chains then reduces to a molecular-weight determination. Investigations of this nature are usually carried out with the aid of the ultracentrifuge [25, 25a]. If the polypeptide chains are not identical, they can be separated in the denatured state by electrophoresis, counter-current distribution, or chromatography.

6. If, as is the case with bacteria, it is possible to obtain an isotopically labelled protein molecule, the hybridization technique may be used: if denaturation results in reversible dissociation of the protein molecule into its sub-units, it is possible to prepare hybrids of "heavy" molecules and "light" molecules; these hybrids can then be separated by centrifugation in a density gradient. The number of sub-units formed on denaturation can be found directly from the differences in the densities of the heavy, the hybrid, and the light molecules.

7. If an enzyme contains several active centers, the determination of the number of sites at which the substrate becomes attached contributes to the study of the quaternary structure.

## IV. The Quaternary Structures of Various Proteins

A number of proteins whose quaternary structures have been studied are listed in Tables 1 and 2 (for others, see [25–30]). Some of these are discussed in the following Sections.

### 1. Respiratory Proteins (Erythrocruorins, Hemocyanins, Hemoglobins)

The respiratory proteins (erythrocruorins and hemocyanins) of invertebrates give pH-dependent association-dissociation equilibria in solution [25, 54, 54a, 56]. The molecular weight in the associated state can be as high as several million, whereas molecular weights of 40000 to 400000 are obtained for the fragments formed on dissociation. The larger dissociation products are prob-

[20] Review: *F. Haurowitz*: The Chemistry and Function of Proteins. 2nd edit., Academic Press, New York, London 1963.

[21] *C. Tanford*, J. Amer. chem. Soc. *84*, 4240 (1962).

[22] *H. K. Schachman*, Cold Spring Harbor Sympos. quantitat. Biol. *28*, 409 (1963).

[23] Examples of the methods mentioned are given in Section IV.

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[25a] *H. Sund* and *K. Weber*, Beckman Report *3/4*, 7 (1965).

[26] *D. F. Waugh*, Advances Protein Chem. *9*, 325 (1954).

[27] *R. Jaenicke*: Habilitation Thesis, Universität Frankfurt/Main 1963.

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Table 1. Quaternary structures of some proteins (for dehydrogenases see Table 2).

| Protein | M. W. | Polypeptide chain | | | Notes | Ref. |
|---|---|---|---|---|---|---|
| | | M. W. | Number | Method [a] | | |
| Beef thrombin | 33700–40000 | ≈ 8000 | 4–5 | D/M | Reversible formation of larger associates. | [31] |
| Hemoglobins from various species | 65000 | 15000–16000 | 4 | C, D/M, EA, F, X, S | See Section IV, 1 | |
| Alkaline phosphatase from *E. coli* | 80000 | 40000 | 2 | D/M, F | Dissociation into polypeptide chains (probably identical) is reversible, with reactivation. | [32] |
| Enolase from rabbit skeletal muscle | 82000 | 40000 | 2 | D/M, EA | Dissociation into polypeptide chains is reversible, with reactivation. | [33] |
| Procarboxypeptidase A-S6 from beef pancreas | 87000 | 34500 and 2 x ≈25000 | 3 | D/M, EA | The polypeptide chain having M.W. 34500 and one of the two having M.W. about 25000 are the inactive forms of carboxypeptidase A and of an endopeptidase. The function of the third polypeptide chain is unknown. | [34] |
| Hexokinase from yeast | 96000 | 24000 | 4 | D/M, EA,F | Dissociation into polypeptide chains (probably identical) is reversible, with reactivation. The molecule can dissociate into two enzymatically active sub-units. | [35] |
| Hemerythrin from *Golfingia gouldii* | 107000 | 13500 | 8 | C, D/M | Dissociation into the polypeptide chains is reversible, with recovery of the ability to bind $O_2$. | [36] |
| Tryptophane synthetase from *E. coli*, B protein | 117000 | 60000 | 2 | C, EA | The sedimentation coefficient of 1.2 S indicates the presence of more than two polypeptide chains. The A protein consists of only one polypeptide chain (M.W. 29500). The A and B proteins form a functional unit. | [37] |
| Aldolase from rabbit skeletal muscle | 142000 | 23500 | 6 | D/M | See Section IV, 4. | |
| γ-Globulins from various species | 150000 | 25000 and 50000 | 2 each | D/M | See Section IV, 3. | |
| Thetin homocysteine methylpherase from horse liver | 180000 | 50000 | 3–4 | D/M | Enzyme aggregates, probably with formation of disulfide bridges. Depolymerized by compounds that cleave disulfides. Specific activity independent of particle size. | [38] |
| Fumarase from pig heart muscle | 194000 | 48500 | 4 | D/M, EA, F | Dissociation into polypeptide chains (probably identical) is reversible, with reactivation. | [39] |
| Catalase from beef liver | 240000-248000 | 65000 | 4 | C, D/M, EM, F | Fingerprint analysis indicates four identical polypeptide chains. The dissociation product (M.W. 65000) may consist of several dissimilar polypeptide chains. At pH 3, catalase dissociates into two sub-units having M.W. 120000. | [40] |
| Edestin from hemp seed | 300000-360000 | 23000 and 27000 | 6–7 each | D/M, EA, F | The two dissimilar polypeptide chains (in one sub-unit) may be joined together by disulfide bridges. | [42] |
| Fibrinogen from beef serum | 340000-390000 | 51000-65000 | 6 | D/M, EA | Six polypeptide chains, probably as three sets of two identical chains. | [44] |
| Lipovitellin from egg yolk | 400000 | 200000 | 2 | D/M | Lipid content 20%. Dissociation is reversible. The molecular weight of the polypeptide chain appears to be less than 100000 (end-group analysis). | [45] |
| Apoferritin from horse spleen | 480000 | 24000 | 20 | D/M, EA, EM, F, X | See Section IV, 2. Dimerization was observed [45a]. | |
| Glycogen phosphorylase from rabbit skeletal muscle | 495000 | 135000 | 4 | C, D/M | See Section IV, 6. | |
| Urease from jack-bean meal | 483000 | 83000 | 6 | D/M | Larger associates were observed. | [46] |
| β-Galactosidase from *E. coli* | 518000 | 35000-40000 | 12–16 | D/M | See Section IV, 7. | |
| DNA-dependent RNA-polymerase from *E. coli* | 600000-900000 | 100000-150000 | 6 | EM | | [47] |
| Bromegrass mosaic virus | 4600000 | 20000 | ≈ 180 | F | RNA content 21.4%. Treatment with 1 M $CaCl_2$ yields sub-units with M.W. 40000. | [48] |

| Protein | M.W. | Polypeptide chain | | | Notes | Ref. |
|---|---|---|---|---|---|---|
| | | M.W. | Number | Method [a] | | |
| Turnip yellow mosaic virus | 5000000 | 21300 | ≈ 150 | D/M, EA, EM, F, X | RNA content 37%. Polypeptide chains are probably identical. | [49] |
| Poliomyelitis virus (Sabin type II) | 5500000 | 27000 | ≈ 130 | D/M | RNA content 36%. | [50] |
| Alfalfa mosaic virus | 7400000 | ≈36000 | ≈ 160 | D/M | RNA content 21%. | [51] |
| Potato X virus | 35000000 | 52000 | ≈ 650 | D/M | RNA content 5%. End-group analysis indicates that the polypeptide chains are identical. | [52] |
| Tobacco mosaic virus | 39400000 | 17530 | 2130 | D/M, EA, F, X, S | RNA content 5%. Dissociation into identical polypeptide chains and RNA is reversible. Sub-units of different sizes occur as dissociation products. | [53] |

[a] C Determination of "cofactor binding sites"; D/M = Molecular weight determination after denaturation; EA = End-group analysis; EM Electron microscopy; F = Fingerprint analysis; X = X-ray analysis; S = Complete or partial sequence analysis.

ably not single polypeptide chains. The geometrical arrangement of the sub-units (Fig. 3) has been found by electron microscopy [55,56].

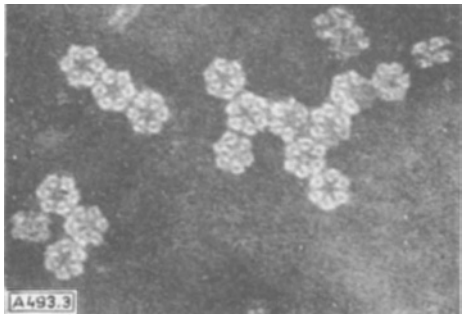


Fig. 3. Erythrocruorin from *Eumenia crassa* (after *Levin* [56]).


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The structures of the respiratory proteins of mammals, *i.e.* hemoglobin and myoglobin, are the best known of all protein structures. Not only has the amino-acid sequence been completely elucidated [57–59], but the spatial structure has also been analysed by X-ray methods [10, 11, 60] (cf. Fig. 1).

The adult human hemoglobin (HB–A, molecular weight 64458) consists of two pairs of identical polypeptide chains, *i.e.* four chains in all [57–60]. The two types of chain are denoted by $\alpha$ and $\beta$, so that HB–A has the formula $\alpha_2\beta_2$. In addition to HB–A, a second hemoglobin (HB–$A_2$:$\alpha_2\delta_2$) is present at a low concentration, while fetal blood contains HB–F ($\alpha_2\gamma_2$). The $\alpha$ chains of these types are all identical; the $\gamma$ and $\delta$ chains differ from the $\beta$ chain, but all four polypeptide chains exhibit numerous coincidences, and they all have the same or similar chain lengths [61].

Each polypeptide chain carries a heme group, which is the point of attachment of oxygen. The binding of oxygen affects the interaction between the polypeptide chains [11, 63], which can be seen from the fact that attachment of the first molecule of oxygen facilitates the uptake of the other three (see Section V.4) [63a].

## 2. Apoferritin from Horse Spleen

Ferritin is an iron-storage protein, and consists of two components: an iron(III) hydroxide-phosphate complex forms the nucleus, and this is surrounded by a protein shell, the apoferritin, which can be isolated and crystallized.

X-ray analysis gives a molecular weight of 480000 for the compact molecule [64]. The native apoferritin molecule has a very stable structure, although the polypeptide chains are only linked by non-covalent bonds. The protein ($s^0_{20,w}$ = 17.6 S) dissociates in the presence of dodecyl sulfate (DS). At a weight ratio of protein: DS = 2:1, the protein dissociates completely into components the sedimentation coefficient of which is 2.5 S. These components are protein-DS complexes (33% DS) with a molecular weight between 38000 and 41000, the protein component having a molecular weight between 25000 and 27000; thus the reaction with DS causes apoferritin to dissociate into about 20 identical polypeptide chains [65]. Reaction with succinic anhydride yields the same protein components (molecular weight 25000) [66].

Fingerprint analysis indicates about 20 peptides (apart from a few trace peptides), only one of which contains tryptophan. This corresponds to 20 identical polypeptide chains having a molecular weight of 24000 each [67]. There are no free N-terminal groups, but 20 acetyl groups can be detected per molecule of apoferritin. Carboxypeptidase B splits off about 20 C-terminal arginyl residues per molecule of apoferritin [66].

According to the results of X-ray analysis, the molecule forms a spherical shell with an outside radius of 61 Å and a ratio of inside radius: outside radius of 0.6 [64, 67a]. The shell has the form of a pentagonal dodecahedron with the 20 polypeptide chains (which, according to electron-microscope studies [68], are roughly spherical) situated at its twenty vertices [64] (Fig. 4).

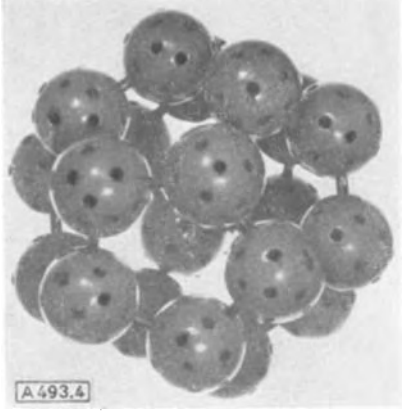


Fig. 4. Model of the quaternary structure of apoferritin, as suggested by *Harrison* [64]: 20 polypeptide chains at the corners of a pentagonal dodecahedron. (Each sphere represents a polypeptide chain; in the real molecule, the chains are in contact with one another and are not perfectly spherical).

## 3. $\gamma$-Globulins

The $\gamma$-globulins, the carriers of the antibody activity, have sedimentation coefficients of about 7 S and molecular weights of about 150000 [69, 70]. The molecules can be described as elongated prisms with an elliptical cross section [71] (see Fig. 5). Investigations on $\gamma$-globulins from various sources [69, 70, 72–75] indicate that they

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$$\begin{matrix}\alpha\beta\\ \beta\alpha\end{matrix} + \alpha^0\beta^0 \rightleftharpoons \begin{matrix}\alpha^0\beta^0\\ \beta\alpha\end{matrix} + \alpha\beta$$

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have the formula $H_2L_2$, *i.e.* they consist of two heavy chains (H, molecular weight about 50000) and two light chains (L, molecular weight about 25000). The two H chains are linked by a disulfide bridge [76], and each of the H chains is attached to an L chain by a disulfide bridge [73, 77, 78]. After reduction of these bridges, H and L chains can be separated by chromatography. Further disulfide bridges are present within the individual chains. In acidic solutions, reduction of the particularly reactive disulfide bridge between the two H chains yields the sub-unit HL [75].

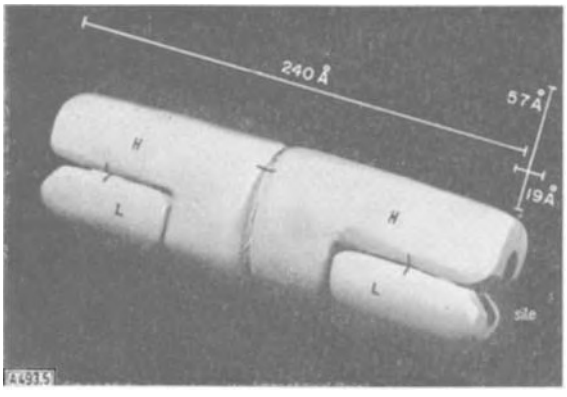


Fig. 5. Model of the 7-S antibody molecule after *Edelman* and *Gally* [74]. H: heavy polypeptide chain; L: light polypeptide chain; Site: one of the two antigen-binding sites. The lines on the model represent the disulfide bridges between the polypeptide chains. The molecular dimensions correspond to the results of low-angle X-ray diffraction measurements [71].

The antibody molecule has two sites at which antigens can become attached [79]; electron-microscope studies [80] indicate that these are situated at the ends of the cylindrical molecule ("site" in Fig. 5). The dissociation into the HL sub-units can be reversed, with recovery of immunological activity [81], although the disulfide bridge seems not to be re-formed. H and L chains obtained by mild reduction and chromatographic separation also re-associate to form the molecule $H_2L_2$, the chains again being held together only by non-covalent bonds [82], and the biological activity being restored. If the polypeptide chains in the renatured molecule are in fact held togehter by non-covalent bonds alone [81, 82], the antibody activity cannot be associated with the presence of disulfide bridges between the chains. Hybrid γ-globulin molecules [84] can be obtained *in vitro* by dissociation and association [81–83].

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## 4. Aldolase from Rabbit Skeletal Muscle [85]

Aldolase catalyses the conversion of fructose 1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. The enzyme molecule is almost spherical, and has a relatively high helical content; its molecular weight is 142000 [88]. Below pH 3, the sedimentation coefficient decreases from 7.9 S (native) to 2.0 S; the aldolase molecule dissociates into three sub-units of equal size, with extensive unfolding and loss of helical structure [88, 89]. This dissociation also takes place in the presence of dodecyl sulfate [88], urea [88], or guanidine hydrochloride [90], as well as on reaction with succinic anhydride [90].

Aldolase that has been treated with acid or urea regains up to 100% of its original activity on dialysis or on rapid dilution with buffer [88, 89, 91]. The hydrodynamic, optical, immunological, and chemical properties of the renatured molecule are identical with those of the native molecule. The association probably proceeds in two steps. Three sub-units combine relatively rapidly to form a complex which is still largely unfolded; the transformation of this into the native compact molecule is accompanied by the return of the enzymatic activity [89]. Kinetic analysis of the re-activation indicates that the first step is not rate-determining [88, 89].

When the pH is increased to 12.6, the aldolase dissociates into six fragments of equal size; these are probably the polypeptide chains. Re-activation after this dissociation has so far not been observed [92]. Equation (2) shows the dissociation scheme of aldolase (A) [92].

$$\underset{(142000)}{\text{Native A}} \rightleftharpoons \underset{(142000)}{\text{unfolded A}} \rightleftharpoons \underset{(3\times 47000)}{\text{sub-units}} \overset{?}{\rightleftharpoons} \underset{(6\times 23500)}{\text{polypeptide chains}}$$

Recent analysis of the N-terminal groups indicates 4 moles of proline per mole of aldolase. This value is regarded as a minimum, and supports the belief that the molecule contains more than three polypeptide chains [90, 92a]. Carboxypeptidase splits off three C-terminal tyrosine residues [93]. The

[84] Regarding the identity of the polypeptide chains and the problem of explaining the specificity of the antibodies obtained by combination of various types of H and L polypeptide chains, see [74].

[85] It was observed as early as the 1930's that aldolase is composed of sub-units [86, 87]. *Gralén* [87] obtained a value of 72000 for the molecular weight in urea, and assumed that the molecule had dissociated into two sub-units (instead of three, see text). *Gralén* also observed the marked decrease in the sedimentation coefficient in alkaline solutions. As far as we know aldolase (formerly known as myogen) is the first enzyme for which the quaternary structure was established.

[86] *R. Stöver*, Biochem. Z. *259*, 269 (1933).

[87] *N. Gralén*, Biochem. J. *33*, 1342 (1939).

[88] *E. Stellwagen* and *H. K. Schachman*, Biochemistry *1*, 1056 (1962).

[89] *W. C. Deal*, *W. J. Rutter*, and *K. E. van Holde*, Biochemistry *2*, 246 (1963).

[90] *L. F. Hass*, Biochemistry *3*, 535 (1964).

[91] *E. W. Westhead*, *L. Butler*, and *P. D. Boyer*, Biochemistry *2*, 927 (1963).

[92] *L. F. Hass* and *M. S. Lewis*, Biochemistry *2*, 1368 (1963).

[92a] According to a recent investigation of the C-terminal and N-terminal groups [*J. A. Winstead* and *F. Wold*, J. biol. Chemistry *239*, 4212 (1964)], the aldolase molecule consists of only three polypeptide chains having a molecular weight of 47000, two of which may be identical. The components with a molecular weight of 23500 [92] could result from the cleavage of an alkali-labile bond within a polypeptide chain.

[93] *A. Kowalsky* and *P. D. Boyer*, J. biol. Chemistry *235*, 604 (1960).

question of whether all the polypeptide chains are identical is of special interest since aldolase consists of six polypeptide chains, but contains only one active center [91,94].

## 5. Lactic Dehydrogenase and the Isoenzyme Problem

Lactic dehydrogenases (LDH) are found in all animal tissues. They catalyse the reversible pyridine nucleotide-dependent oxidation of lactic acid to pyruvic acid. The enzymes have molecular weights of about 130000 [95–98]. It was observed in 1952 that ox heart LDH consists of two enzymatically active components [95]. *Wieland* and *Pfleiderer* subsequently showed [99] that various tissues can contain up to five LDH's, and that it is very rare for one to occur alone. These LDH's can be separated by electrophoresis, and they are found to differ in their amino-acid composition, their sensitivity to heat, and their enzymatic and immunological properties [99–108,110d].

*Appella* and *Markert* showed that in the presence of 5 M guanidine hydrochloride, LDH dissociates into four sub-units, each of which has a molecular weight of 34000 [96]. Every species possesses two LDH's which consist of four identical sub-units [96,100,103,105,106,109]. One of these LDH's occurs mainly in the muscle (M type), the other mainly in the heart (H type); the sub-units are accordingly denoted by M and H, so that the formulae of these LDH's are $M_4$ and $H_4$. Combination of M and H sub-units gives (*in vivo* and *in vitro*) a maximum of five LDH isoenzymes: $H_4$, $H_3M$, $H_2M_2$,$HM_3$, and $M_4$. This is confirmed by the fingerprint analysis [102,109,110,110a].

The dissociation into sub-units can be largely reversed, with re-activation of the enzyme [110c]. Moreover, hybridization between lactic dehydrogenases from various sources, *e.g.* between $H_4$-LDH from cattle and $H_4$-LDH from hens or $M_4$-LDH from frogs, can be carried out *in vitro*. On the other hand, hybridization between frog $H_4$-LDH and frog $M_4$-LDH has not been possible. No information is available which would indicate that the sub-units by themselves are enzymatically active. The interactions between the four sub-units seem to be essential for enzymatic activity.

The enzymatic and immunological properties of the hybrid LDH molecules $H_3M$, $H_2M_2$, and $HM_3$ are roughly equivalent to an additive combination of the contributions from the H and M sub-units [102–104,109,110d]. For example, substrate inhibition is strong in the case of $H_4$-LDH and weak in the case of $M_4$-LDH; for the hybrid types it lies somewhere between these extremes [101–103,107]. In agreement therewith, the H type favors aerobic oxidation of pyruvic acid and occurs mainly in "aerobic" tissue (heart muscle). The M type, on the other hand, favors the anaerobic pyridine nucleotide-dependent formation of lactic acid, and occurs mainly in "anaerobic" tissue (skeletal muscle) [102,103,107,112].

The LDH isoenzyme pattern changes during ontogeny [102,103,112–114]. In the embryonic state, H or M type LDH is present exclusively or mainly depending on the species ("embryonic LDH"). With increasing cell differentiation an isoenzyme pattern is formed which corresponds to the alterations in metabolism of the differentiated cell (Fig. 6). It is assumed that the synthesis of H and M sub-units is controlled by different genes [102].

## 6. Glycogen Phosphorylase from Rabbit Skeletal Muscle

Glycogen phosphorylase occurs in two forms, a and b, which can be interconverted by the action of enzymes: thus in the presence of a phosphorylase b-kinase, the b enzyme takes up four moles of phosphate from ATP to form the a enzyme, which is reconverted into the b enzyme by a phosphorylase a-phosphatase [115].

Sedimentation and diffusion measurements indicate the molecular weight of the a enzyme to be 495000 and that

[94] *E. Grazi, T. Cheng*, and *B. L. Horecker*, Biochem. biophys. Res. Commun. *7*, 250 (1962).

[95] *J. B. Neilands*, J. biol. Chemistry *199*, 373 (1952).

[96] *E. Appella* and *C. L. Markert*, Biochem. biophys. Res. Commun. *6*, 171 (1961).

[97] *R. Jaenicke*, Biochem. Z. *338*, 614 (1963); Biochim. biophysica Acta *85*, 186 (1964).

[98] *G. Di Sabato* and *N. O. Kaplan*, J. biol. Chemistry *239*, 438 (1964).

[99] *T. Wieland* and *G. Pfleiderer*, Biochem. Z. *329*, 112 (1957); Angew. Chem. *74*, 261 (1962); Angew. Chem. internat. Edit. *1*, 169 (1962); *G. Pfleiderer* and *D. Jeckel*, Biochem. Z. *329*, 370 (1957).

[100] *T. Wieland, G. Pfleiderer*, and *F. Ortanderl*, Biochem. Z. *331*, 103 (1959).

[101] *P. G. W. Plagemann, K. F. Gregory*, and *F. Wróblewski*, J. biol. Chemistry *235*, 2282, 2288 (1960); Biochem. Z. *334*, 37 (1961).

[102] *C. L. Markert* and *H. Ursprung*, Development. Biol. *5*, 363 (1962); *C. L. Markert* in *M. Locke*: Cytodifferentiation and Macromolecular Synthesis. Academic Press, New York, London 1963, p. 65.

[103] *R. D. Cahn, N. O. Kaplan, L. Levine*, and *E. Zwilling*, Science (Washington) *136*, 962 (1962).

[104] *J. S. Nisselbaum* and *O. Bodansky*, J. biol. Chemistry *238*, 969 (1963); Ann. New York Acad. Sci. *103*, 930 (1963).

[105] *C. L. Markert*, Science (Washington) *140*, 1329 (1963); Abstracts, 6th int. Congress of Biochemistry, New York 1964, p. 320.

[106] *C. R. Shaw* and *E. Barto*, Proc. nat. Acad. Sci. U.S.A. *50*, 211 (1963).

[107] *A. C. Wilson, R. D. Cahn*, and *N. O. Kaplan*, Nature (London) *197*, 331 (1963).

[108] *E. D. Wachsmuth, G. Pfleiderer*, and *T. Wieland*, Biochem. Z. *340*, 80 (1964).

[109] *T. P. Fondy, A. Pesce, I. Freedberg, F. Stolzenbach*, and *N. O. Kaplan*, Biochemistry *3*, 522 (1964).

[110] It is not yet known whether this also applies to rat liver LDH. This enzyme has a molecular weight of 126000, and contains only two coenzyme-binding sites [111]. Results obtained with the other dehydrogenases (Section IV,10) suggest that this LDH consists of only two polypeptide chains having a molecular weight of 63000 each.

[110a] Studies of the hydrodynamic properties after denaturation [27,97] and of the N-terminal groups, as well as fingerprint analysis [110b] suggest that LDH consists of a total of eight polypeptide chains, each sub-unit containing two.

[110b] *E. Appella* in [110d], in particular p. 151.

[110c] *C. J. Epstein, M. M. Carter*, and *R. F. Goldberger*, Bio chim. biophysica Acta *92*, 391 (1964).

[110d] *N. O. Kaplan*, Brookhaven Symposia in Biology *17*, 131 (1964).

[111] *E. O. Davisson, D. M. Gibson, B. R. Ray*, and *C. S. Vestling*, J. physic. Chem. *57*, 609 (1953); *H. Terayama* and *C. S. Vestling*, Biochim. biophysica Acta *20*, 586 (1956); *C. S. Vestling* in *D. Glick*: Methods of Biochemical Analysis. Interscience, New York, London 1962, Vol. 10, p. 137.

[112] *G. Pfleiderer* and *E. D. Wachsmuth*, Biochem. Z. *334*, 185 (1961).

[113] *D. T. Lindsay*, J. exp. Zoology *152*, 75 (1963).

[114] *I. H. Fine, N. O. Kaplan*, and *D. Kuftinec*, Biochemistry *2*, 116 (1963).

[115] *D. H. Brown* and *C. F. Cori* in *P. D. Boyer, H. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd edit., Academic Press, New York, London 1961, Vol. 5, p. 207; *E. G. Krebs* and *E. H. Fischer*, Advances Enzymology *24*, 263 (1962).

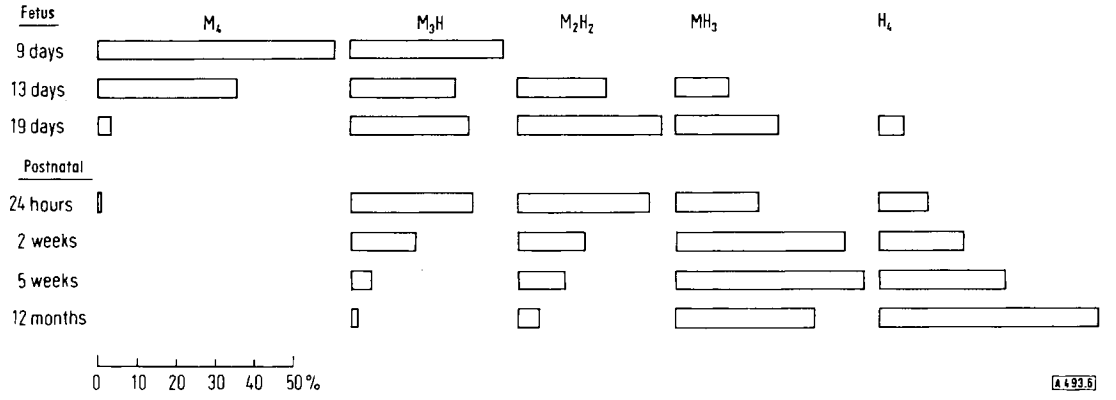


Fig. 6. LDH isoenzyme pattern of the rat heart during ontogeny (values from *Fine et al.* [114]).

of the b enzyme 242000. The conversion of the b enzyme into the a enzyme thus involves dimerization as well as phosphorylation [116].

When treated with *p*-chloromercuribenzoate, both enzymes dissociate into sub-units having a molecular weight of about 135000. The a enzyme contains four of these sub-units, and the b enzyme two [117, 118]. In agreement with this structure, one molecule of the a enzyme binds four molecules of AMP and contains four molecules of pyridoxal 5'-phosphate, whereas the b enzyme binds two molecules of AMP and contains two molecules of pyridoxal 5'-phosphate [115, 119–121]. In the formation of the a enzyme from b enzyme, the four additional phosphate groups (*i.e.* one per sub-unit) are bound by esterification of seryl groups [115]. The pyridoxal phosphate, which probably is covalently bound to lysyl groups, is probably responsible for the conformation of the protein molecule, but is not involved in the enzyme reaction itself [122]. Its removal from the molecule leads to reversible inactivation, accompanied by a change in the conformation of the protein: the a enzyme is largely dissociated into sub-units. The cleavage by *p*-chloromercuribenzoate is also reversible, and the original associated state, together with the enzyme activity, can be restored by treatment with cysteine [117].

At high salt concentrations, phosphorylase a dissociates reversibly to form "half-molecules", which have the same molecular weight as the b enzyme [123, 123a]. Since phosphorylase b is built up from two sub-units, it is understandable that three isoenzymes have been found [124]. The relatively high molecular weight of the sub-units (135000) suggests that they may contain more than one polypeptide chain.

[116] *P. J. Keller* and *G. T. Cori*, Biochim. biophysica Acta *12*, 235 (1953).

[117] *N. B. Madsen* and *C. F. Cori*, J. biol. Chemistry *223*, 1055 (1956).

[118] *N. B. Madsen*, J. biol. Chemistry *223*, 1067 (1956).

[119] *N. B. Madsen* and *C. F. Cori*, J. biol. Chemistry *224*, 899 (1957).

[120] *T. Baranowski, B. Illingworth, D. H. Brown*, and *C. F. Cori*, Biochim. biophysica Acta *25*, 16 (1957).

[121] *A. B. Kent, E. G. Krebs*, and *E. H. Fischer*, J. biol. Chemistry *232*, 549 (1958).

[122] *E. H. Fischer, A. W. Forrey, J. L. Hedrick, R. C. Hughes, A. B. Kent*, and *E. G. Krebs* in *E. E. Snell, P. M. Fasella, A. Braunstein*, and *A. Rossi Fanelli*: Chemical and Biological Aspects of Pyridoxal Catalysis. Pergamon Press, Oxford, London, New York, Paris 1963, p. 543.

[123] *J. H. Wang* and *D. J. Graves*, J. biol. Chemistry *238*, 2386 (1963).

[123a] Note added in proof: Under certain conditions glucose causes partial dissociation of the phosphorylase-a molecule into sub-units (molecular weight 240000). This is accompanied by an increase in the enzymatic activity [*J. H. Wang et al.*, Biochem. biophys. Res. Commun. *18*, 131 (1965); cf. also Biochemistry *4*, 2296 (1965)]. The protein molecule also dissociates at high ionic strength or at low protein concentration [*J. H. Wang* and *D. J. Graves*, Biochemistry *3*, 1437 (1964)].

[124] *C. H. Davis, R. B. Olsgaard, E. H. Fischer*, and *E. G. Krebs*, Federat. Proc. *23*, 488 (1964).

## 7. β-Galactosidase from E. coli

β-Galactosidase from *E. coli* catalyses the hydrolysis of lactose to galactose and glucose. The molecular weight of the protein is about 520000, and its sedimentation coefficient is about 16 S [125–128]. The hydrodynamic data indicate that the molecule can be described as an oblate ellipsoid of revolution [125] with an axial ratio of about 3, assuming 30% hydration. The length and height of the molecule are about 150 and 50 Å respectively [127]. The molecular weight remains unchanged even at extremely high dilutions [129], and is very probably also characteristic of the enzymatically active protein *in vivo* [130, 131].

Urea or guanidine hydrochloride cause reversbile [128] dissociation of the β-galactosidase molecule into four sub-units, which appear from sedimentation and diffusion measurements to be equal in size [132] (molecular weight about 130000). It is therefore possible to obtain hybrids of "light" enzyme ($^{12}C$, $^{14}N$) and "heavy" enzyme ($^{13}C$, $^{15}N$), and to compare the densities. The results again show that the β-galactosidase molecule consists of four sub-units of equal size [128]. Electron-microscope studies [133, 134] indicate that the four sub-units are arranged at the corners of a square (Fig. 7). The dimensions of the molecule are about 120 Å and 70 Å [133]. These values and the molecular weight (500000) calculated from them [133, 134] agree closely with the values obtained from hydrodynamic data.

On oxidation with performic acid, the molecular weight decreases to about 35000 [132, 135]. The β-galactosidase

[125] *H. Sund* and *K. Weber*, Biochem. Z. *337*, 24 (1963).

[126] *A. S. L. Hu, R. G. Wolfe*, and *F. J. Reithel*, Arch. Biochem. Biophysics *81*, 500 (1959).

[127] *K. Weber*, Doctorate Dissertation, Universität Freiburg 1964.

[128] *D. Zipser*, J. molecular Biol. *7*, 113 (1963).

[129] *B. Rotman*, Proc. nat. Acad. Sci. U.S.A. *47*, 1981 (1961). More recent results indicate a molecular weight of about 500000 (personal communication).

[130] *E. Pollard* in *J. L. Oncley et al.*: Biophysical Science. Wiley, New York 1959, p. 273.

[131] *D. Zipser*, J. molecular. Biol. *7*, 739 (1963).

[132] *K. Weber, H. Sund*, and *K. Wallenfels*, Angew. Chem. *75*, 642 (1963); Angew. Chem. internat. Edit. *2*, 481 (1963); *K. Wallenfels, H. Sund*, and *K. Weber*, Biochem. Z. *338*, 714 (1963).

[133] *U. Karlsson, S. Koorajian, I. Zabin, F. S. Sjöstrand*, and *A. Miller*, J. Ultrastructure Res. *10*, 457 (1964).

[134] *E. Mölbert, K. Weber*, and *K. Wallenfels*, unpublished work.

Fig. 7. β-Galactosidase from *E. coli* (after *Mölbert, Weber*, and *Wallenfels* [134]). Magnification 200000. The arrow indicates a β-galactosidase molecule consisting of four sub-units.

molecule also dissociates into the polypeptide chains (molecular weight about 35000) in a mixture of formic and acetic acids [136], showing that each sub-unit of β-galactosidase consists of three or four polypeptide chains, which are not joined by disulfide bridges. This dissociation, too, is at least partly reversible.

Fingerprint analysis gave values of about 40000 [137] and 60000 [137, 138] for the "molecular weight" of the polypeptide chain. If the higher value is correct, it must be assumed, from the discrepancy between this and the much lower value obtained by hydrodynamic methods, that not all polypeptide chains making up the sub-unit are identical [136, 138a].

The β-galactosidase molecule contains four active centers [139], which can be assigned to the four sub-units. However, the number of polypeptide chains is greater than the number of active centers [140].

Enzymatically inactive β-galactosidase proteins have been isolated from some *E. coli* mutants [142]. The molecular weights of these proteins are generally lower than that of the enzymatically active β-galactosidase. Mutation thus appears to have deprived the protein of the ability to associate "correctly". It was possible in some cases to obtain enzymatically active β-galactosidase by complementation between two different inactive samples [142, 143]; the active enzyme ("complementation enzyme") obtained in this way, like the normal enzyme, has a sedimentation coefficient of 16 S.

### 8. Glutamic Dehydrogenase from Beef Liver

Glutamic dehydrogenase catalyses the reversible oxidative deamination of glutamic acid to α-ketoglutaric acid. The spontaneous reversible dissociation of the protein on dilution explains its anomalous sedimentation behavior [144]. The long, associated particle, which has a molecular weight of $2\times10^6$ [29, 145], exists in an association-dissociation equilibrium with its sub-units, the molecular weights of which are $10^6$, $5\times10^5$, and $2.5\times10^5$, and all of which are enzymatically active [29, 146]. Nucleotides, phenanthroline, inorganic ions, steroids, thyroxine, sulfonylurea derivatives, or even the coenzyme can displace the equilibrium in either direction, and act as inhibitors or activators of the enzyme reaction [29, 147–150]. The dissociation leads to an increase in the binding capacity for the coenzyme [151, 153, 155].

In the liver glutamate dehydrogenase occurs almost entirely within the mitochondria. Here the enzyme concentration is very high (between 2 and 9 mg/ml), *i.e.* in a range in which the association-dissociation equilibrium and the influence on it of nucleotides, coenzymes, and the other compounds mentioned are significant [29, 153].

Glutamic dehydrogenase has no absolute substrate specificity for glutamic acid, but can react (although much more slowly) with other amino acids. The oxidation of alanine has been particularly closely studied in connection with quaternary structure [150]: All compounds or experimental conditions that favor spontaneous dissociation of the enzyme into sub-units activate the oxidation of alanine and inhibit the oxidation of glutamic acid. On the other hand, all compounds that favor spontaneous association activate the oxidation of glutamic acid and inhibit that of alanine. Contrary to earlier views [147, 150], the relationship between the effects on quaternary structure and enzyme activity is due to the fact that the compounds react with the functional groups of the enzyme molecule and/or alter the conformation of the latter. This reaction affects both the association-dissociation equilibrium and the enzymatic catalysis, although there is no direct connection between particle size and enzyme activity: both phenomena simply result from the same cause [29, 152–154].

[135] *K. Weber*, unpublished work.

[136] *K. Weber, H. Sund*, and *K. Wallenfels*, Biochem. Z. *339*, 498 (1964).

[137] *I. Zabin*, Cold Spring Harbor Sympos. quantitat. Biol. *28*, 431 (1963).

[138] *G. R. Craven, E. Steers*, and *C. B. Anfinsen*, Federat. Proc. *23*, 263 (1964).

[138a] Cf. also *E. Steers, G. R. Craven, C. B. Anfinsen*, and *J. L. Bethune*, J. biol. Chemistry *240*, 2478 (1965).

[139] *M. Cohn*, Bacteriol. Rev. *21*, 140 (1957).

[140] The size of the structural gene (= z-gene) of the *E. coli* chromosome responsible for the synthesis of β-galactosidase corresponds to a "polypeptide chain equivalent" of 135000 [141]. Since the polypeptide chains of the β-galactosidase molecule are not more than one-third of this size, the z-gene cannot be the polypeptide chain equivalent. It must therefore be assumed that the z-gene is a genetically functional unit, which also corresponds to a certain unit in the protein molecule. This could be the identical sub-units having a molecular weight of about 130000. The z-gene would then consist of several gene segments corresponding to the polypeptide chains, which consequently should not be identical [127, 138a].

[141] *F. Jacob* and *E. L. Wollman*: Sexuality and the Genetics of Bacteria. Academic Press, New York, London 1961, p. 253 *et seq.*

[142] *D. Perrin*, Cold Spring Harbor Sympos. quantitat. Biol. *28*, 529 (1963).

[143] *D. Zipser* and *D. Perrin*, Cold Spring Harbor Sympos. quantitat. Biol. *28*, 533 (1963).

[144] *J. A. Olson* and *C. B. Anfinsen*, J. biol. Chemistry *197*, 67 (1952).

[145] *H. Sund*, Acta chem. scand. *17*, S 102 (1963).

[146] *H. Kubo, T. Yamano, M. Iwatsubo, H. Watari, T. Soyama, J. Shiraishi, S. Sawada, N. Kawashima, S. Mitani*, and *K. Ito*, Bull. Soc. Chim. biol. *40*, 431 (1958); *C. Frieden*, J. biol. Chemistry *237*, 2396 (1962); *J. E. Churchich* and *F. Wold*, Biochemistry *2*, 781 (1963).

[147] *C. Frieden*, J. biol. Chemistry *234*, 809, 815 (1959).

[148] *H. Sund* in *M. Demole*: Proc. 4e Congrès de la Fédération intern. du Diabète. Editions Médecine et Hygiène, Geneva 1961, Vol. 1, p. 726.

[149] *J. Wolff*, J. biol. Chemistry *237*, 230 (1962).

[150] *G. M. Tomkins* and *E. S. Maxwell*, Annu. Rev. Biochem. *32*, 677 (1963); *G. M. Tomkins, K. L. Yielding*, and *J. Curran*, Proc. nat. Acad. Sci. U.S.A. *47*, 270 (1961).

[151] *H. Sund*, Acta chem. scand. *15*, 940 (1961).

[152] *C. Frieden*, J. biol. Chemistry *238*, 3286 (1963).

[153] *H. Sund*: Habilitation Thesis, Universität Freiburg 1964.

[154] *G. M. Tomkins, K. L. Yielding, J. F. Curran, M. R. Summers*, and *M. W. Bitensky*, J. biol. Chemistry *240*, 3793 (1965).

[155] Cf. also *G. M. Tomkins, K. L. Yielding*, and *J. F. Curran*, J. biol. Chemistry *237*, 1704 (1962); *P. M. Bayley* and *G. K. Radda*, Biochem. J. *94*, 31P (1965).

If a protein dissociates spontaneously into its sub-units, or if the dissociation is brought about by conditions under which there is little change in conformation, it is possible to obtain information about the geometrical arrangement of the sub-units by means of viscosity measurements. A decrease in the intrinsic viscosity indicates a decrease in geometrical anisotropy and *vice versa*. This method is successful only for non-globular proteins, since the change in viscosity on dissociation of globular proteins is too small [153].

The sub-unit of glutamic dehydrogenase has a lower intrinsic viscosity than the original molecule, and is only about half as long as the latter [29, 145, 153]. If we regard the glutamic dehydrogenase molecule as an ellipsoid of revolution, this means that the dissociation involves a transverse cleavage. In the associated state, therefore, the sub-units must be held together over relatively small areas, and hence by relatively few bonds. Perhaps this can explain the spontaneous dissociation (cf. Fig. 8).

In the presence of urea or long-chain alkyl sulfates, or at extreme pH values, the sub-unit having a molecular weight of 250000 dissociates into polypeptide chains, with loss of the native conformation and enzymatic activity. The polypeptide chains obtained in this way have a molecular weight of about 50000, and end group analysis indicates that they are all identical [29, 149, 156]. It has recently been shown that this dissociation is also largely reversible, again with re-activation [157] (cf. Fig. 8).

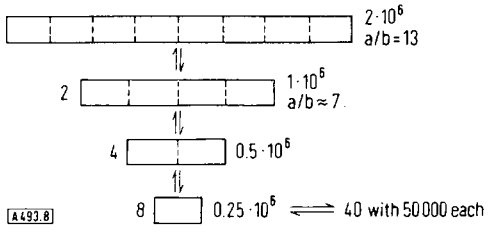


Fig. 8. Diagrammatic representation of the association-dissociation equilibrium of glutamic dehydrogenase from beef liver (after *Sund*[29]). a/b = axial ratio.

## 9. Multienzyme Complexes

Multienzyme complexes, in which the individual enzymes are held together by non-covalent bonds, catalyse successive steps of a reaction sequence. In the course of this process, the substrate and the intermediate products never leave the enzyme complex, but are "passed on" from one reaction site to the next. The occurrence of such complexes *in vivo* is probably relatively frequent. Whether they can be isolated depends on their stability and on the isolation conditions. The most extensively studied of these complexes are the fatty acid synthetase complex from yeast and the pyruvic dehydrogenase complex from *E. coli*.

According to *Lynen et al.* [158, 159], the fatty acid synthetase catalyses the synthesis of fatty acids in seven steps from acetyl-CoA and malonyl-CoA. This multienzyme complex has a molecular weight of $2.3\times10^6$, and consists of seven different sub-units (molecular weight 110000), each of which occurs three times. Electron-microscope studies show that the fatty acid synthetase complex is a hollow oval particle surrounded by an equatorial ring (Fig. 9). The longitudinal diameter of the particles is about 250 Å, and the transverse diameter about 210 Å [160].

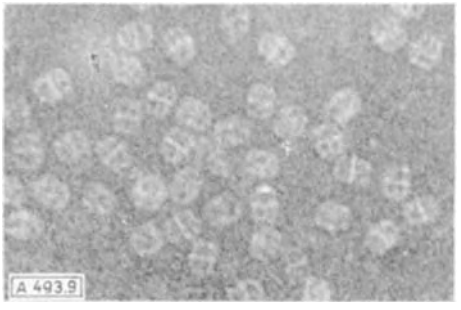


Fig. 9. Fatty acid synthetase from yeast (after *Hagen* and *Hofschneider* [160]). Magnification 200000.

The pyruvic dehydrogenase complex from *E. coli* catalyses the decarboxylation of pyruvic acid to acetyl-CoA, which involves at least three steps. According to *Reed et al.* [161, 162], this multienzyme complex (molecular weight $4.8\times10^6$) can be broken down into three enzymatically active components: pyruvate decarboxylase (molecular weight 183000), lipoic reductase-transacetylase (molecular weight $1.6\times10^6$) and dihydrolipoic dehydrogenase (molecular weight 112000). Lipoic reductase-transacetylase consists of 64 polypeptide chains (molecular weight about 27000), and is present only once in the multienzyme complex. Decarboxylase and dihydrolipoic dehydrogenase, on the other hand, are presen sixteen times and eight times, respectively. Dihydrolipoic dehydrogenase contains two polypeptide chains. The quaternary structure of the decarboxylase has not yet been investigated. Electron-microscope studies indicate that the pyruvic dehydrogenase complex has the form of a decahedron with a diameter of 300 to 400 Å and a height of 200 to 250 Å. The centrally located lipoic reductase-transacetylase is surrounded by the decarboxylase and the dihydrolipoic dehydrogenase both of which are arranged in the form of superimposed octagonal rings [161].

## 10. Other Pyridine Nucleotide-Dependent Dehydrogenases

The molecular weights, coenzyme binding, and quaternary structures of the dehydrogenases studied so far are listed in Table 2. It can be seen from this table that the

[156] *B. Jirgensons*, J. Amer. chem. Soc. *83*, 3161 (1961); *H. F. Fisher, L. L. McGregor*, and *D. G. Cross*, Biochim. biophysica Acta *65*, 175 (1962); *E. Marler* and *C. Tanford*, J. biol. Chemistry *239*, 4217 (1964); *H. Sund*, Biochim. biophysica Acta, in press. Acta *65*, 175 (1962); *H. Sund*, Biochem. Z., in press.

[157] *H. Sund*, Angew. Chem. *76*, 954 (1964); Angew. Chem. internat. Edit. *3*, 802 (1964).

[158] *F. Lynen*, Federat. Proc. *20*, 941 (1961); *F. Lynen* in *T. Bücher*: Redoxfunktionen cytoplasmatischer Strukturen. Eigenverlag der Wiener medizinischen Akademie für ärztliche Fortbildung, Vienna 1962, p. 121; Angew. Chem. *77*, 929 (1965).

[159] *A. Hagen*, Doctorate Dissertation, Universität München 1963.

[160] *A. Hagen* and *P. H. Hofschneider* in *M. Titlbach*: Electron Microscopy 1964 (Proc. 3rd European Regional Conference). Publishing House of the Czechoslovak Academy of Sciences, Prague 1964, Vol. B, p. 69.

[161] *M. Koike, L. J. Reed*, and *W. R. Carroll*, J. biol. Chemistry *238*, 30 (1963); *L. J. Reed*, Abstracts, 6th int. Congress of Biochemistry, New York 1964, p. 523; *H. Fernandez-Moran, L. J. Reed, M. Koike*, and *C. R. Willms*, Science (Washington) *145*, 930 (1964).

[162] For other complexes of α-keto acid dehydrogenases, see *D. R. Sanadi* in *P. D. Boyer, H. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd edit., Academic Press, New York, London 1963, Vol. 7, p. 307.

Table 2. Molecular weight, quaternary structure, and coenzyme binding of pyridine nucleotide-dependent dehydrogenases.

| Dehydrogenase (= DH) | M.W. | Polypeptide chain | | Equivalent weight per binding site | n [b] | Ref. |
|---|---|---|---|---|---|---|
| | | M.W. | Method [a] | | | |
| Vitamin K reductase from beef liver | 52000 | ? | | 56000 | ?; 1 | [163] |
| Isocitric DH from pig heart | 61000–64000 | ? | | ≈30000 | ?; 2 | [164] |
| L-Glycerol 1-phosphate DH from rabbit skeletal muscle | 78000 | 40000 | D/M | 39000 | 2; 2 | [165–167] |
| Malic DH from pig heart | 70000–85000 | 51000 | EA | 35000–42000 [c] | ≈2; 2 | [166, 168, 169] |
| Alcohol DH from horse liver | 84000 | 42000 | S [d] | 42000 | 2; 2 | [172–174] |
| Dihydrolipoic DH from pig heart | 102000 | 50000 [e] | D/M, EA, F | 50000 | 2; 2 | [175] |
| Dihydrolipoic DH from *E. coli* or *Spinacia oleracea* | 102000–112000 | ? | | 56000 | ?; 2 | [176] |
| Glutathione reductase from yeast | 118000 | ? | | 56500 | ?; 2 | [177] |
| 3-Phosphoglyceraldehyde DH from pig or rabbit skeletal muscle | 137000–145000 | 36000–40000 [d,f] | D/M, F, EA, S | 35000–46000 | 4; 4 | [27, 166, 167, 178–181a] |
| 3-Phosphoglyceraldehyde DH from yeast | 122000–140000 | 38000–44000 [d,f] | D/M, F, EA, S | 37000–40000 | 4; 4 | [167, 180–185] |
| Lactic DH from chicken, beef, or pig heart [g] | 118000–140000 | 34000–37000 | D/M, F, S | 36000–39000 | 4; 4 | [27, 95–98, 102, 109, 110d, 166, 186–189a] |
| Lactic DH from rat liver | 126000 | ? | | 64000 | ?; 2 | [111, 188] |
| Alcohol DH from yeast | 150000 | 36000–37000 [d,h] | D/M, F, S | 30000–42000 | 4; 4 | [29, 166, 173, 174, 188, 190] |
| Glutamic DH from *Neurospora crassa* | 267000 | 28000 [h] | F | ? | 8–10; ? | [191, 192] |
| Glutamic DH from beef liver [i] | 2000000 | 50000 | D/M, EA, EM | 31000–49000 | 40; 40–60 | [29, 145, 149, 153, 155–157, 166, 193] |

[a] For abbreviations, see Table 1.
[b] n = M.W. of the DH per M.W. of the polypeptide chain or M.W. of the DH per equivalent weight.
[c] The equivalent weights of the enzymes from horse heart [169], rat liver [170], and beef heart [171] are between 34000 and 50000.
[d] The partial elucidation of the amino-acid sequence suggests that the polypeptide chains are identical.
[e] End-group and fingerprint analyses indicate that the two polypeptide chains, which may be linked by disulfide bridges, are identical.
[f] End-group analysis indicates that the polypeptide chains are identical.
[g] Cf. Section IV, 5.
[h] Fingerprint analysis indicates that the polypeptide chains are identical.
[i] Cf. Section IV, 8.

molecular weights of the polypeptide chains always are approximately the same as the equivalent weights of the coenzyme binding sites. Most of the dehydrogenases consist of polypeptide chains with molecular weights of 30000 to 50000. This is probably also true for dehydrogenases that have not yet been studied [153, 166, 193a].


[163] *F. Märki* and *C. Martius*, Biochem. Z. *333*, 111 (1960).

[164] *J. Moyle* and *M. Dixon*, Biochem. J. *63*, 548 (1956); *G. Siebert*, *J. Dubuc*, *R. C. Warner*, and *G. W. E. Plaut*, J. biol. Chemistry *226*, 965 (1957); *T. A. Langan*, Acta chem. scand. *14*, 936 (1960).

[165] *J. van Eys*, *B. J. Nuenke*, and *M. K. Patterson*, J. biol. Chemistry *234*, 2308 (1959).

[166] *G. Pfleiderer* and *F. Auricchio*, Biochem. biophys. Res. Commun. *16*, 53 (1964).

[167] *W. C. Deal* and *W. H. Holleman*, Federat. Proc. *23*, 264 (1964).

[168] *C. J. R. Thorne*, Biochim. biophysica Acta *59*, 624 (1962).

[169] *C. J. R. Thorne* and *N. O. Kaplan*, J. biol. Chemistry *238*, 1861 (1963).

[170] *C. S. Vestling*, *E. D. Ihnen*, and *A. C. Boyer* in *N. M. Sissakian*: Proc., 5th int. Congress of Biochemistry, Moscow 1961. Pergamon Press, Oxford, London, New York, Paris 1963, Vol. 9, p. 163.

[171] *S. Englard* and *H. H. Breiger*, Biochim. biophysica Acta *56*, 571 (1962); *M. Cassman* and *S. Englard*, Federat. Proc. *23*, 427 (1964).

[172] *A. Ehrenberg* and *K. Dalziel*, Acta chem. scand. *12*, 465 (1958); *H. Theorell* and *A. D. Winer*, Arch. Biochem. Biophysics *83*, 291 (1959); *T. K. Li* and *B. L. Vallee*, Biochemistry *3*, 869 (1964); *T. K. Li*, *D. D. Ulmer*, and *B. L. Vallee*, Biochemistry *1*, 114 (1962).

[173] *H. Sund* and *H. Theorell* in *P. D. Boyer*, *H. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd edit., Academic Press, New York, London 1963, Vol. 7, p. 25.

[174] *I. Harris*, Nature (London) *203*, 30 (1964).

[175] *V. Massey*, *T. Hofmann*, and *G. Palmer*, J. biol. Chemistry *237*, 3820 (1962).

[176] *M. Koike*, *L. J. Reed*, and *W. R. Carroll*, Biochem. biophys. Res. Commun. *7*, 16 (1962); *J. Matthews* and *L. J. Reed*, J. biol. Chemistry *238*, 1869 (1963).

[177] *R. F. Colman* and *S. Black*, Federat. Proc. *23*, 428 (1964); J. biol. Chemistry *240*, 1796 (1965); *V. Massey* and *C. H. Williams*, *ibid. 240*, 4470 (1965).

[178] *W. F. Harrington* and *G. M. Karr*, J. molecular Biol. *13*, 885 (1965).

[179] *J. B. Fox* and *W. B. Dandliker*, J. biol. Chemistry *218*, 53 (1956); *221*, 1005 (1956); *S. F. Velick*, J. biol. Chemistry *233*, 1455 (1958); *H. G. Elias*, *A. Garbe*, and *W. Lamprecht*, Hoppe-Seylers Z. physiol. Chem. *319*, 22 (1960); *I. Harris*, *B. P. Meriwether*, and *J. H. Park*, Nature *198*, 154 (1963); *A. H. Gold* and *H. L. Segal*, Biochemistry *3*, 778 (1964); *A. L. Murdock* and *O. J. Koeppe*, J. biol. Chemistry *239*, 1983 (1964); *W. Ferdinand*, Biochem. J. *92*, 578 (1964).

[180] *J. F. Taylor* and *C. Lowry*, Biochim. biophysica Acta *20*, 109 (1956).

[181] *E. L. Taylor*, *B. P. Meriwether*, and *J. H. Park*, J. biol. Chemistry *238*, 734 (1963).

[181a] *J. I. Harris* in *T. W. Goodwin*, *J. I. Harris*, and *B. S. Hartley*: Structure and Activity of Enzymes. Academic Press, London, New York 1964, p. 97; *J. I. Harris* and *R. N. Perham*, J. molecular Biol. *13*, 876 (1965).

In general, one "active center" is assigned to each coenzyme binding site. This raises the question of the smallest enzymatically active unit. It seems reasonable to assume that each polypeptide chain should be enzymatically active, provided that the single polypeptide chain possesses the same conformation as in the associated molecule. But this is obviously not the case. In the native state one can observe only the associated molecule; so far it was not possible to obtain single polypeptide chains in enzymatically active form. Therefore one can assume that only in the associated state is the number of non-covalent bonds high enough to stabilize that specific three-dimensional structure of the polypeptide chain which is essential for the catalytic activity. In principle there exists also the possibility that several polypeptide chains participate in one active center. In this case only the associated molecule can manifest enzymatic activity. It may be assumed, at least in some cases, that the active centers influence each other by allosteric transition (cf. Section V, 4).

## V. Discussion

### 1. Universal Occurrence

The molecular weights of proteins vary within wide limits, ranging from a few thousand to several million. Proteins with molecular weights higher than $10^5$ are complexes of several polypeptide chains, the molecular weights of the individual chains generally not exceeding 50000. In some cases (*e.g.* hemocyanine, lipovitellin), it appears that the dissociation products obtained so far are not the polypeptide chains (cf. Section IV and Table 1). For other proteins, such as phosphorylase, RNA-polymerase, or myosin (cf. Table 1 and Section IV, 6 as well as [194]), the methods for the study of quaternary structure have not yet been exhausted. Particularly one has to consider methods which can detect very stable non-covalent bonds or non-peptide covalent bonds. In collagen, for example, the sub-units consist of several polypeptide chains held togehter by carbohydrate components [194a]. As shown by the examples of serum albumin [195] and yeast enolase [196], some polypeptide chains have molecular weights as high as about 70000, but such cases are rare.

Quaternary structure is a general structural feature of proteins, since it can be detected in many protein types: in enzymes and respiratory proteins of low and of high molecular weight, in seed globulins, serum proteins, and structural proteins such as collagen [43, 194a, 197], or in the flagella of bacteria (*e.g.* flagellin from *Salmonella typhimurium* or *Bacillus pumilus* [198]), as well as in viruses, multienzyme complexes, and ribosomes (cf. Tables 1 and 2, Section IV,9, and [199]).

In most cases, and particularly in globular proteins, the polypeptide chains are held together exclusively by non-covalent bonds; linkage of the chains by disulfide bridges is less common [200]. The effects of denaturing agents indicate that the stability of the quaternary structure varies widely from one protein to another. Thus a denaturing agent may cause dissociation into the polypeptide chains in some proteins, while in others the dissociation may proceed only to the sub-unit stage, or may not occur at all.

As indicated by Equations (1a) to (1c) (cf. Introduction) protein molecules dissociate, either directly or in steps,

[182] *S. F. Velick*, J. biol. Chemistry *203*, 563 (1953).

[183] *Y. D. Halsey* and *H. Neurath*, J. biol. Chemistry *217*, 247 (1955).

[184] *A. Stockell*, J. biol. Chemistry *234*, 1286 (1959).

[185] *R. N. Perham* and *J. I. Harris*, J. molecular Biol. *7*, 316 (1963).

[186] *G. Pfleiderer*, *D. Jeckel*, and *T. Wieland*, Biochem. Z. *328*, 187 (1956).

[187] *S. F. Velick*, J. biol. Chemistry *233*, 1455 (1958).

[188] *J. van Eys*, *F. E. Stolzenbach*, *L. Sherwood*, and *N. O. Kaplan*, Biochim. biophysica Acta *27*, 63 (1958).

[189] *R. H. McKay* and *N. O. Kaplan*, Biochim. biophysica Acta *79*, 273 (1964).

[189a] *J. J. Holbrook* and *G. Pfleiderer*, Biochem. Z. *342*, 111 (1965); *A. H. Gold* and *H. L. Segal*, Biochemistry *4*, 1506 (1965).

[190] *J. E. Hayes* and *S. F. Velick*, J. biol. Chemistry *207*, 225 (1954); *K. Wallenfels* and *H. Sund*, Biochem. Z. *329*, 59 (1957); *H. Sund*, Biochem. Z. *333*, 205 (1960); *P. J. Snodgrass*, *B. L. Vallee*, and *F. L. Hoch*, J. biol. Chemistry *235*, 504 (1960); *J. H. R. Kägi* and *B. L. Vallee*, J. biol. Chemistry *235*, 3188 (1960); *R. T. Hersh*, Biochim. biophysica Acta *58*, 353 (1962); *A. Arens*, *H. Sund*, and *K. Wallenfels*, Biochem. Z. *337*, 1 (1963).

[191] *R. W. Barratt*, Genetics *46*, 849 (1961); *R. W. Barratt* and *W. N. Strickland*, Arch. Biochem. Biophysics *102*, 66 (1963).

[192] *J. R. S. Fincham* and *A. Coddington*, J. molecular Biol. *6*, 361 (1963).

[193] *R. W. Horne* and *G. D. Greville*, J. molecular Biol. *6*, 506 (1963).

[193a] Note added in proof: This principle has recently also been discovered in malic dehydrogenase from *Bacillus subtilis* [*A. Yoshida*, J. biol. Chemistry *240*, 1113 (1965)] and *Neurospora crassa* [*K. D. Munkres* and *F. M. Richards*, Arch. Biochem. Biophysics *109*, 466 (1965); *K. D. Munkres*, Biochemistry *4*, 2180, 2186 (1965)], in galactose dehydrogenase from *Pseudomonas saccharophila* (*G. Kurz* and *K. Weber*, unpublished results), and in alanine dehydrogenase [*A. Yoshida*, Biochim. biophysica Acta *105*, 70 (1965)] and lactic dehydrogenase [*A. Yoshida* and *E. Freese*, *ibid.* *99*, 56 (1965)] from *Bacillus subtilis*.

[194] *D. R. Kominz*, Biochim. biophysica Acta *51*, 456 (1961); *E. F. Woods*, *S. Himmelfarb*, and *W. F. Harrington*, J. biol. Chemistry *238*, 2374 (1963); *S. Lowey*, *J. Kucera*, and *A. Holtzer*, J. molecular Biol. *7*, 234 (1963).

[194a] Collagen (molecular weight about 300000) consists of three sub-units, in general of two $\alpha_1$ sub-units and one $\alpha_2$ sub-unit. Each sub-unit contains at least four polypeptide chains which are joined by carbohydrate components through ester or ester-like bonds. The carbohydrate component was called collagenalose [43, 194b].

[194b] *J. A. Petruska* and *A. J. Hodge*, Proc. nat Acad. Sci. U.S.A. *51*, 871 (1964); *O. O. Blumenfeld*, *M. Rojkind*, and *P. M. Gallop*, Biochemistry *4*, 1780 (1965); *K. Kühn*, *C. Tkocz*, *B. Zimmermann*, and *G. Beier*, Nature (London) *208*, 685 (1965); *W. Grassmann*, *J. Engel*, *K. Hannig*, *H. Hörmann*, *K. Kühn*, and *A. Nordwig*, Fortschr. Chem. org. Naturstoffe *23*, 195 (1965).

[195] *J. Stauff* and *R. Jaenicke*, Kolloid-Z. *175*, 1 (1961).

[196] *B. G. Malmström* in *P. D. Boyer*, *H. Lardy*, and *K. Myrbäck*: The Enzymes. 2nd edit. Academic Press, New York, London 1961, Vol. 5, p. 471.

[197] *W. F. Harrington* and *P. H. von Hippel*, Advances Protein Chem. *16*, 1 (1961).

[198] *D. Abram* and *H. Koffler*, J. molecular Biol. *9*, 168 (1964); *S. Asakura*, *G. Eguchi*, and *T. Iino*, J. molecular Biol. *10*, 42 (1964).

[199] *J. P. Waller*, J. molecular Biol. *10*, 319 (1964).

[200] Chymotrypsinogen is converted into chymotrypsin by specific hydrolysis of peptide linkages. This "activation" involves the conversion of the single polypeptide chain of chymotrypsinogen into the three polypeptide chains of chymotrypsin. These three polypeptide chains are linked by disulfide bridges [201]. It has also been suggested that insulin (two polypeptide chains) may be formed in a similar manner from a single-chain precursor [202]. Recently, however, evidence was obtained [*R. E. Humbel*, Proc. nat. Acad. Sci. U.S.A. *53*, 853 (1965)] that the two polypeptide chains of insulin are synthesized separately.

[201] *H. Neurath*, Sci. American *211*, No. 6, p. 68 (1964).

[202] *W. J. Dreyer* quoted in *M. Vaughan* and *D. Steinberg*, Advances Protein Chem. *14*, 115 (1959).

into polypeptide chains. The dissociation scheme represented by Equation (1c) is much less common than the other two schemes. First results indicate that the dissociation of the heterogeneous type of quaternary structure into the sub-units [Equation (1b)] proceeds symmetrically, *i.e.* the sub-units formed are identical.

In some enzymes, the number of polypeptide chains is equal to the number of active centers (cf. Section IV,10). In other cases (*e.g.* aldolase or β-galactosidase) the number of polypeptide chains is greater than the number of active centers (cf. Sections IV,4 and 7). It might be thought that the polypeptide chains are not all identical in these cases. However, there are also proteins, such as hemoglobin, or the isoenzymes of lactic dehydrogenase (cf. Section IV,1 and 5), in which the number of polypeptide chains is equal to the number of active centers, although not all the polypeptide chains are identical.

## 2. Spontaneous Formation of the Native Conformation

X-ray analysis shows that every protein molecule in the native state has a defined structure [203]. The question arises of whether this structure is determined by the amino-acid sequence or by special mechanisms. After the molecule has been dissociated into the polypeptide chains, generally with complete loss of the folded structure, it is often possible to restore both the native conformation and the original biological activity (cf. Section IV). The "correct" disulfide bridges between different parts of a "reduced" polypeptide chain can also be spontaneously re-formed in the presence of oxygen. However, recently discovered enzyme systems [204] catalyse the re-formation of the "correct" disulfide bridges in reduced ribonuclease. It is therefore possible that when disulfide bridges are involved, the formation of the native conformation *in vivo* is accelerated by an enzyme system.

Renaturation [20] and the estimated stabilization of the conformation by non-covalent bonds [21, 22] support the hypothesis [205–207] that the conformation of a protein molecule is simply a function of the sequence of amino acids in the polypeptide chains, *i.e.* the "structural information" is contained in the primary structure. However, it is not yet possible to predict the overall structure of a protein molecule from the amino-acid sequence.

[203] *R. E. Dickerson* in *H. Neurath*: The Proteins. 2nd edit. Academic Press, New York, London 1964, Vol. 2, p. 603.

[204] *P. Venetianer, E. G. Krause*, and *F. B. Straub* in *T. W. Goodwin, J. I. Harris*, and *B. S. Hartley*: Structure and Activity of Enzymes. Academic Press, London, New York 1964, p. 31; *R. F. Goldberger, C. J. Epstein*, and *C. B. Anfinsen*, J. biol. Chemistry *239*, 1406 (1964).

[205] *R. Lumry* and *H. Eyring*, J. physic. Chem. *58*, 110 (1954).

[206] *L. Pauling* in *A. Neuberger*: Symposium on Protein Structure. Methuen, London 1958, p. 17.

[207] *F. H. C. Crick* in: The Biological Replication of Macromolecules (Symposia of the Society for Experimental Biology, No. XII). The University Press, Cambridge 1958, p. 138.

## 3. Svedberg's Law of Multiples

Any discussion of quaternary structure must mention the pioneering work carried out by *Svedberg* in the 1920's [25, 208]. He was the first to show that proteins are macromolecules with a definite size. He also showed that the molecules of some proteins consist of smaller sub-units. From comparative investigations he concluded that the molecular weights of globular proteins are multiples of a "unit molecular weight" of 17500 ("*Svedberg*'s sub-unit"). His assumption that proteins with high molecular weights are not single polypeptide chains was found to be correct. We now know, however, that the molecular weights of the polypeptide chains vary over a wide range, and that there is no unit molecular weight.

## 4. Feedback and Allostery

The synthesis of the end product of a metabolic pathway may be controlled by inhibition of the first enzyme in the synthesis chain by the product itself when it reaches a certain concentration. In this case the substrate of the first enzyme is not structurally related to the end product. This control principle is known as end-product or feedback inhibition. To explain this phenomenon, *Monod, Changeux*, and *Jacob* introduced the concept of "allostery" [209]: An allosteric effector (*e.g.* a metabolite) becomes attached, not to the active center, but to the allosteric site of the enzyme. This is then thought to cause a change in conformation (allosteric transition), which affects the binding of the substrate to the active center, and hence also the rate of the enzymatic reaction. This change in conformation may even lead to dissociation or association. These ideas are not confined to enzymes, but can be extended to other proteins (*e.g.* hemoglobin).

The inhibition of aspartate transcarbamylase (reaction: carbamyl phosphate + aspartate → carbamyl aspartate) by the end product of the synthesis chain, *i.e.* cytidine triphosphate, is observed only with the associated enzyme molecule (molecular weight $3.1 \times 10^5$) [41]. On dissociation, it is possible to detect two different sub-units: the "regulatory" sub-unit and the "catalytic" one. The regulatory sub-unit (molecular weight about 30000) combines with the inhibitor, *i.e.* the cytidine triphosphate, and is enzymatically inactive. The "catalytic" sub-unit (molecular weight about 96000) is enzymatically active, does not combine with the inhibitor, and is therefore not inhibited by the latter. Since interaction between the sub-units is possible only in the associated enzyme molecule, the catalytic sub-unit, unlike the associated molecule, exhibits normal Michaelis kinetics even in the presence of the inhibitor. Homoserine dehydrogenase provides an example of the modification of quaternary structure by an end-product inhibitor [210].

If a protein contains several active centers and several polypeptide chains, the principle of allostery suggests that the active centers of regulatory proteins should influence one another by changes in conformation. Thus the attachment of one oxygen molecule to hemoglobin, which consists of four polypeptide chains, facilitates the attachment of the other three [11, 63a]. X-ray analysis shows that the attachment of oxygen is accompanied by a change in conformation. The

[208] *T. Svedberg*, Nature (London) *123*, 871 (1929); Kolloid-Z. *51*, 10 (1930).

[209] *J. Monod, J. P. Changeux*, and *F. Jacob*, J. molecular Biol. *6*, 306 (1963).

[210] *P. Datta, H. Gest*, and *H. L. Segal*, Proc. nat. Acad. Sci. U.S.A. *51*, 125 (1964).

distances between the iron ions in the two β chains of hemoglobin in the presence and absence oxygen differ by about 7 Å [111]. The oxygen dissociation curve of "monomeric" myoglobin is therefore fundamentally different from that of the "tetrameric" hemoglobin [209].

## 5. Quaternary Structure and the Biosynthesis of Proteins

According to current views [211–213] the biosynthesis of proteins is controlled by a section of the DNA, namely the structural gene. The information contained here is transported by a "mobile template" (messenger RNA) to the ribosomes, where the biosynthesis of the protein takes place. In the ribosomes the amino-acid residues attached to transfer RNA are arranged in the correct order from the information of the messenger RNA.

A point mutation in the structural gene can lead to the replacement of an amino-acid unit by another in the polypeptide chain. This is shown particularly impressively in the case of the hemoglobins. A change of only one amino-acid unit (replacement of glutamic acid by valine) gives sickle-cell hemoglobin, the modified physicochemical properties of which lead to a hemoglobinopathy [58]. Mutation can also result in a change in quaternary structure, as in β-galactosidase (cf. Section IV,7).

In some cases, active enzymes with the native quaternary structure (complementation enzymes) can be obtained *in vivo* and *in vitro* by hybridization of different inactive enzyme proteins resulting from point mutations (*e.g.* β-galactosidase [142, 143] and glutamic dehydrogenase [192]. It is very likely that the genetic phenomenon of interallelic complementation can be explained on the basis of quaternary structure, and that it does not occur in enzymes consisting of a single chain [214].

The quaternary structure and its changes are biologically important, *e.g.* in the control of enzyme activities. Metabolic products can control their own biosynthesis by allosteric transition. Where isoenzymes exist, they can be adapted to the metabolism by modification of their composition (cf. Section IV,5 and 6). A high biological activity can be achieved with no increase in osmotic pressure by the fitting together of sub-units [214a].

The fact that the native conformation of a protein molecule forms spontaneously from the polypeptide chains is in agreement with current views on the biosynthesis of proteins [215]. It also explains the universal importance of quaternary structure: this principle permits the synthesis of macromolecular protein molecules from a relatively small amount of genetic information if only the complexes formed by association are biologically active. This economy principle is particularly obvious for molecules with high molecular weights consisting of identical polypeptide chains, *e.g.* virus-sheath proteins (the sheath protein of tobacco mosaic virus has a molecular weight of $37\times10^6$, and consists of 2130 identical polypeptide chains) and structural proteins. Apoferritin (cf. Section IV,2) and glutamic dehydrogenase from *Neurospora crassa* [192] also consist of identical polypeptide chains. A simple calculation shows that with the aid of a triplet code, *ca.* 600 pairs of bases in DNA store the information for the biosynthesis of the apoferritin polypeptide chain, which consists of about 200 amino acids (molecular weight 24000). If, on the other hand, the apoferritin molecule would consist of a single polypeptide chain, then 20 times this number of base pairs would be required. The same is true of the messenger RNA. The economy principle also applies to proteins that, while not consisting of identical polypeptide chains, do contain identical sub-units.

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[211] *F. H. Crick*, Angew. Chem. *75*, 425 (1963).

[212] *M. H. F. Wilkins*, Angew. Chem. *75*, 429 (1963).

[213] *J. D. Watson*, Angew. Chem. *75*, 439 (1963).

[214] *F. H. C. Crick* and *L. E. Orgel*, J. molecular Biol. *8*, 161 (1964); *D. G. Catcheside*, Brookhaven Symposia in Biology *17*, 1 (1964).

[214a] *C. Baglioni*, Brookhaven Symposia Biol. *17*, 191 (1964).

[215] The size of the gene as a "functional" unit can be estimated by various genetic methods. The values for the molecular weight of the polypeptide chain equivalent range from about 10000 to more than 100000 [216]. Since a gene may be the functional unit for several polypeptide chains at the DNA level, the polypeptide chain equivalent (particularly for high values) often corresponds to several polypeptide chains (cf. [140]). This agrees with the discussion in Section V,1.

[216] *R. C. Clowes* in *I. C. Gunsalus* and *R. Y. Stanier*: The Bacteria. Academic Press, New York, London 1964, Vol. 5, p. 253.

## Low-Temperature Photolysis of Cyclopentadiene [1]

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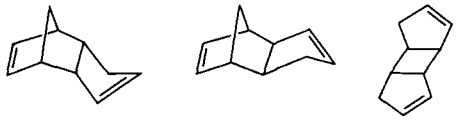
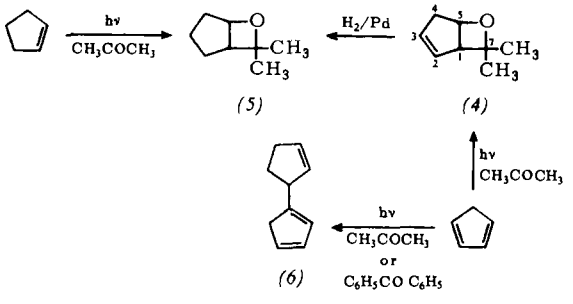
*Dedicated to Professor K. Freudenberg on his 80th birthday*

The photolysis of cyclopentadiene at *ca.* −10 °C in the presence of ketonic sensitizers is reported [2] to afford the products *(1)*–*(3)* in equal proportions. We found that photolysis at −78 °C with either acetone or benzophenone as sensitizer [3] yields in addition to *(1)*–*(3)*, the compounds *(4)* and *(6)*, and various polymers of cyclopentadiene.



*(1)* *(2)* *(3)*

Irradiation [3b] of 30 g of a mixture consisting of cyclopentadiene plus 10 % by weight of acetone under *Hammond*'s conditions [2a] (*ca.* −10 °C, 2 h) yields the compounds *(1)*–*(4)* and *(6)* in a weight ratio of [*(1)* + *(2)* + *(3)*]:*(4)*:*(6)* = 11:11:1, whereas at *ca.* −78 °C [3] the ratio is 3:14:1. On irradiation of a 1:1 mixture of cyclopentadiene and acetone at *ca.* −78 °C, the product ratio is 2.4:8.5:1.




A temperature effect is also observed on photolysis [3a] of cyclopentene/acetone (1:1 w/w): at −78 °C the oxetane *(5)* is formed in 28 % yield [4], whereas the yield is only 16 % at room temperature [3a, 5].

When 35 g of cyclopentadiene is irradiated [3b] with 5 g of benzophenone for 2.5 h at *ca.* −78 °C, no oxetane *(4)* is formed, and the product ratio is [*(1)* + *(2)* + *(3)*]:*(6)* = 2:1 (*ca.* 13 % overall reaction). This ratio increases upon further irradiation with concurrent polymer formation. That these polymers are formed from *(6)* is also shown by the fact that the ratio of olefinic to aliphatic hydrogens (NMR) is 1:2 for both types of compounds. At *ca.* −10 °C, the product ratio [*(1)* + *(2)* + *(3)*]:*(6)* = 11.5:1 in good agreement with the results of *Hammond*, who obtained 130 g of the mixture *(1)*–*(3)* from 140 g of cyclopentadiene.

Neither acetone nor benzophenone undergo pinacol formation under these conditions.

The structures of the products *(4)*–*(6)* follow from their ultraviolet, infrared, and NMR spectra:

*(4)*: b.p. 38 °C/17 mm; IR: 955 $cm^{-1}$; NMR: τ = 4.06 (m, H–2), 4.30 (m, H–3), 4.99 (m, H–5), 6.81 (m, H–1), 7.63 (m, H–4), 8.53 (s, $CH_3$), 8.94 (s, $CH_3$), relative areas: 1.0:1.0:1.0:1.0:2.1:3.0:2.9. – The fact that the chemical shift of the signal of H–5 in oxetane *(5)* is the same as in *(4)* whereas the signal of H–1 in oxetane *(5)* is shifted upfield relative to *(4)* is in accord with the double bond in *(4)* being between C–2 and C–3. This is the structure to be expected according to the Büchi mechanism [6].

*(5)*: IR: 961 $cm^{-1}$; NMR: τ = 5.05 (q, H–5.H–1, H–2), 7.42 (q, H–3), *ca.* 8.2 (m, H–4), 8.61 (s, $CH_3$), 8.93 (s, $CH_3$), relative areas: 0.96:0.96:12.1.

*(6)*: UV: $\lambda_{max}$ = 248 mμ (ε = 2730) in ethanol; NMR: τ = 3.63–4.37 (m, olefinic H,) 6.3 (m, allylic tert. H), 7.18 (m, cyclopentadienyl H), 7.5–8.6 (m, aliphatic H), relative areas: 4.8:0.95:2.2:4.0. Hydrogenation of *(6)* over Pt (3 moles of $H_2$) affords only bicyclopentyl. With tetracyanoethylene, *(6)* forms only one adduct (yield 70–80 %), the NMR spectrum of which shows four olefinic and two tertiary allylic hydrogen atoms.

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[1] This work was supported in part by Grant No. F2-MH-10,498 of the National Institutes of Mental Health of the Department of Health, Education and Welfare of the U.S.A.

[2] a) *G. S. Hammond, N. J. Turro*, and *S. H. Liu*, J. org. Chemistry *28*, 3297 (1963); b) *N. J. Turro* and *G. S. Hammond*, J. Amer. chem. Soc. *84*, 2841 (1962).

[3] a) Hanau Q 81 high-pressure lamp with pyrex filter; b) Hanovia 450 watt high-pressure lamp with corex filter.

[4] Determined by gas chromatography.

[5] *H. D. Scharf* and *F. Korte*, Chem. Ber. *97*, 2425 (1965).

[6] *G. Büchi, C. G. Inman*, and *E. S. Lipinsky*, J. Amer. chem. Soc. *76*, 4327 (1954).

## Bis(2,5-di-t-butylphenyl)methyl, a Non-associating Diarylmethyl

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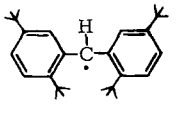
*Dedicated to Professor K. Freudenberg on his 80th birthday*

Whereas, unlike hexaphenylethane, 1,1,2,2-tetraphenylethane does not dissociate in solution into free radicals, such dissociation does occur at elevated temperature for 1,1,2,2-tetraphenylethanes that carry methyl groups at all *ortho*-positions [1], and at room temperature 1,1,2,2-tetra-(*o*-t-butylphenyl)ethane dissociates into radicals to about the same extent as hexaphenylethane [2]. Considerable dissociation is shown also by 1,1,2,2-tetrakis(2,6-diethylphenyl)ethane [3], and 1,1,2,2-tetrakis(2,6-diisopropylphenyl)ethane appears to be fully dissociated into radicals [3], which however are stable only at low temperature.

We have now found that, in distinction to 1,1,2,2-tetra-(*o*-t-butylphenyl)ethane, 1,1,2,2-tetrakis(2,5-di-t-butylphenyl)ethane as a 6 % solution in benzene is completely dissociated at room temperature into the deep yellow bis(2,5-di-t-butylphenyl)methyl *(1)*. Whereas 27 h after preparation from the diarylmethyl chloride and thallium amalgam only about 70 %




*(1)*
⟩ = tert. Butyl

of radicals is found with the magnetic balance (35 % after 150 h), this can be traced to disproportionation: if one extrapolates to half the time of preparation, 100 % of radicals is found. That complete dissociation occurs is confirmed by the fact that increase in temperature causes no increase but rather an accelerated decrease in radical content.

It is surprising that a t-butyl group in position 5 reinforces the effect of a 2-t-butyl group to such an extent that no radical association then takes places. It seems, therefore, that the steric effect plays a notable role in the dissociation of tetraarylethanes, as it does in that of hexaarylethanes.

The ESR spectrum of the radical *(1)* shows a splitting due to the proton on the central carbon atom into two line groups with a separation of 15.2 gauss.

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[1] *J. Coops, W.Th. Nauta, et al.*, Recueil Trav. chim. Pays-Bas *59*, 1109 (1940); *60*, 245 (1941).
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[3] *K. H. Fleurke*, Dissertation, University of Amsterdam, 1963.

## Ammonothermal Synthesis of Magnesium and Beryllium Amides

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*Dedicated to Professor Karl Freudenberg on the occasion of his 80th birthday*

The preparation of metal amides from a metal and liquid ammonia at room temperature or gaseous ammonia at 1 atm and higher temperatures has its limitations. The reaction is successful with barium, strontium, and calcium, but with magnesium no amide is obtained at higher temperatures, and on using liquid ammonia at room temperature we obtained only small quantities of amorphous (to X-rays) magnesium amide after 1.5 years[1]. For preparative purposes we are therefore now using liquid ammonia up to its critical point (132.5 °C, 111.5 atm), and ammonia pressures up to 4000 atm in the supercritical region. We have developed autoclaves made from "Vacumelt ATS 115" in which the closures also can be heated. The reagents are placed in small silver tubes. The pressure in the autoclave is calculated from the specific volume of ammonia.

$Mg(NH_2)_2$ was obtained quantitatively at 250 °C and 2500 atm in 40 hours as a finely crystalline material. On addition of $NaN_3$ (which forms $NaNH_2$) at 300 to 350 °C we obtained products suitable for X-ray single-crystal investigations. $Be(NH_2)_2$, which is not formed from $BeI_2$[2] or from $Be(CH_3)_2$[3] and ammonia at room temperature, was obtained in well-crystallized form from the metal at 360 °C and 2500 atm in five days.

We have also obtained imides and nitrides by this method. For instance, reaction of beryllium with ammonia at 400 °C and 200 atm for about a week gives pure cubic $Be_3N_2$, whereas with an ammonia stream at 1000 °C this preparation succeeds only on repeated heating and pulverization.

The study of metal amides is often complicated by the difficulty that the materials are formed only in amorphous or poorly crystalline form. Such difficulties can often be overcome by use of the procedure described above, which is patterned on hydrothermal synthesis. For instance, amorphous $Zn(NH_2)_2$, obtained from $Zn(C_2H_5)_2$ and ammonia, can be recrystallized without difficulty.

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German version: Angew. Chem. *78*, 208 (1966)

[1] Cf. *R. Juza*, Angew. Chem. *76*, 290 (1964); Angew. Chem. internat. Edit. *3*, 471 (1964).
[2] *R. W. Bergstrom*, J. Amer. chem. Soc. *50*, 657 (1928).
[3] *R. Masthoff* and *Ch. Vieroth*, Z. Chem. *5*, 142 (1965).

## Cyclopentadienylbis(trifluorophosphine)cobalt [1]

By Doz. Dr. Th. Kruck, Prof. W. Hieber, and Dipl.-Chem. W. Lang

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*Dedicated to Professor Karl Freudenberg on the occasion of his 80th birthday*

Cyclopentadienylbis(trifluorophosphine)cobalt *(1)* is formed in 20–30 % yield on treatment of dicyclopentadienylcobalt with $PF_3$ at 300 atm and 170 °C:

$$(C_5H_5)_2Co + 2\ PF_3 \rightarrow C_5H_5Co(PF_3)_2 + \bullet C_5H_5$$
*(1)*

As a consequence of the similarity in complex-chemical behavior between trifluorophosphine and carbon monoxide[2], cyclopentadienyl-trifluorophosphine-metal complexes, of which *(1)* is the first representative, resemble their CO analogues $[C_5H_5Co(CO)_2$[3] in this case] closely in their chemical and physical properties. Compound *(1)* is a deep red, oily liquid, m.p. −8 °C, b.p. 51 °/13 mm, readily soluble in organic solvents. Its stability to atmospheric oxygen is poor, as is to be expected for a trifluorophosphine complex with a central metal in the (formal) oxidation stage +1. However, it is stable in a sealed tube up to 195 °C.

Nuclear magnetic resonance and infrared spectra confirm a structure containing a π-bonded, pentagonal, symmetrical cyclopentadienyl ligand. The $^1$H-NMR signal of the aromatic ring occurs at $-5.02\times10^{-6}$ (measured for the pure liquid *versus* tetramethylsilane), which is in the range expected for such a structure; there is no splitting due to coupling of the nuclear spins of the protons with those of the P and F nuclei. In the infrared spectrum bands appear at 1112 $cm^{-1}$ (C–H deformation) and 325 $cm^{-1}$ (metal-ring vibration) with medium intensity, characteristic of the π-bonded cyclopentadienyl ring. The P–F stretching frequencies are at 905 (vs), 856 (vs), and 842 (vs) $cm^{-1}$[4]. They are thus only slightly shifted from the positions for trifluorophosphine and it can be concluded that there is considerable π-bond contribution to the metal-phosphorus linkage.

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[1] Part XIII of Metal-Trifluorophosphine Complexes. – Part XII: *Th. Kruck* and *W. Lang*, Z. anorg. allg. Chem. (1965), in press.
[2] Cf. *Th. Kruck* and *K. Baur*, Chem. Ber. *98*, 3070 (1965).
[3] *E. O. Fischer* and *R. Jira*, Z. Naturforsch. *10b*, 355 (1955); *T. S. Piper, F. A. Cotton*, and *G. Wilkinson*, J. inorg. nucl. Chem. *1*, 165 (1955).
[4] vs = very strong.

## Adsorption of Methylene Blue on Clays

By Prof. Dr. U. Hofmann, Dipl.-Chem. H. Kottenhahn, and Dr. S. Morcos

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*Dedicated to Professor Karl Freudenberg on the occasion of his 80th birthday*

Some time ago we found[1] that adsorption of Methylene Blue on charcoal offers a good possibility of determining the surface area.

Methylene Blue is a quaternary ammonium chloride, $C_{16}H_{18}N_3SCl$, so it was expected[2] that it would undergo cation exchange on clay earths; the Table shows that this indeed occurs. The amount of Methylene Blue taken up is

always approximately equivalent to the amount of exchangeable cation, and it is substantially independent of the surface area. Moreover, the nature of the cation is without influence.

The solution separated from the clay after treatment with Methylene Blue contains 90–100 % of the chloride ion of the dye and about 95 % of the exchangeable cation originally bound to the clay. The amount of Methylene Blue entering the exchange is substantially independent of the concentration of Methylene Blue in the equilibrium solution.

| Clay (and Source) | Surface area by BET ($m^2/g$) [a] | Exchangeable cations (meq./100 g) | Methylene Blue taken up (meq./100g) | Cations |
|---|---|---|---|---|
| Kaolin OF (Schnaittenbach) | 6 | 1.9 | 1.4 | Ca, Mg |
| Kaolin (Zettlitz) | 22 | 6.3 | 6.3 | Ca, Mg |
| Colloidalkaolin (Chodau) | 23 | 9.85 | 10.15 | Ca, Mg |
| Kaolinite clay JL (Provins) | 70 | 17.9 | 17.2 | Ca, H |
| Illite (Füzerradvany) | 37 | 18.6 | 17.8 | $NH_4$ |
| Halloysite (Djebel Debar) | 66 | 9.2 | 10.8 | Ca, Mg |
| Halloysite (Morocco) | 61 | 24.4 | 21.9 | Ca, Mg |
| Montmorillonite (Wyoming) | 770 [b] | 82 | 84 | Na |
| Montmorillonite (Bavaria) | 770 [b] | 93 | 96 | Ca, Mg |
| Montmorillonite (Switzerland) | 770 [b] | 106 | 111 | Ca, Mg |

[a] Freeze-dried preparations.
[b] Total surface area, inclusive of the surfaces between silicate layers accessible by intracrystalline swelling.

Received: December 2nd, 1965 [Z 117/949 IE]
German version: Angew. Chem. 78, 208 (1966)

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[2] *J. E. Gieseking* and *H. Jenny*, Soil Science *42*, 273 (1936); *J. E. Gieseking, ibid. 47*, 1 (1938).

## Synthesis of Nortricyclenes from Bicyclic Ketones in a One-Stage Reaction

By Prof. Dr. G. Kempter[1], Prof. Dr. M. Mühlstädt, and Dipl.-Chem. D. Heilmann

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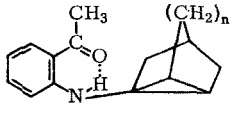
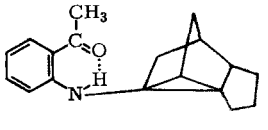
der Universität Leipzig (Germany)

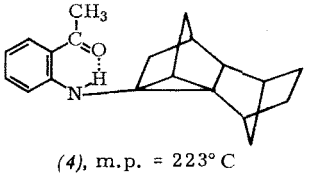
We have found that compounds containing the skeleton of nortricyclene (tricyclo[2.2.1.$0^{2,6}$]heptane) are formed in a one-stage reaction if norcamphor, bicyclo[2.2.2]octan-2-one, 5,6-*exo*-trimethylenenorcamphor, or *exo,endo*-1,4;5,8-dimethano-2-decalone is allowed to react with *o*-aminoacetophenone hydrochloride. The products are compounds *(1)* to *(4)*; product *(2)* contains the ring skeleton of homotricyclene (tricyclo[2.2.2.$0^{2,6}$]octane).



*(1)*, n = 1, m.p. = 155.5° C, yield 37%
*(2)*, n = 2, m.p. = 172.5° C, yield 14.5%

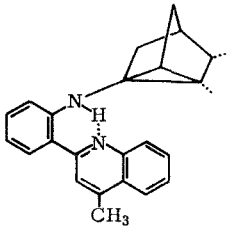


*(3)*, m.p. = 192.5-194°C
yield 26.3%



*(4)*, m.p. = 223° C
yield 30.6%

Compounds *(1)* and *(3)* react with a further quantity of *o*-amino ketone hydrochloride to give *N*-nortricyclyl-substituted *o*-flavanilines of type *(5a,b)*, which also appear as by-products in the preparation of compounds *(1)* and *(3)*.

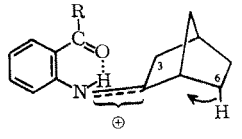


*(5a)*, m.p. = 214.5-216° C
*(5b)*, m.p. = 232.5-234.5° C

30 mmoles of bicyclo-ketone and 20 mmoles of *o*-aminoacetophenone hydrochloride are allowed to react at 155 to 170 °C by the hydrochloride method[2]. When the product is rubbed with ethanol/ligroin the products *(1)*–*(4)* crystallize; the by-products of type *(5)* are separated by fractional crystallization.

The structures of compounds *(1)* to *(5)* were proved by elemental analysis, NMR spectra [no olefinic proton, ratio of aromatic: aliphatic protons in the tricyclic system = 4:9 for *(1)* and 4:11 for *(2)*], ultraviolet and infrared spectra, and mass-spectrometric determination of the molecular weight.

We assume that reaction is initiated by nucleophilic attack by the amino ketone on the carbonyl group of the bicyclic ketone, followed by removal of the OH group produced, which is protonated under the reaction conditions. The mesomeric cation *(6)*[3] may be an intermediate.



*(6)*

A derivative containing the tetracyclic skeleton present in *(3)* has already been synthesised by *Schleyer*[4], although only in 1.5 % yield. The pentacyclic skeleton present in *(4)* was not, to our knowledge, previously known.

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[1] New address: Institut für Organische Chemie der Pädagogischen Hochschule, Potsdam-Sanssouci (Germany).

[2] *G. Kempter, P. Andratschke, D. Heilmann, H. Krausmann*, and *M. Mietasch*, Chem. Ber. *97*, 16 (1964); *G. Kempter* and *S. Hirschberg, ibid. 98*, 419 (1965); *G. Kempter*, Habilitation Thesis, Universität Leipzig, 1964.

[3] Experiments with other amine hydrochlorides showed that an RCO group next to the nitrogen function is essential for success of the above synthesis.

[4] *L. Kaplan, H. Kwart*, and *P. v. R. Schleyer*, J. Amer. chem. Soc. *82*, 2341 (1960).

## Ecdysterone, a New Metamorphosis Hormone of Insects

By Dr. H. Hoffmeister

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The first insect hormone, ecdysone, was isolated in 1954[1]. It is a moulting hormone of silk-worms (*Bombyx mori*) but is active in all the arthropods investigated.

From whole-body extracts of *Bombyx mori* we have now obtained a further substance, which we term ecdysterone, that has moulting activity. Starting material was an aqueous extract[2] that still showed hormone activity in the Calliphora test[3] after separation of the ecdysone. It was extracted exhaustively with ethyl acetate. The residue remaining after evaporation of the ester was fractionated on an alumina column with gradient-elution by methanol and benzene. The pure hormone was then obtained from the hormone-containing fractions by repeated thin-layer chromatography on silica gel. Ecdysterone is three to five times as active as ecdysone in the Calliphora test. It is soluble in water and crystallizes in large anhydrous plates, m.p.226 °C, from ethyl acetate/methanol.

The mass spectrum gives $C_{27}H_{44}O_6$ as the molecular formula of ecdysterone. The substance contains an α,β-unsaturated keto group (UV: $\lambda_{max}$ = 240 mμ, ε = 13600). Its infrared spectrum is very similar to that of ecdysone but there are differences in the fine structure; the carbonyl band lies at 1645 $cm^{-1}$, the ethylenic band at 1612 $cm^{-1}$ (in KBr). The NMR spectrum contains a signal at 8.66 τ for the terminal $-(CH_3)_2C-OH$ group of the steroid side chain; the steroid methyl groups at C-10 and C-13 also appear in the spectrum.

Ecdysterone is probably a $C_{27}$-steroid with a cholesterol side chain. On thin-layer chromatography (silica gel) it appears to be more polar than ecdysone; when sprayed with vanillin/sulfuric acid it develops an intense turquoise color.

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[1] *A. Butenandt* and *P. Karlson*, Z. Naturforsch. *9b*, 389 (1954).
[2] *P. Karlson, H. Hoffmeister, W. Hoppe*, and *R. Huber*, Liebigs Ann. Chem. *662*, 1 (1963).
[3] *P. Karlson*, Vitamine u. Hormone *14*, 227 (1956).

## New Metal-Azide Complexes [1]

By Priv.-Doz. Dr. W. Beck, Dr. E. Schuierer, and Dipl.-Chem. K. Feldl

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In continuation of previous investigations[2] we have prepared the following azide complexes of platinum(II), platinum(IV), and gold(III) by treating the corresponding chloro complexes with sodium azide in aqueous solution and precipitation of the azidometallate anions with tetraphenylarsonium chloride:

Orange-red tetraphenylarsonium tetraazidoplatinate(II), $[C_6H_5)_4As]_2[Pt(N_3)_4]\cdot H_2O$, decomp. at 185 °C, from a solution of $K_2[PtCl_4]$ and $NaN_3$ (molar ratio 1:100) at 80 °C.

Orange-yellow tetraphenylarsonium hexaazidoplatinate(IV), $[(C_6H_5)_4As]_2[Pt(N_3)_6]$, decomp. at 205 °C, from hydrogen hexachloroplatinate(IV) and $NaN_3$.

Brownish-red tetraphenylarsonium tetraazidoaurate(I), $(C_6H_5)_4As[Au(N_3)_4]$, decomp. at 145 °C, from $K[AuCl_4]$ and $NaN_3$ (molar ratio 1:40).

These compounds can be recrystallized from acetone/water or methylene chloride/ligroin. As expected, the azidometallate anions $[Pt(N_3)_4]^{2-}$, $[Pt(N_3)_6]^{2-}$, and $[Au(N_3)_4]^-$ are diamagnetic (measurements in acetone or nitrobenzene)[3]. An aqueous solution of $[Pt(N_3)_4]^{2-}$ reacts in the same way as azidopalladate(II)[2] with triphenylphosphine, giving colorless diazidobis(triphenylphosphine)platinum(II), $[(C_6H_5)_3P]_2Pt(N_3)_2$, decomp. at 225 °C.

After treatment of cadmium(II) sulfate with $NaN_3$ (molar ratio 1:15), the salt $(C_6H_5)_4P[Cd_2(N_3)_5]\cdot H_2O$, decomp. at 265–266 °C, can be precipitated by addition of tetraphenylphosphonium chloride.

The crystalline complex salts with bulky cations are thermally very stable and are insensitive to touch; however, they deflagrate in a flame.

In the infrared spectra of the azido complexes of platinum and gold the symmetric and asymmetric $N_3$ stretching vibrations appear at 1270 and 2030 $cm^{-1}$, but additional $\nu_{as}N_3$ bands at larger wave numbers, probably attributable to azido bridges[4], are observed for the cadmium compound and for the salt $[C_6H_5)_4As]_2[Pd(N_3)_6]$[2].

Benzylmercuric azide, $C_6H_5CH_2HgN_3$ [from $C_6H_5CH_2HgCl$ and $NaN_3$ in anhydrous methanol; decomp. at 120 °C] and diphenylthallium(III) azide, $(C_6H_5)_2TlN_3$ [from $(C_6H_5)_2TlF$ and $NaN_3$ in water; decomp. at 321 °C] are very similar to the corresponding fulminates in solubility and thermal stability[5].

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German version: Angew. Chem. 78, 267 (1966)

[1] Part 12 of Pseudohalogen-Metal Compounds. – Part 11: *W. Beck, W. Hieber*, and *G. Neumair*, Z. anorg. allg. Chem., in press.
[2] *W. Beck, K. Feldl*, and *E. Schuierer*, Angew. Chem. 77, 458 (1965); Angew. Chem. internat. Edit. *4*, 439 (1965).
[3] By the NMR method; cf. *H. P. Fritz* and *K. Schwarzhans*, J. organomet. Chem. *1*, 208 (1964).
[4] Azido bridges have already been assumed to exist in an analogous copper complex, $NR_4[Cu_2(N_3)_5]$, by *M. Straumanis* and *A. Cirulis*, Z. anorg. allg. Chem. *252*, 9 (1943). In principle, when azido bridges occur, the structure M–N–N–M as well as bonding through the α-nitrogen atom require consideration.
[5] *W. Beck* and *E. Schuierer*, J. organomet. Chem. *3*, 55 (1965).

## A New Synthesis of L-Felenine

By Prof. Dr. A. Schöberl, Dipl.-Chem. J. Borchers, Dr. H. Gräfje, and Dr. Ch.-V. Grewe-Pape

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We have found that L-felenine [*S*-(3-hydroxy-1,1-dimethylpropyl)cysteine *(3)*], which previously was difficultly accessible[1], can be prepared in yields of up to 80% by heating 3-methyl-1,3-butanediol *(1)* and L-cysteine *(2)* (molar ratio 2:1) in methanol/2 N HCl at 80 to 100 °C for 0.5 to 1 h with exclusion of oxygen.

$$\underset{(1)}{HO-(CH_2)_2-C(CH_3)_2-OH} + \underset{(2)}{HS-CH_2-CH(NH_2)-COOH} \rightarrow \underset{(3)}{HO-(CH_2)_2-C(CH_3)_2-S-CH_2-CH(NH_2)-COOH}$$

Oxidation of unchanged cysteine by passage of air is followed by chromatography on Dowex W50, $H^+$ form, with 2 N $NH_3$. The eluted L-felenine is purified by precipitation from aqueous solution with acetone: $R_f$ = 0.52 in butanol/glacial acetic acid/water (2:1:1), m.p. 185° (decomp.), $[\alpha]_D^{22}$ = −12.5° (c = 2 in $H_2O$), + 9.0° (c = 2 in 1 N HCl).

L,L-2,10-Diamino-5,5-dimethyl-4,8-dithiaundecanedioic acid *(4)* is obtained as by-product in the condensation. Its formation is favored by longer reaction times: heating for 4 days in the stated conditions leads to a 50% yield [recrystallization from methanol/$H_2O$; $R_f$ = 0.30 in butanol/glacial acetic acid/water (2:1:1); $[\alpha]_D^{20}$ = +18.8° (c = 2 in 1 N HCl); m.p. *ca.* 240 °C (decomp.)]. Separation from felenine and purification of the bissulfide *(4)* are achieved by chromatography[2] on Dowex W50, $H^+$ form, with citrate buffer (pH = 3.4). When L-felenine is treated with 6 N HCl at 70 or 80 °C for 4 h the bissulfide *(4)* is formed as decomposition product[3].

$$\underset{(4)}{HOOC-CH(NH_2)-CH_2-S-CH_2-CH_2-C(CH_3)_2-S-CH_2-CH(NH_2)-COOH}$$

L-Cysteine condenses smoothly with t-butyl alcohol under similar conditions (heating in 5 N HCl for 10 h on the water bath under $N_2$), giving *S*-t-butyl-L-cysteine (yield about 70 %). Recrystallization from butanol/$H_2O$ gives shiny needles; $R_f$ = 0.73 in butanol/glacial acetic acid/water (2:1:1); $[\alpha]_D^{20}$ = +9.9° (c = 1 in 1 N HCl); m.p. = 244 °C (decomp.).

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German version: Angew. Chem. *78*, 209 (1966)

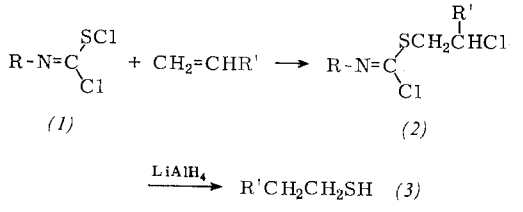
[1] Cf. *H. Eggerer*, Liebigs Ann. Chem. *657*, 212 (1962).
[2] *S. Moore* and *W. Stein*, J. biol. Chemistry *192*, 663 (1951).
[3] Cf. *R. G. Westall*, Biochem. J. *55*, 244 (1953).

## N-Aryl- and N-Alkyl-S-(2-chloroalkyl)isothiocarbamoyl Chlorides [*]

By Dr. G. Ottmann and H. Hooks, Jr.

Olin Mathieson Chemical Corporation
Chemicals Division, New Haven, Conn. (U.S.A.)

We reported recently[1,2] on the synthesis of *N*-aryl- and *N*-alkyl-*S*-chloroisothiocarbamoyl chlorides *(1)* by careful chlorination of the corresponding isothiocyanates. *S*-Chloroisothiocarbamoyl chlorides *(1)* react predominantly as sulfenyl chlorides but some of their properties also resemble those of imidoyl chlorides. As derivatives of sulfenyl chlorides, they react with olefinic double bonds[3] to form *N*-aryl- and *N*-alkyl-*S*-(2-chloroalkyl)isothiocarbamoyl chlorides *(2)* (cf. Table), compounds which have not been described previously.



*(1)* *(2)*

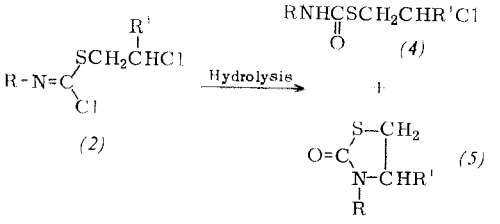


*(3)*

The exothermic reaction is performed either by adding the *S*-chloroisothiocarbamoyl chloride slowly and with stirring to the olefin at 0–20 °C under complete exclusion of moisture, or in case of ethylene by passing the gaseous hydrocarbon into a solution of *(1)*. Excessive olefin or an inert solvent ($CCl_4$, ether) are employed as reaction media. Evaporation of the solvent *in vacuo* renders compounds *(2)* in satisfactory purity. Analytically pure products are obtained by recrystallizing the solid representatives from pentane at low temperature (*e.g.* 50 °C) or by extracting the liquid representatives with pentane at room temperature. Reactions of *(1)* with vinyl alkyl ethers lead to highly reactive *S*-(2-chloro-2-alkoxyalkyl)isothiocarbamoyl chlorides *(2)*, R′ = $OC_nH_{2n+1}$, which are only stable at low temperatures or in solution.

The structure *(2)* was secured by $LiAlH_4$-reduction to the corresponding n-alkylthiols *(3)*, by elemental analysis, and by infrared, NMR, and mass spectroscopy.

*S*-(2-Chloroalkyl)isothiocarbamoyl chlorides *(2)* behave like imidoyl chlorides and are readily converted by nucleophiles to a variety of open-chain or cyclic compounds depending on the nature of R′. Hydrolysis[4] of compounds *(2)*, R′ = H, alkyl, chloroalkyl, or cycloalkyl, leads to *N*-alkyl- and *N*-aryl-*S*-(2-chloroalkyl)thiocarbamates *(4)* (cf. Table). If R′ is a more strongly electron-attracting moiety such as a phenyl group, hydrolysis affords the corresponding compounds *(4)*, albeit in reduced yields since 4-aryl-1,3-thiazolidin-2-ones *(5)* are predominantly formed, *e.g.* 3,4-diphenyl-1,3-thiazolidin-2-one *(5)*, R = R′ = $C_6H_5$, m.p. 159–160 °C, besides a minor amount of the thiocarbamate *(4)*.



*(2)* *(4)* *(5)*

*(4)*, R′ = H, alkyl, cycloalkyl, chloroalkyl
*(5)*, R′ = phenyl

*S*-(2-Chloroalkyl)isothiocarbamoyl chlorides RN=C(Cl)—S—X—Cl *(2)*.

| R | X | M.p. [°C] | Yield [%] |
|---|---|---|---|
| Phenyl | Ethylene | liquid | 83 |
| Phenyl | $-CH_2-CH(C_3H_7)-$ | liquid | 91 |
| Phenyl | $-CH_2-CH(C_6H_5)-$ | 49–50 | 65 |
| Phenyl | 1,2-Cyclohexylene | 41–42 | 92 |
| *p*-Chlorophenyl | 1,2-Cyclohexylene | 43–44 | 97 |
| 2,5-Dichlorophenyl | 1,2-Cyclohexylene | 58–59 | 97 |
| n-Butyl | 1,2-Cyclohexylene | liquid | 78 |
| Phenyl | $-CH_2-CH(CH_2Cl)-$ | liquid | 83 |

*S*-(2-Chloroalkyl)thiocarbamates RNH—CO—S—X—Cl *(4)*

| | | | |
|---|---|---|---|
| Phenyl | Ethylene | 88–89 | 68 |
| Phenyl | $-CH_2-CH(C_3H_7)-$ | 71–72 | 82 |
| Phenyl | 1,2-Cyclohexylene | 114–115 | 82.5 |
| Phenyl | $-CH_2-CH(C_6H_{13})-$ | liquid | 88 |
| Phenyl | $-CH_2-CH(CH_2Cl)-$ | 73–74 | 62 |

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German version: Angew. Chem. *78*, 210 (1966)

[*] Chlorination of Isothiocyanates, Part III. – Part II: [2].

[1] *G. Ottmann* and *H. Hooks, Jr.*, Angew. Chem. *77*, 427 (1965); Angew. Chem. internat. Edit. *4*, 432 (1965).
[2] *G. Ottmann* and *H. Hooks, Jr.*, J. org. Chemistry, in press.
[3] *N. Kharasch*: Organic Sulfur Compounds. Pergamon Press, London 1961, Vol. I, p. 353.

[4] Conditions: (a) dilute alkali at 20–30°C; (b) water at 50–100°C; reaction time: 10–60 minutes.

## Reactions of Trithiocarbonic Acid with Malonyl Chloride [1]

By Dr. B. Krebs and Priv.-Doz. Dr. G. Gattow

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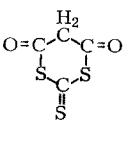
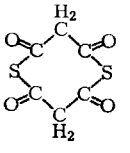
Whereas the wine-red 4,5-dioxo-2-thioxo-1,3-dithiolane[3] is formed by reaction of trithiocarbonic acid $SC(SH)_2$[2] with oxalyl chloride, use of malonyl chloride leads to the dimeric thiomalonic anhydride [2,4,6,8-tetraoxo-1,5-dithiocane]*(2)*[4] by way of the unstable red 4,6-dioxo-2-thioxo-1,3-dithiane *(1)*.



*(1)*



*(2)*

A solution of 7.1 g of freshly distilled malonyl chloride in 50 ml of $CHCl_3$ is dropped slowly into a solution of 5.5 g of $SC(SH)_2$ in 50 ml of $CHCl_3$ at 0 ° with exclusion of moisture; much HCl is evolved. Colorless crystals of product *(2)* separate in several hours or days from the solution, which is initially red owing to the presence of the intermediate *(1)*; the crystals are filtered off and washed with $CHCl_3$.

The compound *(2)*, m.p. 124 ± 1 °C, $d_4^{25}$ = 1.710 ± 0.005 g/cm³, is not soluble without decomposition in any of the usual solvents. It is not decomposed by cold water or alcohols, but hydrolysis occurs in hot water or in acids or aqueous

alkali hydroxides. Heating of compound *(2)* in a high vacuum affords $C_3O_2$, COS, and thioacetic acid, but heating in the presence of $P_2O_5$ affords $C_3O_2$, $H_2S$, $C_3S_2$, COS, and ketenethiocarboxylic acid *(3)* (colorless crystals; m.p. 60 °C) (cf. [5]).

O=C=CH–COSH *(3)*

Infrared spectrum of *(2)* (in Nujol and hexachlorobutadiene): 2980(m), 2910(m), 1720(vs), 1685(vs), 1395(s), 1388(s), 1298(s), 1210(m), 1055(s), 980(s), 970(s), 910(m), 800(s), 750(w), 640(s), 558(m), 463(w) $cm^{-1}$ [6].

X-Ray investigations showed that compound *(2)* forms tetragonal crystals with Z = 4 in space group $D_{2d}^4$–$P\bar{4}2_1c$ (No. 114): a = 11.88 ± 0.02, c = 5.61$_1$ ± 0.01 Å; X-ray density 1.714 g/cm³. From consideration of the structure it follows that the eight-membered ring of compound *(2)* is symmetrically puckered (symmetry $C_{2v}$).

If the red solution of compound *(1)* in $CHCl_3$ is cooled immediately after the reaction to −30 °C and the solvent is distilled off in a vacuum, compound *(1)* remains behind as an oil. When warmed it decomposes to a yellow oil, which gives off large amounts of $CS_2$ in a vacuum at 25 °C. This oil is a polymer of composition *(4)*; its distillation at 0.5 mm (b.p. 150–200 °C) affords polymers *(4)* with x = 4–6, having –SH (and –Cl) end groups. The distillation residue contains polymers of higher molecular weight (x > 6) as decomposition products.

[–S–CO–$CH_2$–CO–]x *(4)*

Infrared spectrum of *(4)* with x = 4–6: 3380(w), 2970(m), 2900(m), 2580(m), 1720–1708–1690–1675(vs), 1550(w), 1402(m), 1375(m), 1300(s), 1196(m), 1085(s), 1056(s), 1035(s), 950(w), 885(m), 790(w), 642(s), 552(w), 465(w) $cm^{-1}$ [6].

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German version: Angew. Chem. *78*, 210 (1966)

[1] Part XXII of Chalcogenocarbonates. – Part XXI: *A. Müller* and *B. Krebs*, Z. anorg. allg. Chem., in press.

[2] *G. Gattow* and *B. Krebs*, Z. anorg. allg. Chem. *321*, 143 (1963).

[3] *B. Krebs* and *G. Gattow*, Angew. Chem. *75*, 978 (1963); Angew. Chem. internat. Edit. *2*, 618 (1963).

[4] Compound *(2)* has previously been obtained only by reaction of $H_2S$ and $C_3O_2$ in a bomb tube for several days; cf. [5].

[5] *O. Diels*, *R. Beckmann*, and *G. Tönnies*, Liebigs Ann. Chem. *439*, 76 (1924).

[6] vs = very strong, s = strong, m = medium, w = weak.

## Rotational Isomerism in Vinylcyclopropanes

By Dr. H. Günther and Dipl.-Chem. D. Wendisch

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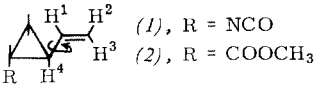
der Universität Köln (Germany)

The angular dependence of vicinal H,H-coupling constants has been employed for the conformational analysis of ethanes, propenes, and butadienes [1]. We have used this method to study the rotational isomerism of the vinyl group in *trans*-2-vinylcyclopropyl isocyanate *(1)* [2] and methyl *trans*-2-vinylcyclopropylcarboxylate *(2)* [2] (see Table).

With respect to the orientation of the vinyl group relative to the three-membered ring, results obtained for bicyclopropyl [3] indicate that in *(1)* and *(2)* there is an equilibrium between an s-*trans* form (A, Θ ≈ 180°) [4] and two *gauche* forms (B, Θ ≈ 40°; B′, Θ ≈ 320°) of equal energy ($p_B = p_{B'}$). Because interconversion between rotamers A, B, and B′ is rapid in the temperature range studied, only a mean value is observed for the coupling constant $J_{14}$:

$$J_{14} = p_A J_{14}^{trans} + 2p_B J_{14}^{gauche} \quad (a)$$

where $J_{14}^{trans} \gg J_{14}^{gauche}$. If all rotamers are of equal energy [$p_A = p_B = p_{B'} = 1/3$; $J_{14} = 1/3\ J_{14}^{trans} + 2/3\ J_{14}^{gauche}$ (b)], a value of *ca.* 6 cps is found for $J_{14}$ [5]. The observed coupling constants therefore indicate a domination of the s-*trans* form in *(1)* and *(2)*, that increases from + 37 °C to −40 °C. The changes $\Delta\nu_i$ of the chemical shifts with decreasing temperature are consistent with this interpretation and may have their origin in the diamagnetic anisotropy of the cyclopropane ring.




*(1)*, R = NCO
*(2)*, R = $COOCH_3$

| | Temp. [°C] | $J_{14}$ [cps] | $\Delta\nu_1$ [cps] [a] | $\Delta\nu_2$ [cps] | $\Delta\nu_3$ [cps] | $p_A$ | $p_B = p_{B'}$ |
|---|---|---|---|---|---|---|---|
| *(1)* | +37 | 7.82 | +8.29 | +0.40 | −1.97 | 0.53 | 0.23 |
| | −40 | 8.50 | | | | 0.61 | 0.20 |
| *(2)* | +37 | 8.17 | +7.71 | −0.31 | −2.23 | 0.58 | 0.21 |
| | −40 | 9.03 | | | | 0.67 | 0.16 |

[a] The $^1$H-NMR-spectra were recorded at 60 Mc/s in $CS_2$ (20 % by vol.) with a Varian A 60 spectrometer. $p_i$ are the mole fractions of rotamers (see text). Positive $\Delta\nu_i$ denotes a shift to higher field.

With a value of 12 cps for $J_{14}^{trans}$ [6], $J_{14}^{gauche}$ and the equilibrium concentrations of the rotamers may be estimated using the Equations (b) and (a), respectively. With $K = p_A/p_B$ for the equilibrium constant the enthalpy difference ΔH between the *gauche* and s-*trans* forms is obtained from the temperature dependence of K. For *(1)* and *(2)* ΔH values of *ca.* 0.6 and *ca.* 0.7 kcal/mole, respectively, were found.

Received: December 3rd, 1965 [Z 133/951 IE]
German version: Angew. Chem. *78*, 266 (1966)

[1] *H. S. Gutowsky*, Pure appl. Chem. *7*, 93 (1963); *A. A. Bothner-By*, *S. Castellano*, and *H. Günther*, J. Amer. chem. Soc. *87*, 2439 (1965); *A. A. Bothner-By* and *R. K. Harris*, *ibid. 87*, 3445, 3451 (1965).

[2] *E. Vogel*, *R. Erb*, *G. Lenz*, and *A. A. Bothner-By*, Liebigs Ann. Chem. *682*, 1 (1965).

[3] *O. Bastiansen* and *A. de Meijere*, Angew. Chem. *78*, 142 (1966); Angew. Chem. internat. Edit. *5*, 124 (1966).

[4] Θ is the azimuthal angle.

[5] *H. Günther* and *H. Klose*, unpublished results for methylcyclopropanes.

[6] *A. A. Bothner-By*, *C. Naar-Colin*, and *H. Günther*, J. Amer. chem. Soc. *84*, 2748 (1962).

## A Stable Methylenenorcaradiene

By Prof. Dr. H. Prinzbach [1], Dipl.-Chem. U. Fischer, and Dipl.-Chem. R. Cruse

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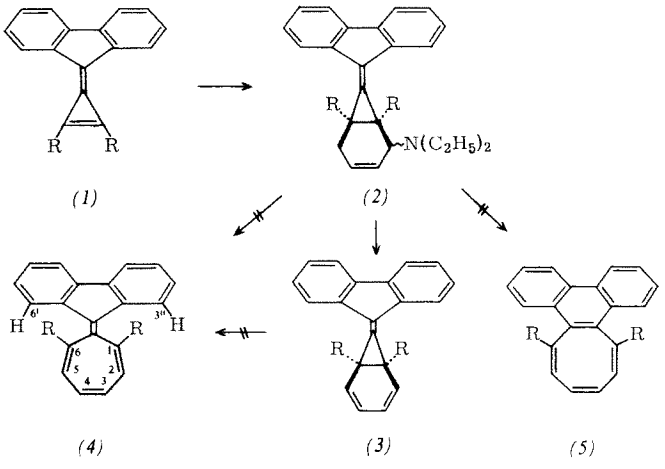
der Universität Freiburg (Germany)

Calculations of the molecular geometry of dibenzosesquifulvalene *(4a)* [3] by means of a simple model [2] show that the spheres of influence of the H atoms at positions 1 and 6 interpenetrate appreciably those of the H atoms at positions 3″ and 6′ if the fluorenylidene and cycloheptatrienylidene parts of the molecule are assumed to be coplanar, but that in spite of this an approximately planar conformation is not improbable. On the other hand, 1,6-dimethyldibenzosesquifulvalene *(4b)* cannot, according to an analogous calculation, assume an even approximately planar conformation. An attempt to synthesize compound *(4b)* should therefore lead to the methylenenorcaradiene structure *(3b)*. We have confirmed this experimentally.

Treatment of dimethyldibenzocalicene *(1b)* [4] (6.85 mmoles) with *N,N*-diethylbutadienylamine (10.3 mmoles) in anhydrous benzene (60 ml) at 90 °C for 20 h and subsequent addition of 2 N HCl affords the hydrochloride of the adduct *(2b)* in 70 to 75 % yield. The free base, whose structure was

proved by elemental analysis, and infrared, ultraviolet, NMR, and mass spectroscopy[5], can be liberated from the crude hydrochloride by NaOH (yield *ca.* 60 %). When heated at 160–180 °C and 0.1 mm its trifluoroacetate liberates diethylamine; simultaneously a colorless compound (fine needles from ethanol; m.p. 208–209 °C) sublimes which elemental analysis and mass spectroscopy[5] indicate to have the composition $C_{22}H_{18}$ (M = 282); we assign to it the structure *(3b)*.




*(a)*: R = H; *(b)*: R = $CH_3$

This structure is supported by the following data: The NMR spectrum ($CDCl_3$) consists of a multiplet between 2.10 and 2.90 τ, an $A_2B_2$ group of signals around 3.64 τ, and a singlet at 7.73 τ (ratio of areas 8:4:6). The ultraviolet spectrum [in $CH_3CN$: $\lambda_{max}$ = 325 mμ (ε = 9000), 312.5 (10700), 296.5 (10400), 279 (16000), 267 (16200), 258 (33500), 249 (31500), and 230.5 (51500)] shows, *inter alia*, the maxima of the methylenefluorene chromophore. The infrared spectrum includes C=C absorption bands of medium intensity at 6.1 and 6.26 μ; the intense bands of the sesquifulvalene system at 6.3–6.4 μ are absent. The most important peaks in the mass spectrum[5] are at m/e = 282, 267, 252, 202 and 165. Contrary to *(4a)*, *(3b)* is not protonated in $CF_3CO_2H$. Ozonolysis in ethyl acetate at −15 °C and oxidative working-up give fluorenone (52 %). Hydrogenation (Pd, ethanol, 20 °C) leads to a mixture whose NMR spectrum comprises two multiplets between 2.13 and 2.95 τ and between 7.25 and 9.47 τ (ratio of areas 8:18), and whose ultraviolet spectrum is almost identical with that of fluorene.

The sesquifulvalene structure *(4b)* and the mechanistically plausible cyclooctatetraene structure *(5b)* are thus excluded.

The norcaradiene *(3b)* is stable up to at least 275 °C; its NMR spectrum is unchanged up to 200 °C. Irradiation with ultraviolet light filtered through Vycor glass does not cause isomerisation to *(4b)*; photolysis of the cyclohexadiene ring is opposed by the three-membered ring fused to it, which prevents conrotative ring opening[6]. At temperatures up to 200 °C the compound *(3b)* reacts neither with maleic anhydride nor with dimethyl acetylenedicarboxylate. Treatment with tetracyanoethylene leads to a π-complex that is stable in solution ($\lambda_{max}$ in $C_{16}H_{12}$ = 545 mμ, in $CH_2Cl_2$ 570 mμ).

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[1] Present address: Laboratoire de Chimie organique de l'Université Lausanne, Place du Château, Lausanne/Switzerland.

[2] *H. Prinzbach*, *W. Rosswog*, and *R. Cruse*, unpublished work; *W. Rosswog*, Dissertation, Universität Freiburg, 1965.

[3] *H. Prinzbach* and *W. Rosswog*, Tetrahedron Letters *1963*, 1217; *D. Seip*, Dissertation, Universität Freiburg, 1965.

[4] *H. Prinzbach* and *U. Fischer*, Angew. Chem. *77*, 621 (1965); Angew. Chem. internat. Edit. *4*, 598 (1965).

[5] We are grateful to Dr. *J. Seibl*, ETH Zurich, and Dr. *H. Achenbach*, Freiburg, for the mass-spectroscopic investigations.

[6] *R. B. Woodward* and *R. Hoffmann*, J. Amer. chem. Soc. *87*, 395 (1965).

## Alkoxycarbonylation of Secondary and Primary Amines by Alkoxycarbonylmercury Compounds

By Prof. Dr. U. Schöllkopf and cand. chem. F. Gerhart

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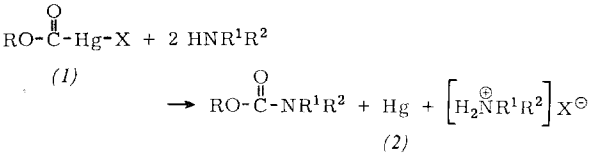
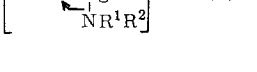
der Universität Göttingen (Germany)

When alkoxycarbonylmercury halides or acetates *(1)*[1] are allowed to react with 2 moles of a secondary or primary amine in tetrahydrofuran or dimethoxyethane, urethanes *(2)* are formed with separation of metallic mercury.




R = Alkyl
X = OAc, Br, Cl
$R^1$ = Alkyl, Aryl
$R^2$ = H, Alkyl




| R | X | Amine | Solvent | Temp. [°C] | Urethane | Yield [%] |
|---|---|---|---|---|---|---|
| $CH_3$ | OAc | Piperidine | Dimethoxyethane | 0 | Methyl piperidine-1-carboxylate | 60 |
| $CH_3$ | Br | Piperidine | Tetrahydrofuran | 0 | Methyl piperidine-1-carboxylate | 67 |
| $CH_3$ | OAc | Diethylamine | Dimethoxyethane | 0 | Methyl *N,N*-diethylcarbamate | 56 |
| $CH_3$ | Br | Diethylamine | Tetrahydrofuran | 0 | Methyl *N,N*-diethylcarbamate | 59 |
| $CH_3$ | OAc | Isopropylamine | Methanol | 0 | Methyl *N*-isopropylcarbamate | 63 |
| $C_2H_5$ | Cl | Piperidine | Dimethoxyethane | 0 | Ethyl piperidine-1-carboxylate | 59 |
| $C_6H_5CH_2$ | Cl | Piperidine | Dimethoxyethane | 25 | Benzyl piperidine-1-carboxylate | 43 |
| $C_2H_5$ | OAc | Ethanolamine | Dimethoxyethane | 25 | Ethyl *N*-(2-hydroxyethyl)carbamate | 68 |
| $CH_3$ | OAc | Glycine ethyl ester | Dimethoxyethane | 25 | *N*-(Methoxycarbonyl)glycine ethyl ester | 84 |
| $CH_3$ | OAc | Aniline | Dimethoxyethane | 100 | Methyl carbanilate | 53 |
| $CH_3$ | OAc | *p*-Tolnidine | Dimethoxyethane | 100 | Methyl *N*-(*p*-tolyl)carbamate | 86 |
| $CH_3$ | OAc | α-Naphthylamine | Dimethoxyethane | 100 | Methyl *N*-(α-naphthyl)carbamate | 35 |

Complexes *(3)* probably are intermediates in these reactions as there the nitrogen atom is favorably placed for attack on the carbonyl group. On reaction with alcohols the compounds *(1)* afford carbonates. Since, however, hydroxy group reacts appreciably more slowly, selective alkoxycarbonylation can be achieved with amino alcohols.

Received: November 25th, 1965 [Z 118/950 IE]
German version: Angew. Chem. *78*, 209 (1966)

[1] *W. Schoeller*, *W. Schrauth*, and *W. Essers*, Ber. dtsch. chem. Ges. *46*, 2864 (1913).

## Reaction of Tungsten Hexacarbonyl with Azide [1]

By Priv.-Doz. Dr. W. Beck and Dipl.-Chem. H. S. Smedal

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Tungsten hexacarbonyl reacts with alkali or tetraalkylammonium halides or pseudohalides $M^IX$ (X = halogen or NCS) with elimination of one CO ligand, giving compounds of the type $M^I[W(CO)_5X]$ [2]. However, tetraethylammonium azide [3] and $W(CO)_6$ (molar ratio 1:15) in diethylene glycol dimethyl ether (diglyme) at 80 °C afford yellow, diamagnetic tetraethylammonium isocyanatopentacarbonyltungstate(0), $[N(C_2H_5)_4][W(CO)_5NCO]$. The anion $[W(CO)_5NCO]^-$ is also directly accessible from $W(CO)_6$ and potassium cyanate in diglyme at 100 °C and can be precipitated by tetraphenylarsonium chloride in ethanol/water as a lemon-yellow, crystalline salt, $[As(C_6H_5)_4][W(CO)_5NCO]$, m.p. 157 °C (decomp.), soluble in ethanol, acetone, and tetrahydrofuran. This complex corresponds in analysis and infrared spectrum to the product obtainable from $W(CO)_6$, azide, and $As(C_6H_5)_4Cl$; conductivity and molecular-weight determinations indicate the salt to be extensively dissociated ($M_{exp.}$ = 377). In accord with $C_{4v}$ symmetry, the infrared spectrum of the anion $[W(CO)_5NCO]^-$ (in acetone) contains three CO bands, at 2067(w), 1927(st), and 1868(m) $cm^{-1}$, and pseudoasymmetric and symmetric NCO stretching vibrations at 2236(m) and 1323(m) $cm^{-1}$ [4]. The positions of the $\nu_{as}NCO$ and $\nu_sNCO$ vibrations prove the anion $[W(CO)_5NCO]^-$ to be an isocyanate complex containing a W–NCO bond.

Reaction of $W(CO)_6$ with azide probably occurs by nucleophilic attack of azide on a CO ligand, loss of nitrogen, and rearrangement to the stable isocyanate, analogously to the Curtius azide degradation. Several reactions of metal carbonyls involving nucleophilic attack on carbon monoxide bound in a complex have been discovered recently [5]. The first such reaction of $W(CO)_6$ observed was that with carbanions [6].

Received: December 15th, 1965 [Z 124/955 IE]
German version: Angew. Chem. 78, 267 (1966)

[1] Part 13 of Pseudohalogen-Metal Compounds. – Part 12: *W. Beck, E. Schuierer,* and *K. Feldl,* Angew. Chem. *78*, 267 (1966); Angew. Chem. internat. Edit. *5*, 249 (1966).

[2] *E. O. Fischer* and *K. Öfele,* Chem. Ber. *93*, 1156 (1960); *E. W. Abel, I. S. Butler,* and *J. G. Reid,* J. chem. Soc. (London) *1963*, 2068; *A. Wojcicki* and *M. F. Farona,* J. inorg. nuclear Chem. *26*, 2289 (1964).

[3] Prepared according to *V. Gutmann, G. Hampel,* and *O. Leitmann,* Mh. Chem. *95*, 1034 (1964).

[4] $\nu_3NCO$ from the infrared spectrum of solid $[As(C_6H_5)_4][W(CO)_5NCO]$ (in KBr).

[5] *Th. Kruck* and *M. Noack,* Chem. Ber. *97*, 1693 (1964).

[6] *E. O. Fischer* and *A. Maasböl,* Angew. Chem. *76*, 645 (1964); Angew. Chem. internat. Edit. *3*, 580 (1964).

## 1,3-Dioxolan-2-yl Hydroperoxide

By Prof. Dr. A. Rieche, Dr. H.-E. Seyfarth, and
Dipl.-Chem. A. Hesse

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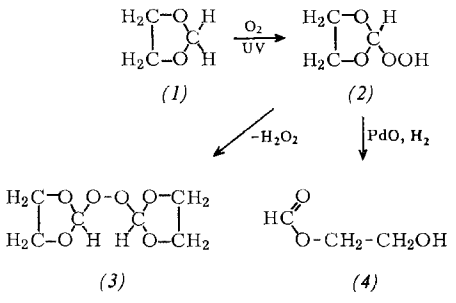
1,3-Dioxolane (ethylene glycol formal) *(1)* is an excellent solvent but, because of its marked tendency to peroxide formation in air, it cannot always be used [1].

We have isolated 1,3-dioxolan-2-yl hydroperoxide after peroxidation of the formal *(1)*. After peroxidation to 15 % conversion (18 °C, $O_2$, UV-irradiation) enrichment was effected by distillation at 20 °C (bath temperature) and 10 mm. The colorless oily residue contained 90 % of the peroxide *(2)* (determined iodometrically), which gave hydroperoxy-OH bands at 3350 $cm^{-1}$. $H_2O_2$ and a little of the peroxide distilled at 80 °C (bath temperature) and 0.2 mm. The crystalline distillation residue was bis-(1,3-dioxolan-2-yl) peroxide *(3)* (white leaflets, m.p. 73.5–74.5 °C from alcohol, peroxide content 97.8 %, peroxide bands at 810 and 870 $cm^{-1}$).




*(1)* *(2)* *(3)* *(4)*

Hydrogenation of the hydroperoxide *(2)* (PdO in ether, 20 °C) gave 2-hydroxyethyl formate *(4)* quantitatively. After hydrolysis (1 N $H_2SO_4$, 20 °C, 2 h) of *(2)*, 98 % of $H_2O_2$ was found.

The cyclic acetals of acetaldehyde, propionaldehyde, and isobutyraldehyde behave similarly. The derived hydroperoxides were isolated in 90 to 95 % purity. Hydrogenation afforded the corresponding glycol monoesters, and peroxides of type *(3)* were either detected or isolated [2].

Received: December 20th, 1965 [Z 120/952 IE]
German version: Angew. Chem. 78, 269 (1966)

[1] *A. Rieche, E. Schmitz,* and *E. Beyer,* Chem. Ber. *91*, 1935 (1958).

[2] *R. Criegee* and *M. Lederer* have described di-(2-methyl-1,3-dioxolan-2-yl) peroxide; Houben-Weyl: Methoden der organischen Chemie. 4th Edit., Thieme-Verlag, Stuttgart 1952, Vol. VIII/3, p. 23; *M. Lederer,* Diploma Thesis, Technische Hochschule Karlsruhe, 1950.

## New Initiators for Low-Temperature Polymerization

By Priv.-Doz. Dr. Ch. Rüchardt, Dipl.-Chem. H. Böck, and
Dipl.-Chem. I. Ruthardt

Institut für Organische Chemie
der Universität München (Germany)

t-Butyl peroxycarboxylates *(1)* containing in α-position to the carboxy group an aryloxy or alkoxy group or a corresponding sulfur function have been obtained in good yields

Half-lives of peresters *(1)* in ethylbenzene.
$X{-}CR_2{-}CO{-}O{-}O{-}C(CH_3)_3$ *(1)*

| X [a] | $t_{1/2}$ (min) |
|---|---|
| R = H; 70.5 °C | |
| H (38; 17) | *ca.* 45000 |
| 2,4,5-Trichloro-$C_6H_2$–O– | 200 |
| 4-$NO_2$–$C_6H_4$–O– (31; 13) | 171 |
| 2,4-Dichloro-$C_6H_3$–O– | 123 |
| 4-$C_2H_5O$–CO–$C_6H_4$–O– | 72 |
| 4-Br–$C_6H_4$–O– | 45 |
| 4-Cl–$C_6H_4$–O– | 40 |
| $C_6H_5$–S– | 30 |
| $C_6H_5$–O– (27; 4) | 26 |
| 4-$CH_3$–$C_6H_4$–O– | 16 |
| 4-$CH_3O$–$C_6H_4$–O– (25; –1) | 8 |
| R = H; 40.0 °C | |
| $C_6H_5$–$CH_2$–S– (24; –2,5) | 440 |
| $C_6H_5$–$CH_2$–O– (24; 2) | 86 |
| $CH_3$–O– (25; 4) | 52 |
| $C_2H_5$–O– (25; 3,5) | 39 |
| i-$C_3H_7$–O– (24; 2) | 24 |
| R = $CH_3$; 40.0 °C | |
| 4-Cl–$C_6H_4$–O– | 16 |

[a] Values in parentheses are $\Delta H^{\neq}$ (kcal/mole) and $\Delta S^{\neq}$ (cal $deg^{-1}$ $mole^{-1}$).

from acid chlorides and t-butyl hydroperoxide by the Schotten-Baumann procedure or with pyridine in pentane, ether, methylene chloride, or benzene at −20 °C. They have been characterized by their spectra and elemental analyses. They undergo thermolysis up to 50000 times faster than t-butyl peracetate or other simple peresters and thus have significance as low-temperature initiators. Product analyses, dependence of the reaction rate on solvent and concentration, activation parameters, and polymerization experiments with styrene and acrylonitrile indicate a homolytic fragmentation [1] as the rate-determining step.

Since decomposition of the compounds with oxygen-containing substituents is faster than that of those with the corresponding sulfur-containing substituents, and that of alkoxy compounds is faster than that of aryloxy compounds, it is concluded that a polar effect [1] is responsible for the thermolability of these substances. Acyloxy groups have a similar but weaker effect. The compounds should be prepared only with special precautions and in small quantities (grams), since some of them deflagrate at room temperature. Explosions have not yet occurred [2].

Received: December 14th, 1965 [Z 125/956 IE]
German version: Angew. Chem. 78, 268 (1966)

[1] Review and references: *Ch. Rüchardt*, Fortschr. chem. Forsch., in the press.

[2] The compounds listed in the Table under 70.5°C can be prepared and handled in 50–100 g lots if the temperature is maintained at or below 0°C by efficient cooling. Larger amounts have so far not been prepared. The more labile α-peroxyacetates should be prepared and stored only in dilute solution at −20°C except in dealing with small amounts.

# CONFERENCE REPORTS

## Eighth European Congress on Molecular Spectroscopy

The Eighth European Congress on Molecular Spectroscopy was held in Copenhagen from August 14th to 20th, 1965. Four hundred lectures were delivered to about 800 participants in up to ten simultaneous sessions.

From the lectures:

*M. Zander* (Castrop-Rauxel, Germany) discussed the continued interest in the systematic changes in absorption, fluorescence, and phosphorescence bands, brought about by systematic variation of the basic structure of a molecule. In single or multiple ortho-fusion to carbazole, for example, fusion in the 2,3-position and the 6,7-position leads to an appreciable bathochromic shift, whereas the latter is small when fusion takes place in the 3,4-position and the 5,6-position. *J. H. Eggers et al.* (Aarhus, Denmark) used the dichroism of molecules oriented in stretched films to determine the transition moment directions of individual bands.

This parameter is increasingly used in the classification of spectra and electronic excitation states. *F. Dörr* and *G. Hohlneicher* (Munich, Germany) determined the relative transition moment directions of biphenylene derivatives from the emission anisotropy, and compared the results with those of model calculations. Until recently only the energies of excited molecular states were known, and only now have attempts been made to determine other physical parameters of these states. Thus *D. E. Freeman* and *W. A. Klemperer* (Cambridge, Mass., USA) have determined the dipole moment of formaldehyde in the $^1A_2$ state (excited at 339 mμ) from the Stark shift of single rotational lines and obtained a value of 1.57 D (the dipole moment in the ground state is 2.34 D). There is a lack of detailed data on the intramolecular transitions between the energy levels, and this problem requires thorough quantitative investigations of the type carried out by *H. Labhart* (Zurich, Switzerland) to determine the probability of singlet-triplet transitions occurring when optically excited molecules return to the ground state. This new technique can also be applied to the measurement of triplet-triplet absorption spectra. *M. A. El-Sayed* (Los Angeles, USA) discussed a further means of studying the singlet-triplet transition probabilities by the perturbation of phosphorescence through incorporation of a heavy atom, or by resonance effects in the host lattice. *R. M. Hochstrasser* (University of Pennsylvania, USA) investigated the line splitting, often caused by lattice defects, in the singlet-triplet transitions taking place in crystalline derivatives of benzene and naphthalene. *H. H. Jaffé* (Cincinnati, USA) used the Pariser-Parr-Pople method to interpret the electronic spectra of *trans*-stilbene and *trans*-azobenzene.

The results of the Pariser-Parr-Pople calculations and similar approximations are known to depend on the choice of the parameters (one-electron one-center and two-center integrals and two-electron one-center integrals), and *I. Fischer-Hjalmars* (Stockholm, Sweden) attempted to deduce from theoretical considerations parameters applicable to as many compounds as possible, particularly to π-electron systems containing heteroatoms. By contrast, *M. Klessinger* (Göttingen, Germany) estimated the parameters from experimental data (transition energies, oscillator strengths, dipole moments) for simple molecules such as aniline, so as to improve the agreement between experimental values and the results of the Pariser-Parr-Pople treatment. These calculations were used to interpret the electronic spectra of merocyanines and indigoids. *F. F. Seelig* (Marburg, Germany) reported on the use of digital computers in further developments of the theory of π-electron systems on the basis of the Kuhn model of a two-dimensional electron gas. *J. Linderberg* and *Y. Öhrn* (Uppsala, Sweden) investigated a new model for the spectra of π-electron systems, particularly alternant aromatic hydrocarbons, the model being based on Green's Functions.

The model used in most theoretical treatments is still based on the assumption that the nuclear configuration does not change in the course of electronic transitions. The fact is, however, that excitation may be accompanied by a change in the nuclear configuration and even in the symmetry of the molecule. Non-vertical transitions are then determined by Franck-Condon factors. *W. L. Smith* and *P. A. Warsop* (Dundee, U. K.) calculated these factors for HCN, and compared the results with those obtained from the analysis of molecular rotations. The theoretical investigations of *L. Burnelle* (Balto, Md., USA) confirmed that, in the lowest triplet state, the $CH_2$ groups in ethylene are staggered and tilted with respect to each other.

As can be seen from the last example, the applicability of the Pariser-Parr-Pople method is not restricted to the interpretation of electronic spectra. Thus *J. Hinze* (Stuttgart, Germany) developed a theory for the excimers of alternant hydrocarbons. *H. Dreeskamp* (Stuttgart) calculated the indirect, heteronuclear spin-spin coupling, and compared his results with experimental values. *M. J. S. Dewar et al.* (University of Texas, USA) calculated the π-electron densities in monofluorinated aromatic hydrocarbons and correlated the results with the fluorine-NMR spectroscopic data. *E. A. C. Lucken*

(Geneva, Switzerland) reported on the ESR spectra of conjugated free radicals containing a bivalent sulfur atom. He found that, when the 3d orbitals of the sulfur are taken into account, the experimental data are in very poor agreement with the theoretical values.

One application of infrared spectroscopy is the determination of molecular symmetry. *F. A. Miller* and *I. Matsubara* (Pittsburgh, Pa., USA) showed definitely that the butatriene molecule, $H_2C{=}C{=}C{=}CH_2$, is planar ($D_{2h}$). In the analysis of normal coordinates and calculation of the force constants in molecules of the type $(CH_3)_3CX$ and $(CH_3)_3C{-}C{\equiv}CX$ (X = H, D, F, Cl, Br, I), *W. Zeil et al.* (Kiel, Germany) found that, owing to strong coupling, a number of vibrations can no longer be considered to be localized on one bond alone. With the improvement of experimental techniques, the long-wavelength IR region (up to 10 $cm^{-1}$) has assumed a certain interest. *W. G. Fateley* and *F. A. Miller* (Pittsburgh, Pa., USA) carried out comparative measurements with a Michelson interferometer and with a lattice-filter spectrophotometer concluding that the latter is generally a more suitable instrument. *N. T. McDevitt, F. F. Bentley*, and *A. D. Davidson* (Wright Patterson Air Force Base, Ohio, USA) showed that the far IR spectra of inorganic compounds such as simple metal oxides, sulfides, and halides are generally complex and depend on the crystal structure, the coordination number, and the lattice constant. *I. J. Wick* (Morse Laboratories, USA) has obtained some information from long-wavelength IR absorption in connection with the molecular configuration, particularly the *cis-trans* configuration of double bonds and the configuration of cyclohexane derivatives. *G. C. Hayward* and *P. J. Hendra* (London, England) showed that the spectra of charge-transfer complexes in the short-wavelength IR region are essentially superpositions of the spectra of the components, but in the long-wavelength IR region new lines may appear. This phenomenon may be due partly to the activation of forbidden transitions. The absorption lines appearing in the region of 20 to 50 $cm^{-1}$ in polar liquids such as nitriles, ketones, and nitro compounds were attributed by *G. W. Chantry* and *H. A. Gebbie* (Teddington, England) to the "lattice" of the liquid and by *E. R. Lippincott* (College Park, Maryland, USA) to the stretching vibrations of dipole complexes (dimers or clusters). The investigations may provide detailed information on the intermolecular attraction between polar molecules, and possibly also on the structure of polar liquids. The long-wavelength IR absorption of molecules linked by hydrogen bonds can contribute to the elucidation of such bonding. *K. Nakamoto* (Chicago, USA) determined the force constants and identified the bands of dimeric acetic and formic acid. *R. J. Jakobsen* and *J. W. Brasch* (Columbus, Ohio, USA) found a splitting in the OH-stretching and the OH-deformation vibrations of several hydroxy compounds, and attributed it to intermolecular association.

*H. E. Hallam* and *D. Jones* (Swansea, Wales, U. K.) used short-wavelength IR absorption to investigate the intermolecular association of alcohols and fluorinated alcohols and the formation of hydrogen bonds with various proton-acceptors in the gaseous state. *L. P. Kuhn* and *E. E. Bowman* (Aberdeen Proving Ground, Md., USA) used a similar method for determining the equilibrium constants and the frequency shifts of the hydrogen-bonded complexes of phenol with unsaturated hydrocarbons. *W. Luck* (Ludwigshafen, Germany) obtained data on the variation of the hydrogen-bond energy with the bond angle by investigating the formation of hydrogen bonds between pyrrolidone and various proton-acceptors as a function of concentration and temperature. On the basis of theoretical and experimental studies, *K. Szczepaniak* (Warsaw, Poland) concluded that charge-transfer interactions must be basically responsible for the bonding forces in hydrogen-bond complexes in which a $\pi$-electron-donor acts as a proton-acceptor, whereas in complexes in which the proton-acceptor is a non-bonding electron-donor, electrostatic attractions are also significant.

The formation of charge-transfer complexes has recently been studied on many electron donors and acceptors in solutions. This work has now been extended to gases. *M. Tamres* (Ann Arbor, Mich., USA) reported on the diethyl sulfide-iodine complex, and *J. Prochorov* and *A. Tramer* (Warsaw, Poland) on charge transfer complexes formed by carbonyl cyanid $CO(CN)_2$ with a number of electron donors. In comparison with the charge-transfer bands in the gaseous state, those in solution exhibit a relatively strong red-shift (1500 to 3000 $cm^{-1}$), as expected on the basis of the great increase in dipole moment on excitation. Besides the extinction of the fluorescence of aromatic hydrocarbons by electron donors such as anilines or amines, *A. Weller et al.* (Amsterdam) observed the appearance of a new long-wavelength fluorescence band in solvents of low polarity. This may be explained by the formation of a charge-transfer complex from an excited molecule of hydrocarbon and an electron-donor. The new emission band is due to fluorescence of the complex. The formation of charge-transfer complexes from an excited molecule and an electron-donor has also been observed in the case of the excimers of aromatic hydrocarbons such as naphthalene, and *M. D. Lumb* and *D. A. Weyl* (Manchester, England) discussed the excimer fluorescence of alkylated benzenes. Short-lived (10 to 100 $\mu$sec) ions of organic compounds have been studied by *A. Terenin et al.* (Leningrad, USSR), together with the kinetics of decomposition of these ions. These authors found that, by the use of a "superfast" spectrophotometer, the spectra (300 to 1200 m$\mu$) of ions formed by a flash can be recorded in 20 $\mu$sec on an oscillograph.

Systematic investigations carried out by *W. Brügel* (Ludwigshafen, Germany) on the NMR spectra of numerous derivatives of naphthalene and anthracene have led to a more accurate picture of the influence of substituents on the NMR parameters. *G. Karagounis* (Freiburg, Germany) studied the NMR spectra of adsorbed molecules.

Of the many possible applications of lasers in molecular spectroscopy, the excitation of Raman spectra is of particular importance and has been extensively investigated by *W. W. Ward, K. P. George*, and *R. C. Hawes* (Monrovia, Calif., USA) and by *R. C. Gove* (Norwalk, Conn., USA). *R. Deen* (Delft, The Netherlands) reported on the vibrational structure associated with the $n{\rightarrow}\pi^*$ transitions manifested in the absorption and the circular dichroism of optically active ketones. The results will be useful in interpreting many of the complicated circular dichroism and optical rotational dispersion spectra. *R. Briat, M. Billardon*, and *J. Badoz* (Paris, France) designed an instrument for recording magneto-optical rotation (Faraday effect).

Particularly many lectures dealt exclusively or predominantly with theoretical problems. Thus many groups are engaged in calculations based on simplified models. In this connection, the Hückel method is being increasingly superseded by the Pariser-Parr-Pople treatment. It appears that satisfactory approximations can now be obtained for many problems with the aid of computers, although the theoretical prerequisites (and hence the limitations of the methods) are not entirely understood. While we may either welcome or regret the increasing theoretical trend in chemistry, we certainly cannot ignore it in research and particularly in the training of students of chemistry. [VB 962/271 IE]

German version: Angew. Chem. *78*, 270 (1966)
Translated by Express Translation Service, London

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## Photoalkylations

*D. Elad*, Rehovot (Israel)

The photoamidation of terminal olefins[1] (addition of formamide to the olefin induced directly by light or initiated photochemically by acetone with higher yields) has also been applied to non-terminal olefins. Here, it leads to a mixture of the two possible amides resulting from addition of the carbamoyl group, $CONH_2$, to either carbon atom of the double bond.

Cyclic olefins, such as cyclohexene and norbornene, as well as dienes, like 4-vinylcyclohexene and 1,5-cyclooctadiene,

were found to react with formamide under ultraviolet irradiation to give the higher amides. The addition of formamide to α,β-unsaturated esters was achieved through the use of benzophenone as a sensitizer and high yields of succinic amide esters have been obtained.

It is proposed that the photoaddition of formamide to olefins is a free radical chain reaction involving carbamoyl radicals $\bullet CONH_2$ and that the olefin serves as a scavenger for these radicals. The formation of the carbamoyl radicals is assumed to take place through hydrogen atom abstraction from formamide by the excited carbonyl compound.

The photoaddition of cyclic ethers to olefins can be achieved by direct irradiation or through photochemical initiation with a ketonic compound, *e.g.* acetone or acetophenone, with considerably higher yields. α-Substituted cyclic ethers are the major products of the reaction [2].

γ-Butyrolactone and 2-pyrrolidone were found to add to terminal olefins under ultraviolet irradiation to give 2-alkylated γ-butyrolactones in high yields [3], and mixtures of 3-alkylated and 5-alkylated 2-pyrrolidones [4], respectively.

*N*-Acetylglycine ethyl ester has been shown to react with olefins or toluene when irradiated in the presence of acetone, to yield the derivatives of higher amino acids and phenylalanine, respectively.

[Lecture at Marl (Germany), October 22nd, 1965] [VB 961/268 IE]

German version: Angew. Chem. *78*, 211 (1966)


[1] *D. Elad* and *J. Rokach*, J. org. Chemistry *29*, 1855 (1964).

[2] *D. Elad* and *R. D. Youssefyeh*, J. org. Chemistry *29*, 2031 (1964).

[3] *D. Elad* and *R. D. Youssefyeh*, Chem. Commun. *1*, 7 (1965).

[4] *D. Elad* and *J. Sinnreich*, Chem. and Ind. *1965*, 768.


## Studies of Chemical Reactions by Pulse Radiolysis: Free Electrons and Free Radicals in Aqueous Solution


*A. Henglein*, Berlin


Reactions of OH radicals and hydrated electrons that are produced by decomposition of water can be followed by pulse radiolysis (pulses of about $10^{-6}$ sec duration), the absorption of the hydrated electrons at 7200 Å immediately after the irradiation pulse being shown oscillographically as a function of time or the absorption spectra of the reaction products being measured.

Hydrated electrons react with tetranitromethane in a bimolecular process of rate constant (at 20 °C) $6.0\times10^{10}$ l mole$^{-1}$ sec$^{-1}$, with formation of the anion of *aci*-nitroform. From simultaneous observations of the disappearance of the absorption of the hydrated electrons and of the appearance of the nitroform absorption, the extinction coefficient of electrons in water was found to be $\varepsilon_{7200\,Å} = 1.55\times10^4$ l mole$^{-1}$ sec$^{-1}$.

Nitromethane reacts with hydrated electrons, giving the anion $CH_3NO_2^-$. This is an example of the first reduction stage of an aliphatic nitro compound. The anion absorbs at 2700 Å ($\varepsilon$ = 2800 l mole$^{-1}$ cm$^{-1}$) and undergoes a further reaction which is of the second order. In acidic solution the undissociated radical acid $CH_3N^{\bullet}\!\!<^{O}_{OH}$ is formed (pK = 4.5, $\lambda_{max}$ = 2500 Å, $\varepsilon_{max} = 2.0\times10^3$ l mole$^{-1}$ cm$^{-1}$). Two examples of reactions of this radical acid or its anion are charge transfer to tetranitromethane ($k = 1.2\times10^9$ l mole$^{-1}$ sec$^{-1}$) and reaction with oxygen.

The solvated electron reacts with hydrogen sulfide in aqueous solution by a diffusion-controlled process, *i.e.*, without activation energy, although the reaction in the gas phase has an energy barrier of 1.6 eV. The rapidity of the reaction in solution is considered due to solvation effects. The heat of hydration of the electron is materially less than that of a heavy negative ion. From the kinetic results it is concluded that values below 2.0 eV are commonest in the distribution of solvation energy of the hydrated electron, which agrees with calculations from the absorption spectrum of the hydrated electron.

The reaction of catalase with the OH radical is diffusion controlled, as shown by a comparison of the measured rate constant of $8.3\times10^{10}$ l mole$^{-1}$ sec$^{-1}$ with that calculated from the Smoluchowski equation [1]. For this purpose the radius of catalase, known from diffusion measurements, and the self-diffusion coefficient of water (which was treated as equal to the diffusion coefficient of the OH radical) were used. The reaction OH + catalase is diffusion controlled although 30 % of the individual amino acids of catalase react with OH in a process that is not diffusion controlled. This result was discussed in the light of *Noyes'* theory [2] of the probability of re-encounters in diffusion-controlled reactions. It is expected that macromolecules will react with radicals of lower molecular weight by a diffusion-controlled process, even when reaction of the isolated monomer, though fast, is not wholly diffusion-controlled.

[Lecture at Mülheim (Germany), November 3rd, 1965] [VB 963/269 IE]

German version: Angew. Chem. *78*, 212 (1966)


[1] *M. v. Smoluchowski*, Z. physik. Chem. B *42*, 129 (1918).

[2] *R. M. Noyes*, J. chem. Physics *22*, 1349 (1954).


## Amidothio-, Fluoroamidothio-, and Fluorothiophosphates


*H. H. Falius*, Braunschweig (Germany)


Reaction of phosphorus sulfide trichloride with aqueous ammonia gives ammonium diamidothiophosphate $NH_4[POS(NH_2)_2]$ and diammonium amidothiophosphate $(NH_4)_2[PO_2S(NH_2)]$. These salts can be readily isolated in pure form. The anions are quite stable in neutral aqueous and alkaline solution, but in acidic solution the diamidothiophosphate is rapidly hydrolysed to the monoamidothiophosphate; an acidic solution of the latter can be kept for several days in the cold without significant hydrolysis.

These compounds react extremely rapidly with hydrofluoric acid. In an excess of 20 % HF the amido groups are replaced by fluoride. The diamidothiophosphate thus gives the difluorothiophosphate $[POSF_2]^-$ with a small amount of the monofluorothiophosphate $[PO_2SF]^{2-}$, and the monoamidothiophosphate gives monofluorothiophosphate. The difluorothiophosphate is hydrolysed in acidic, HF-free solution to the monofluorothiophosphate.

The diamiodthiophosphate reacts with $F^-$ also in neutral solution, but not as far as in acidic solution. Only one amido group is replaced in an aqueous solution of the diamidothiophosphate containing ammonium fluoride: the resulting anion is fluoroamidothiophosphate, which exchanges its second amido group in hydrofluoric acid with formation of difluorothiophosphate.

The two fluorothiophosphates are also formed on reaction of phosphorus sulfide trichloride with aqueous fluoride solutions. Products formed by reaction with ammonium fluoride and ammonia include the fluoroamidothiophosphate.

The phosphorus-sulfur bond in fluorothiophosphates is much stronger than in thiophosphates or amidothiophosphates owing to the electronegativity of the fluorine. This is shown by the resistance of the phosphorus sulfur bond to hydrolysis and by the fact that silver sulfide is formed only slowly on reaction with silver nitrate. The reason is clearly the increased strength of the $d_\pi$–$d_\pi$ bond between phosphorus and sulfur, evidence of which is being sought by spectroscopic methods.

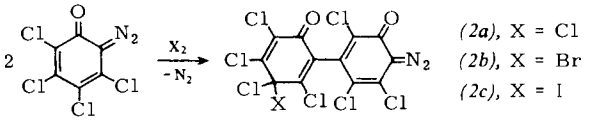
[Lecture at Braunschweig (Germany), November 29th, 1965] [VB 967/275 IE]

German version: Angew. Chem. *78*, 272 (1966)

## New Results in the Preparative Chemistry of Diazocarbonyl Compounds

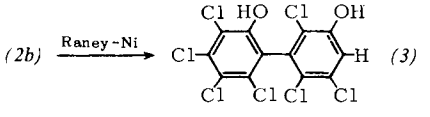
*E. Ried*, Frankfurt/Main (Germany)

Chlorine, bromine, or iodine react with tetrachloro-*o*-quinone diazide *(1)* already at room temperature, with elimination of nitrogen. Two molecules of quinone diazide dimerize by loss of one diazo group to compounds for which structure *(2)* is proposed.

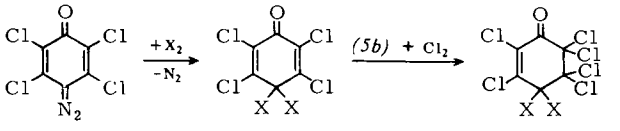


*(1)* *(2)* *(2a)*, X = Cl; *(2b)*, X = Br; *(2c)*, X = I

Raney nickel removes the halogen X again from *(2)*; simultaneously the oxo groups are converted into phenolic OH groups and the diazo group is exchanged for a H atom, giving the product *(3)*.

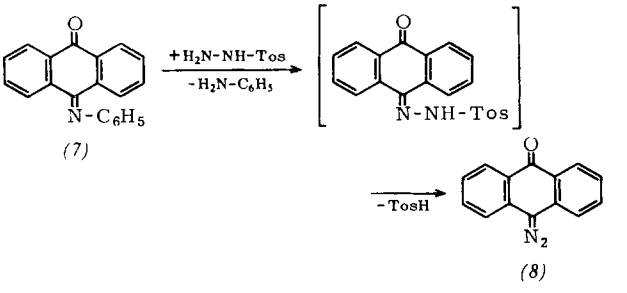


Tetrachloro-*p*-benzoquinone diazide *(4)* also loses nitrogen in presence of bromine or chlorine in ethanol. The halogen adds to the methylene-carbon [cf. *(5)*]. If an excess of halogen is used there is also addition to the C=C bond [cf. *(6)*].



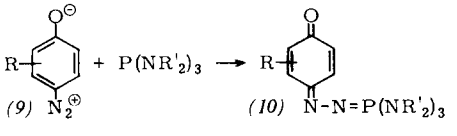
*(4)* *(5a)*, X = Cl; *(5b)*, X = Br *(6)*

Reaction of anthraquinone anil *(7)* with *p*-toluenesulfonylhydrazide leads smoothly to anthraquinone diazide *(8)*, but direct treatment of anthraquinone with the hydrazide is fruitless.



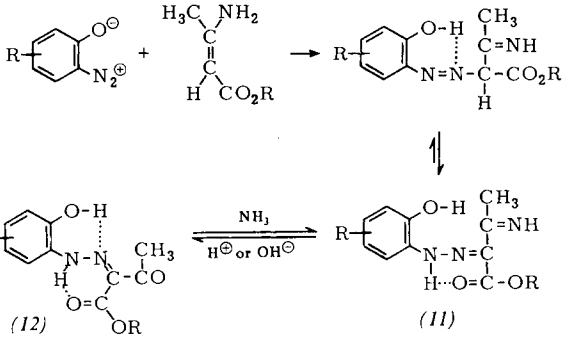
*(7)* *(8)*

*p*-Benzoquinone diazides *(9)*, analogously to *o*-quinone diazides[1], and triaminophosphines afford phosphorotriamide 4-oxocyclohexadienylidenehydrazones ("*p*-quinone triaminophosphazines") *(10)* which were previously unknown and are stable towards heat and hydrolysis.



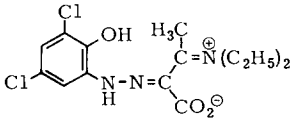
*(9)* *(10)*

In contrast to the reaction of ketenes, that of enamines with *o*-benzoquinone diazides does not lead to formation of oxadiazepines, but instead to coupling, with formation of *o*-hydroxyphenylhydrazones or *o*-hydroxyazo compounds. 3-Aminocrotonic esters or their *N*-monoalkyl derivatives give *o*-hydroxyarylhydrazones *(11)* of 3-imino-2-oxobutyric ester, which are cleaved by acid hydrolysis to *o*-hydroxyarylhydrazones of 2,3-dioxobutyric esters. In many cases the hydrolysis products can be isolated by coupling of *o*-quinone diazides with acetoacetic ester.



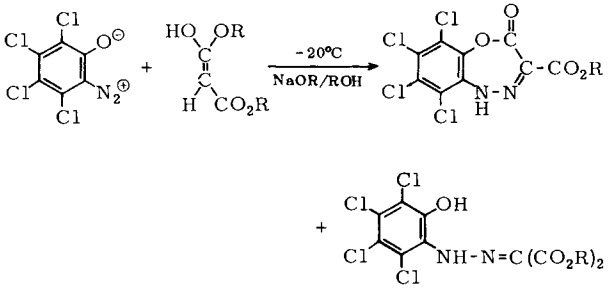
*(12)* *(11)*

*N,N*-Dialkyl derivatives of 3-aminocrotonic esters and *o*-quinone diazides couple only in sodium carbonate solution, the ester being hydrolysed to the acid and betaines [*e.g.*, *(13)*] formed.

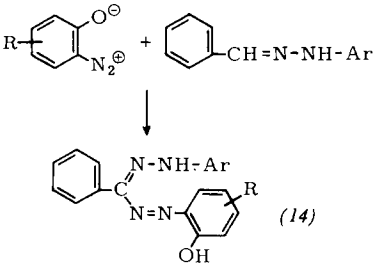


*(13)*

In certain cases sodiomalonic ester, which can be regarded as a concealed ketene derivative, adds to *o*-quinone diazides, *e.g.*:



Aldehyde arylhydrazones and *o*-quinone diazides couple to give hydroxylated formazans *(14)*, which function as indicators and give stable complexes with heavy-metal ions.



*(14)*

[Colloquium held at the Max-Planck-Institut für Medizinische Forschung, Heidelberg, on December 6th, 1965]
[VB 960/267 IE]
German version: Angew. Chem. *78*, 211 (1966)

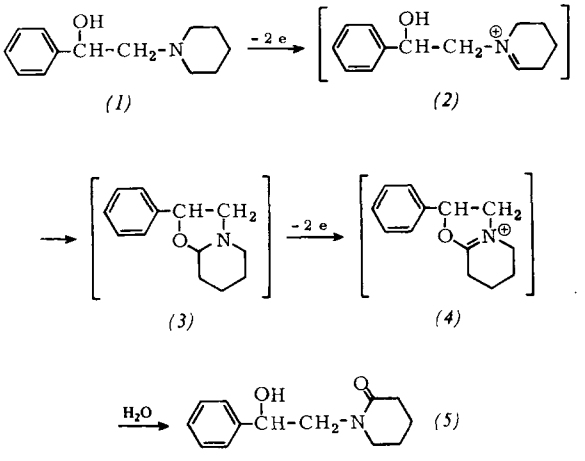
[1] *W. Ried* and *K. Wagner*, Liebigs Ann. Chem. *681*, 45 (1965).

## Dehydrogenation of Amine Derivatives with Hg-EDTA

*H. Möhrle*, Tübingen (Germany)

Since the work of *Gadamer* mercury(II) acetate has been used for dehydrogenation of amines, a variant of the method, due to *Knabe*, being addition of disodium EDTA. Comparative

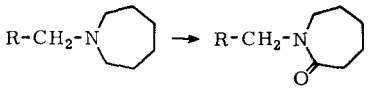
experiments have shown that Hg(II) acetate dehydrates at a higher redox potential but more slowly. When applied to amino alcohols, the two methods on occasions give different results. With Hg(II)-EDTA, lactams are formed in a reaction for which the following mechanism is assumed on the basis of model experiments. The amino alcohol, say *(1)*, is oxidized to an imonium compound *(2)*, which rearranges intramolecularly to the oxazolidine *(3)*. Further oxidation affords the hydroxy-lactam *(5)* by way of the oxazolinium cation *(4)*.



Whereas the existence of the imonium structure can be proved indirectly for open-chain amino alcohols through their hydrolysis products, this structure cannot be isolated from simple *N*-heterocyclic compounds. Nevertheless, formation of the oxazolidine from tetrahydro-2-(2-hydroxyethyl)isoquinolines involves increased ring strain, so that in these cases the hydroxy-imonium form [cf. *(2)*] can be isolated as a salt or, if worked up in an alkaline medium, as an oxazolidine.

For these relatively stable oxazolidines the rates of dehydrogenation with and without addition of disodium EDTA to the Hg(II) acetate solution have been compared as far as the hydroxy-lactam stage; here too, faster reaction was found with Hg(II)-EDTA.

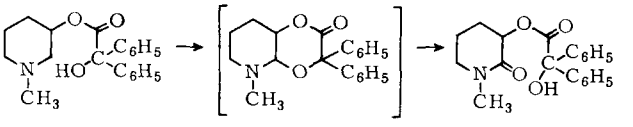
On variation of the heterocyclic component the lactams *(5')* were obtained from the amino alcohols *(1')*.



*(1')* *(5')*

R = $C_6H_5$-CH(OH), $C_6H_5$-CH(OH)-$CH_2$, $C_6H_5$-O-$CH_2$-CH(OH)

The ester *(6)* gives a lactam *(7)*, which shows that there is no necessity for the nitrogen to be the bridgehead-atom of an intermediate bicyclic compound.



*(6)* *(7)*

[Lecture at Tübingen, December 17th, 1965]

[VB 968/276 IE]

German version: Angew. Chem. *78*, 273 (1966)

# SELECTED ABSTRACTS

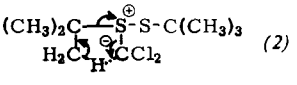
**The hydrogenation of carbodiimides to N,N'-disubstituted formamidines** with $Pd(OH)_2/BaSO_4$ and with Raney nickel has been studied by *J. C. Jochims*. On catalytic hydrogenation (room temperature, normal pressure) in ethanol, aliphatic, aromatic, and mixed carbodiimides rapidly take up 1 mole of $H_2$ to form *N,N'*-disubstituted formamidines *(1)*. The yields are generally higher than 90 %.

$$R{-}N{=}C{=}N{-}R' \rightarrow R{-}NH{-}CH{=}N{-}R'$$
*(1)*

Examples: *N,N'*-dicyclohexylformamidine, m.p. 97–99 °C, yield 99 %; *N*-isopropyl-*N'*-cyclohexylformamidine, m.p. 69–71 °C, yield 99 %; *N,N'*-bi(benzhydryl)formamidine, m.p. 90–91 °C, yield 99 %, *N,N'*-bis-(4-methoxyphenyl)-formamidine, m.p. 114–115 °C, yield 50 %. / Chem. Ber. *98*, 2128 (1965) / –Ma. [Rd 385/594 IE]

**The selective cleavage of a carbon-sulfur bond** in a disulfide has been observed for the first time by *S. Searles jr.* and *R. E. Mann*. The reaction of t-butyl disulfide with dichlorocarbene gives an 80 % yield of t-butyl dichloromethyl disulfide *(1)*, the S–S bond remaining intact.

$$(CH_3)_3C{-}S{-}S{-}C(CH_3)_3 + Cl_2C: \rightarrow (CH_3)_3C{-}S{-}S{-}CHCl_2 + (CH_3)_2C{=}CH_2$$
*(1)*



*(2)*

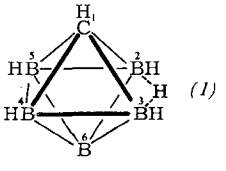
The reaction involves treatment of a boiling solution of the disulfide in glycol dimethyl ether with sodium trichloroacetate. It probably proceeds *via* the ylide *(2)*. / Tetrahedron Letters *1965*, 2899 / –Ma. [Rd 382/591 IE]

**Bis(trifluoromethylsulfonyl) peroxide and trifluoromethyl trifluoromethanesulfonate** have been prepared by *R. E. Noftle* and *G. H. Cady*. When trifluoromethanesulfonic acid is electrolysed at –23 °C, bis(trifluoromethanesulfonyl) peroxide $CF_3SO_2{-}OO{-}SO_2CF_3$ is formed at the anode. When heated to 10 °C, the peroxide decomposes to form perfluoroethane, sulfur trioxide, and the new ester trifluoromethyl trifluoromethanesulfonate $CF_3SO_3CF_3$. The ester is stable towards water; hydrolysis occurs only at 100 °C in 0.1 N sodium hydroxide solution. The decomposition products formed when the peroxide is heated can be accounted for by the following hypothetical mechanism:

$$(CF_3SO_3)_2 \rightarrow 2\ CF_3SO_3\bullet$$
$$CF_3SO_3\bullet \rightarrow CF_3\bullet + SO_3$$
$$CF_3SO_3\bullet + CF_3\bullet \rightarrow CF_3SO_3CF_3$$
$$2\ CF_3\bullet \rightarrow C_2F_6$$

/ Inorg. Chem. *4*, 1010 (1965) / –Sch. [Rd 432/641 IE]

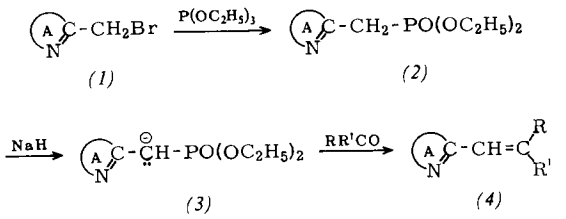
**Monocarbahexaborane(7)** *(1)*, the first carborane with only one carbon atom, was made by *T. Onak, R. Drake*, and *G. Dunks* by passing a silent electrical discharge through 1-methylpentaborane: 0.15 mole yielded 13 mg of *(1)*, which has a



*(1)*

vapor pressure of 503 mm at 26 °C. The structure *(1)* is supported by the infrared and NMR spectra, but the bridging hydrogen could also be located between B–2 and B–6. / J. Amer. chem. Soc. *87*, 2505 (1965) /–Ma. [Rd 347/556 IE]

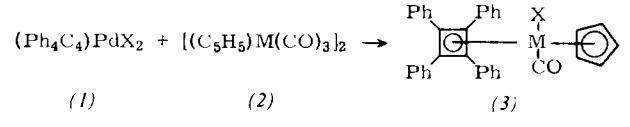
**The synthesis of basic heterocyclic alkenes** by the Horner reaction has been described by *E. B. Knott*. The reaction of the bromomethyl compounds *(1)* (A = 2-benzothiazolyl or 2-quinolyl) with $P(OC_2H_5)_3$ gives *(2)*. Treatment of *(2)* with NaOH yields the anion *(3)*, which reacts with a wide range of aldehydes and ketones to form the alkenes *(4)*.



*(1)* *(2)* *(3)* *(4)*

Example: A = 2-benzothiazolyl, R = H, R′ = $C_6H_4N(CH_3)_2$, m.p. 206 to 208 °C; A = 2-quinolyl, R = $CH_3$, R′ = $C_6H_5$, m.p. 102 to 103 °C. / J. chem. Soc. (London) *1965*, 3793 / –Kü. [Rd 416/625 IE]

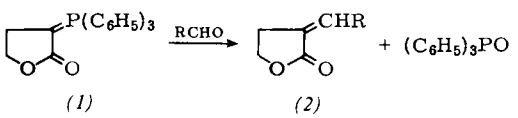
**(π-Cyclopentadienyl)(π-tetraphenylcyclobutadiene)-molyb-denum and -tungsten carbonyl halides** have been by prepared *P. M. Maitlis* and *A. Efraty*. The heterogeneous reaction of tetraphenylcyclobutadienepalladium halides *(1)* with cyclopentadienylmetal tricarbonyl *(2)* leads to the formation of (π-cyclopentadienyl) (π-tetraphenylcyclobutadiene)-metal carbonyl halides *(3)*.



*(1)* *(2)* *(3)*

[*(3a)*: M = Mo, X = Cl, decomp. p. 261 to 266 °C; *(3b)*: M = Mo, X = Br, decomp. p. 248 to 250 °C; *(3c)*: M = W, X = Br, decomp. p. 227 to 228 °C]. The molybdenum complexes *(3a)* and *(3b)* are formed in xylene in yields of approximately 18 %, whereas the tungsten complex *(3c)* is formed in benzene in a yield of about 1 %. *(3a)* and *(3b)* form red-brown crystals, which are stable in air; however, their solutions are very sensitive to heat and to air. In the NMR spectrum of *(3a)*, the areas of the phenyl-proton and the cyclopentadienyl-proton signals are in the ratio of 20:5. The infrared spectra of all the compounds are identical, indicating that the complexes all have the same structure. / J. organomet. Chemistry *4*, 172 (1965) / –Sch. [Rd 429/638 IE]

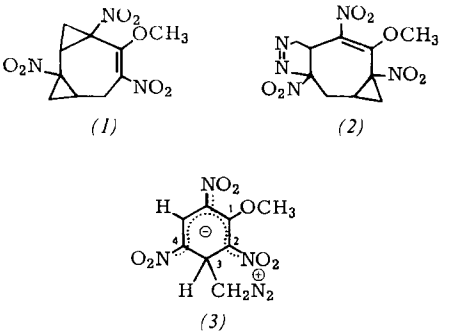
**Substituted α-benzylidene-γ-butyrolactones** *(2)* have been synthesized by *H. Zimmer* and *T. Pampalone* using a Wittig carbonyl olefination. α-Benzylidene derivatives could previously be obtained only with difficulty, if at all, by the direct reaction of butyrolactone with substituted aromatic aldehydes, but were now made in excellent yields by treating substituted aldehydes with *(1)* in refluxing tetrahydrofuran. Compounds made include *(2)* with R = 3-nitrophenyl, m.p. 147–148 °C



*(1)* *(2)*

(81 % yield); R = 4-cyanophenyl, m.p. 157–159 °C (82 %); and R = 4-acetamidophenyl, m.p. 199–200 °C (89 %). / J. heterocycl. Chemistry *2*, 95 (1965) / –Ma. [Rd 346/555 IE]

**Diazomethane adds to picric acid** to form the cycloheptene derivatives *(1)* and *(2)*, as has been reported by *Th. J. de Boer*.



*(1)* *(2)*



*(3)*

The first step is the addition of one molecule of diazomethane to form 2,4,6-trinitroanisole, and this is followed by the addition of a second molecule of diazomethane on C-3, with formation of the compound *(3)*. A three-membered ring can be formed by elimination of nitrogen accompanied by ring closure on C-2 or C-4. The compounds isomerize to form 2,4,6-trinitro-5-methoxycyclohepta-1,3,5-triene and 2,4,6-trinitro-5-methoxycyclohepta-2,4,6-triene. Further molecules of diazomethane can now add readily to the double bonds, which are strongly activated by the nitro groups. Addition of one molecule of $CH_2N_2$ to the double bond between C-3 and C-4 in the cyclohepta-1,3,5-triene derivative yields a substituted homotropilidene, *i.e.* a molecule with a fluctuating structure. *(1)* and *(2)* can be converted by oxidative degradation into nitrocyclopropanes, which are difficult to obtain by other methods. / Tetrahedron *20*, Suppl. 1, 339 (1964) / –Bu. [Rd 446/655 IE]

**Mitochondria are not the only cell organelles with an oxidizing function.** *P. Baudhuin et al.* describe a new type of microscopic particle which they have discovered in rats' liver and kidneys and in *Tetrahymena pyriformis*. The particles are characterized as containing uric acid oxidase, D-amino acid oxidase, and catalase, *i.e.* two enzymes that form hydrogen peroxide and one that decomposes hydrogen peroxide. It is thought that the particles are the site of non-phosphorylating oxidations, which lead to the formation of $H_2O_2$. / Biochem. biophys. Res. Commun. *20*, 53 (1965) / –Hö. [Rd 406/615 IE]

**Succinyl phosphate is an intermediate in the biosynthesis of succinyl-coenzyme A** from succinate, CoA, and ATP in *Escherichia coli*, which is catalysed by succinyl-CoA synthetase. *J. S. Nishimura* and *A. Meister* have shown that the reaction proceeds by the route:

$$\text{Succinate} + \text{ATP} \rightleftharpoons \text{succinyl phosphate} + \text{ADP}$$
$$\text{Succinyl phosphate} + \text{CoA} \rightarrow \text{succinyl-CoA} + \text{phosphate}$$

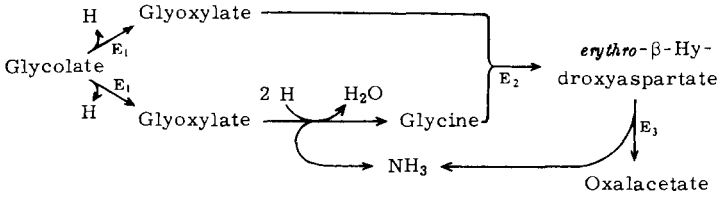
This scheme involves four reaction steps: 1. succinyl-CoA is formed from succinyl phosphate and CoA; 2. incubation of the enzyme with ADP and succinyl phosphate leads to the formation of ATP; 3. labelled succinyl phosphate (which was identified by paper chromatography) is formed from [$\gamma$-$^{32}$P]-ATP and succinate; 4. the enzyme is phosphorylated during incubation with succinyl phosphate, the phosphorylation being reduced in the presence of CoA or ADP. Thus the synthesis of succinyl-CoA differs from that of acetyl-CoA, which proceeds by the following scheme:

$$\text{Acetate} + \text{ATP} \rightleftharpoons \text{acetyl-AMP} + \text{pyrophosphate}$$
$$\text{Acetyl-AMP} + \text{CoA} \rightarrow \text{acetyl-CoA} + \text{AMP}$$

The carboxyl-activated acyl derivatives remain bound to the enzyme in both cases. / Biochemistry *4*, 1457 (1965) / –Hö. [Rd 408/617 IE]

**8,9,13-Triacetoxydocosanoic acid** is produced by yeast (NRRL YB-2501) as an extracellular lipid. *F. H. Stodola, R. F. Vesonder,* and *L. J. Wickerham* have found that 1.5 g/l of the acid are excreted into the medium (aqueous solution of glucose and salts) in seven days at 25 °C. The crude lipid was extracted with hexane and purified by chromatography on silica gel. Its composition was $C_{28}H_{50}O_8$ (oil), after hydrolysis $C_{22}H_{44}O_5$ (m.p. 157 to 158 °C). This trihydroxy acid was reduced with hydrogen iodide to docosanoic acid; reaction with periodic acid gave an aldehydo acid, which could be oxidized to suberic acid. The other fragment was the liquid 5-hydroxytetradecanal. / Biochemistry *4*, 1390 (1965) / –Hö. [Rd 407/616 IE]

**A new route for the utilization of glycolic acid** has been found by *H. L. Kornberg* and *J. G. Morris* in *Micrococcus denitrificans*. The bacteria were grown on [2-$^{14}$C]-glycolate as their only source of carbon. The first reaction product was glyoxylate, and other labelled products found included glycine, aspartate, malate, and glutamate, and after a time, phosphoglycerate. The key intermediate was *erythro*-β-hydroxyaspartate, giving the following "β-hydroxyaspartate metabolic path":




The glycolate oxidase ($E_1$) could be induced by glycolate. The enzymes $E_2$ and $E_3$, which catalyse the synthesis of β-hydroxyaspartate and its conversion into oxalacetate, could be induced by glycolate and glyoxylate. Glyoxylate carboligase and aldehydotartronic acid reductase were present only in negligible concentrations. / Biochem. J. *95*, 577 (1965) / –Hö. [Rd 409/618 IE]

**1,2-Diphenyl-1,2-diarsacyclopentane and 1,2-diphenyl-2,1-diarsacyclohexane** have been prepared by *A. Tzschach* and *G. Pacholke*. Alkali metal organoarsides *(1)* react exothermically with 1,2-dibromoethane in tetrahydrofuran or benzene:

$$C_6H_5\text{-}\underset{\text{Li}}{\text{As}}\text{-}(CH_2)_n\text{-}\underset{\text{Li}}{\text{As}}\text{-}C_6H_5 + Br\text{-}CH_2\text{-}CH_2\text{-}Br \rightarrow$$

*(1)*

$$\text{(}(CH_2)_n\text{ with }\underset{}{\text{As}}\text{-}C_6H_5\text{ and }\underset{}{\text{As}}\text{-}C_6H_5\text{)} + 2\ LiBr + H_2C{=}CH_2$$

*(2a)*: n = 3
*(2b)*: n = 4

*(2a)*, b.p. 193–195 °C/3 mm, yield 56 %
*(2b)*, b.p. 203–206 °C/4 mm, yield 68 %

The first step in the reaction may be a metal-halogen exchange to form the compound *(3)*, which is then thought to undergo an intromolecular elimination of LiBr, with formation of the cyclic biarsines *(2a)* and *(2b)*. The As–As bond in *(2a)* and *(2b)* can be broken by both nucleophilic and electrophilic reagents.

$$(2) + LiR \rightarrow \underset{(4)}{R(C_6H_5)As\text{–}(CH_2)n\text{–}As(C_6H_5)Li}$$

$R = C_6H_5, C_4H_9$

The compounds *(4a)*, n = 3, and *(4b)*, n = 4, were isolated as the dioxane adducts. / Z. anorg. allg. Chem. *336*, 270 (1956) / –Sch. [Rd 433/642 IE]

**Potassium dioxofluoroselenate(IV)** has been obtained by *R. Paetzold* and *K. Aurich* by the fusion of equimolar quantities of KF and $SeO_2$ and by reaction of $K_2SeO_3$ with $SeOF_2$.

$$KF + SeO_2 \rightarrow FSeO_2K \quad KSeO_2F$$

$$K_2SeO_3 + SeOF_2 \rightarrow 2\ SeO_2FK$$

Potassium fluoroselenate(IV) is a white crystalline substance which melts at 250 °C without decomposing, and which is very sensitive to water. Study of the hydrolysis by infrared spectroscopy showed that the products include potassium hydrogen selenite, potassium hydrogen fluoride, and selenious acid. The hydrolysis proper:

$$KSeO_2F + H_2O \rightarrow KSeO_2OH + HF$$

is followed by the reaction:

$$2\ HF + KSeO_2OH \rightarrow KHF_2 + (HO)_2SeO$$

which evidently takes place because of the high stability of $KHF_2 \cdot KSeO_2F$ reacts with methanol in the same way as with water. / Z. anorg. allg. Chem. *335*, 281 (1965) / –Sch. [Rd 434/643 IE]

**Organosilicon radicals,** according to *C. Eaborn, R. A. Jackson,* and *R. W. Walsingham*, are formed by photolysis or by pyrolysis (195 °C, 2 weeks, light excluded) of bis(trimethylsilyl)mercury in toluene. In addition to the expected Hg and hexamethyldisilane, the products include trimethylsilane, bibenzyl, benzyltrimethylsilane, and a number of polysilane derivatives. The reaction in benzene under the same conditions yields trimethylsilane and phenyltrimethylsilane. These findings can be explained by the following scheme:

$$Hg[Si(CH_3)_3]_2 \rightarrow Hg + 2\ CH_3Si^{\bullet}$$

$$2\ (CH_3)_3Si^{\bullet} \rightarrow (CH_3)_3SiSi(CH_3)_3$$

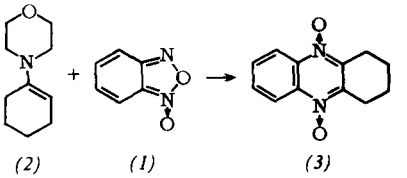
$$(CH_3)_3Si^{\bullet} + CH_3\text{–}Ph \rightarrow (CH_3)_3SiH + Ph\text{–}CH_2^{\bullet}$$

$$Ph\text{–}CH_2^{\bullet} + {}^{\bullet}Si(CH_3)_3 \rightarrow Ph\text{–}CH_2\text{–}Si(CH_3)_3$$

$$2\ Ph\text{–}CH_2^{\bullet} \rightarrow Ph\text{–}CH_2CH_2\text{–}Ph$$

/ Chem. Commun. (London) 1965, 300 / –Ma. [Rd 389/598 IE]

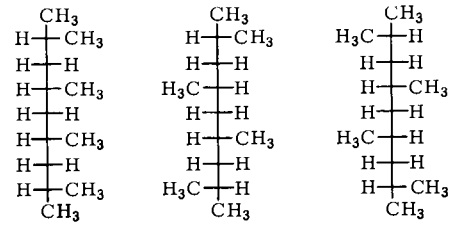
**A new synthesis of quinoxaline di-N-oxides** from enamines and benzofuran *N*-oxide *(1)* is described by *M. J. Haddadin* and *C. H. Issidorides*. When 1-morpholinocyclohex-1-ene *(2)* is added to a warm methanolic solution of *(1)*, 1,2,3,4-tetrahydrophenazine di-*N*-oxide *(3)* [m.p. 185 °C (decomp.)]



*(2)* *(1)* *(3)*

is formed in 48 % yield. Enamines of cyclopentanone, acetophenone, and cholestan-3-one react with *(1)* to form similar compounds having the melting points 182 °C (decomp.), 210 °C, and 208 °C, respectively. / Tetrahedron Letters 1965, 3253 / –Ma. [Rd 387/596 IE]

**The synthesis of meso-, racemic, and (−)-(4R:6R)-2,4,6,8-tetramethylnonane,** the simplest model compounds for isotactic and syndiotactic polypropylenes, is described by *P. Pino, S. Pucci, E. Benedetti,* and *P. Bucci.* The starting material



*(a)* *(b)*

(4S:6R) (4R:6R) (4S:6S),

*Meso*, isotactic, b.p. = 82.5 °C/20 mm Hg *(a)*

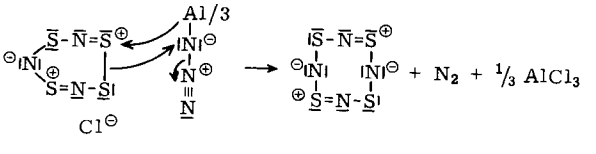
*rac.*, syndiotactic, b.p. = 85 °C/22 mm Hg *(b)*

was (+)-*(R)*-2,6,8-trimethylnonan-4-one, which was converted *via* the intermediate 2,4,6,8-tetramethylnonan-4-ol and a mixture of isomeric olefins, into 2,4,6,8-tetramethylnonane. The diastereoisomers *(a)* and *(b)* of this last compound were separated by distillation. / J. Amer. chem. Soc. *87*, 3263 (1965) / −Ma. [Rd 388/597 IE]

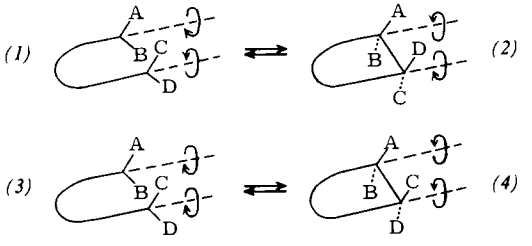
**Cycasin, a natural carcinogenic compound,** exhibits radiomimetic effects. Cycasin (methylazoxymethyl β-glucoside) is found in cycad plants (fern palms), *e.g., Cycas circinalis* L. Investigations by *H. J. Teas, H. J. Sax,* and *K. Sax* have shown that cycasin causes changes in the chromosomes in the root-tip cells *of Allium cepa* (var. Dowing Yellow Globe). Germination and growth of the onion plants in aqueous solutions containing cycasin at only 3 % of the concentration present in *Cycas circinalis* leads to chromosome changes corresponding to those caused by a γ-radiation dose of 200 Röntgen. / Science (Washington) *149*, 541 (1965) / −De. [Rd 435/644 IE]

**A synthesis of nitriles from aldehydes** is given by *K. N. Parameswaran* and *O. M. Friedman.* The aldehyde is dissolved in anhydrous benzene and dry ammonia is passed in under nitrogen. Lead tetraacetate is then added in portions over 0.5–2.5 h, and the solution is stirred for several hours. The nitrile, which is presumably formed by oxidation of the aldimine resulting from condensation of the aldehyde with the ammonia, can then be isolated. An approximately five-fold excess of oxidizing agent is used. Products obtained in this way include 3,4,5-trimethoxybenzonitrile (75.4% crude yield), *p*-nitrobenzonitrile (81 %), *trans*-cinnamonitrile (89 %), furfuronitrile (36.5 %), n-heptanenitrile (59 %), and n-butyronitrile (14 %). / Chem. and Ind. *1965*, 988 / −Ma. [Rd 357/566 IE]

**A ring expansion of the thiotrithiazyl cation** $[S_4N_3]^{\oplus}$, a planar 7-membered ring system, to give the 8-membered cage system of sulfur nitride $S_4N_4$ was achieved by *M. Becke-Goering* and *G. Magin.* When $S_4N_3^{\oplus}Cl^{\ominus}$ was added to a solution of aluminum azide in tetrahydrofuran, nitrogen was released. The reaction was completed at 40–50 °C, and when the reaction mixture was filtered and the filtrate evaporated to dryness and extracted with benzene, $S_4N_4$ was obtained in 85–90% yield. A yield of about 70% was obtained with lithium azide in acetonitrile. / Z. Naturforsch. *20b*, 493 (1965) / −Ma. [Rd 358/567 IE]




**An explanation for the stereospecificity of electrocyclic reactions** has been advanced by *R. B. Woodward* and *R. Hoffmann.* Electrocyclic reactions are isomerizations in which a σ-bond is formed between the terminal C atoms of an open-chain π-electron system, or in which the reverse process takes place. The stereochemistry of the products depends on whether the groups attached to the terminal C atoms rotate in opposite directions [disrotative, *e.g.*: *(1)* → *(2)*] or in the same direction [conrotative, *e.g.*: *(3)* → *(4)*].

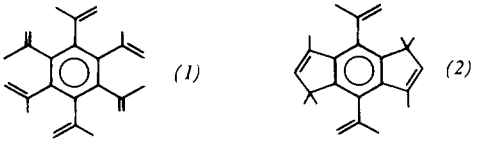



The stereochemical course of the reaction is determined by the symmetry of the highest occupied molecular orbitals of the open-chain reactant. In a 4n π-electron system, bonding between the ends of the system must be accompanied by conrotation, while in a(4n+2) π-electron system, bonding must be accompanied by disrotation. This is in fact found to be the case in all thermally induced electrocyclic reactions. In photolytic reactions, on the other hand, an electron is raised into the first excited state, so that the symmetry conditions are reversed. Thus the reactions of 4n π-electron systems is accompanied by disrotation, and those of (4n + 2) π-electron systems by conrotation.

This approach can also be used in the case of intermolecular synchronous cycloadditions (*e.g.* Diels-Alder reactions). If an open-chain system containing n π-electrons reacts with an open-chain system containing m π-electrons, so that two σ-bonds are formed in place of two π-bonds, the thermal reaction is possible if n + m = 4q + 2, while the photochemical reaction is possible if n + m = 4q (where q is a whole number).

Similar rules can also be formulated for reactions in which x σ-bonds are formed from x π-bonds. All these rules apply only to synchronous reactions. Where the course of a reaction is contrary to these rules, it must be assumed to proceed in more than one step (*e.g.* the dimerization of allenes and ketenes). / J. Amer. chem. Soc. *87*, 395, 2046 (1965) / −Bu. [Rd 447/656 IE]

**Hexaisopropenylbenzene *(1)*, an inert polyolefin,** is described by *E. M. Arnett, J. M. Bollinger,* and *J. C. Sanda.* Compound *(1)* ought to be highly reactive but is almost inert towards even very strong double-bond reagents. It was made in 4% yield from di-isopropenylacetylene and dicobalt octacarbonyl by heating the reagents in refluxing Skellysolve C and melts at 260–263 °C. It cannot be hydrogenated catalytically, does not react with tetracyanoethylene, and is only slightly substituted after prolonged standing with bromine in




carbon tetrachloride. It is however sensitive towards irradiation and strong acids. Concentrated sulfuric acid converts *(1)* into an orange carbonium ion, which yields an isomer, possibly of structure *(2)*, on treatment with base. The amazing lack of reactivity of *(1)* can be explained by the mutual shielding of the neighboring isopropenyl groups. / J. Amer. chem. Soc. *87*, 2050 (1965) / −Ma. [Rd 359/568 IE]

**Methoden der organischen Chemie** (Methods in Organic Chemistry) (Houben-Weyl). Edited by *Eugen Müller*, Vol. XII, Part 2. Organische Phosphorverbindungen (Organic Phosphorus Compounds). Compiled by *K. Sasse*. Georg Thieme Verlag, Stuttgart 1964. 4th completely revised Edition, LXXXVII + 1131 pp., 195 tables, one diagram, DM 280.–.

The user of Part 1 of "Organische Phosphorverbindungen" will have eagerly awaited the publication of the present Part 2. This part deals with compounds containing no phosphorus–carbon bonds, *i.e.* mainly with compounds that can be regarded as derivatives of phosphoric and phosphorous acids. Variation of the nature and number of organic groups, replacement of oxygen by sulfur, halogen or nitrogen, anhydride formation, *etc.*, permits the derivation of an almost countless number of types of compounds.

*Kosolapoff*'s monograph "Organophosphorus Compounds" (which now, fifteen years after its publication, is no longer adequate) has until now been the only existing review of this subject. A complete account of the field as a whole is difficult, not only because of the volume of the relevant literature, but also because of its heterogeneity. Owing to the great technical importance of these compounds (as insecticides, plasticizers, *etc.*), a very large proportion of the literature is represented by patents. Moreover, many important original papers have appeared in Russian journals, which are not always accessible. The fact that, in spite of such difficulties, a single author has managed to compile a complete and comprehensive review can be regarded as an achievement of the highest order in the field of scientific literature.

Part 2, like Part 1, is arranged according to classes of compounds. For example, the *O,O* diesters of thiophosphoric acid are discussed in the section of "Organic derivatives of phosphoric acid Derivatives of thiophosphoric acids", under "Esters and ester halides of thiophosphoric acids". The thiophosphoric acids are divided into 24 sub-groups.

The preparation and transformations of the various types of compounds are described in special sections. The preparative procedures are grouped according to starting materials, and are illustrated by representative examples. Many tables are included to show the compounds prepared by given methods. The short section on "Transformations" can be confined to little more than a brief list of properties together with a few notes, since the "transformation" is generally discussed in detail under "Preparation". The subject index contains about 10000 compounds.

To sum up, it can be said that *K. Sasse* has produced a new standard work on the organic chemistry of phosphorus. In view of the rapid progress being made in this field, however, it is impossible to predict how long it will be valid. In any case, by virtue of the numerous suggestions offered, the book will undoubtedly make a considerable contribution to further progress and hence to its own "obsolescence".

*H. Hoffmann* [NB 421/292 IE]

**Nuclear Techniques in Analytical Chemistry.** By *A. J. Moses*. International Series of Monographs on Analytical Chemistry. Edited by *R. Belcher* and *L. Gordon*. Pergamon Press, Oxford - London - Edinburgh - New York - Paris - Frankfurt 1964. 1st Edit., VII + 142 pp., numerous illustrations and tables, 1 color plate, £ 2.5.0.

There is probably no other branch of chemistry in which radiochemical methods find such varied and valuable use as in analysis.

The present book, which describes the principal analytical applications of radiochemical methods (*i.e.* the methods of activation analysis, isotope-dilution analysis, radiometeric measurements, *etc.*), is therefore very welcome. However, those who hope to satisfy completely their thirst for knowledge in this field will be disappointed in many places; thus the book repeatedly recommends special methods of measurement or special practical procedures, but when the eager reader then seeks for details, he finds that he has to turn to other publications. On the other hand, where a method is described in detail, the description is very well presented and is supplemented by practical directions.

The value to the reader would have been greater, however, had the author commented on the directions, since these alone frequently do not explain to the inexperienced worker the need for a special procedure. Nevertheless, the reader will undoubtedly be pleased by the comprehensive bibliography provided.

*F. Baumgärtner* [NB 427/297 IE]

**Radionuklid-Tabellen** (Radionuclide Tables). Compiled by *W. Seelmann-Eggebert* and *G. Pfennig*; published by the Bundesministerium für wissenschaftliche Forschung. Verlag Gersbach & Sohn. München 1964. 1st edit., 79 pp., cardboard DM 4.– ($ 1.00).

The booklet lists the radionuclides in order of increasing nuclear charge, nuclides of the same element being arranged in order of increasing mass number. Owing to this simple arrangement, it is easy to find any given radionuclide. The types of decay, abundances, half-lives, and radiation energies are given for each nuclide. The table also gives the conversion coefficients and daughter nuclides, so that all the essential data are reported. Two additional tables show the estimated yields of a number of longer-lived fission products from tomic explosions and the cumulative yields for various fission reactions. Two diagrams are included to show the time-dependence of the percentage contributions of longer-lived fission products from atomic explosions to the total β-activity.

This book is an indispensible aid to all who work with radionuclides. Its publication is therefore very welcome, and its low price places it within the reach of all.

*W. Strohmeier* [NB 412/284 IE]

**Klinische Chemie, Theorie und Praxis** (Clinical Chemistry, Theory and Practice). By *R. Richterich*. Akademische Verlagsgesellschaft, Frankfurt/M., S. Karger AG., Basel 1965. 1st Edit., XII + 416 pp., 76 illustrations, 89 tables, DM 59.50 (about $ 15.–).

This new book by *Richterich* (whose Enzyme Pathology, which was published in 1957, is still a valuable reference work) is unusual in several respects. On glancing through it, one is impressed by the excellent layout. The divisions of the individual chapters are well marked and attention is drawn to important details by the use of "boxes". The divisions (in the case of experimental procedures these are: principle, reagents, procedure, calculation, and normal values) are marked in the margin, and this arrangement quickly familiarizes the reader with the book. It would be very gratifying if this clear, concise style were to become generally used in textbooks!

It is also unusual, at least in German-language books, to find advertisements in an appendix. However, anyone who has experienced the difficulty of equipping a small clinical-chemistry laboratory with apparatus and reagents will applaud the author's and publishers' courage in introducing this novel feature. It is to be hoped that the size of this appendix will be doubled in the next edition.

The book is not a reference work and is not claimed to be exhaustive; it can probably be best described as an introduction to clinical chemistry. It is accordingly dominated by the chapters on units of measurement, introduction to statistics,

normal values, reliability of samples, the sampling of blood, *etc.* The author makes many references to his own practical experience in this field. This can be seen already from the Table of Contents, which includes a code used by the author for classification purposes and as a key for punched cards.

Having been pampered by these excellent chapters on general clinical chemistry, which serve as an introduction to the special chapters, the reader becomes aware of the following shortcomings when he turns to the special chapters themselves: The arrangement of the material becomes unclear when he tries to refer to the book for details of methods. For example, the enzyme determinations are to be found in a number of different chapters. Furthermore, the selection of methods included is very narrow, and a number of important clinical determinations, such as the determination of iron, are omitted altogether.

However, this criticism ignores the aim of the book. As the author himself stresses in the preface, the emphasis is placed on the general part, which will still be valid when all the special methods are obsolete. It is to be hoped, and indeed it can almost be predicted, that this book will enjoy a very wide circulation. *F. W. Schmidt* [NB 422/293 IE]

**Handbuch der physiologisch- und pathologisch-chemischen Analyse, für Ärzte, Biologen und Chemiker** (Handbook of Physiological and Pathological Chemical Analysis, for Physicians, Biologists, and Chemists). By *Hoppe-Seyler/Thierfelder*, edited by *K. Lang* and *E. Lehnartz*, with the collaboration of *O. Hoffmann-Ostenhof* and *G. Siebert*. Vol. 6. Enzymes, Part A. Springer-Verlag, Berlin-Göttingen-Heidelberg-New York 1964. 10th Edit., XX + 1052pp., 119 illustrations, DM 360.–(subscription price DM 288.–).

Enzymatic methods are finding increasing use in quantitative analysis, and they have become indispensable in biochemical, clinical, and forensic medical laboratories. We therefore welcome the publication of this, the last volume of "Hoppe-Seyler/Thierfelder", which was originally intended to comprise only 5 volumes. The present book is the first of three parts of Vol. 6.

The first third of this sub-volume contains the general chapters on nomenclature and methods. *Hoffmann-Ostenhof* describes the classification and nomenclature of enzymes as well as enzyme units in a short, clear summary of the "Report of the Commission on Enzymes", published in 1961. Unfortunately, the rules given here and on page 348 are only partly adopted in the book. For example, the "suggested abbreviations" on page 19 do not correspond to those recommended by the Enzyme Commission, and it is particularly confusing when NAD and $DPN^+$ or $NADPH_2$ and TPNH are used side by side. An instructive introduction to enzyme kinetics (*Lumper*) should enable even workers with little experience to carry out a detailed and correct evaluation of kinetic experiments. The manometric methods are discussed (*Süllmann*) lucidly and at some length (224 pp.); this is followed by a brief outline of the use of the pH-stat (*Cunningham*) and a detailed account of the important Warburg optical test (*Bücher, Luh, Pette*). The scope of this method is clearly shown in this discussion: almost any enzyme or any metabolite can be determined optically. A chapter on the measurement of phosphate uptake during oxidative phosphorylation (*Klingenberg*) completes this excellent general section; probably the only important omissions are fluorescence methods and automatic methods.

The description of the enzymes, which are classified according to the five principal groups given in the "Report", begins with the oxidoreductases. This volume includes the pyridine nucleotide and flavin enzymes, as well as the copper enzymes and hydroxylases. A number of chapters, *e.g.* those on steroid dehydrogenases (*Breuer*, 125 pp.), isocitric acid dehydrogenase (*Siebert*, 27 pp.), 3-phosphoglyceraldehyde dehydrogenase (*Mohn*, 58 pp.), "lesser known pyridine nucleotide enzymes" (*Mohn*, 99 pp.) (are they really lesser known? The literature reference is ambiguous) and hydroxylases (*Abraham* et al., 131 pp.) are dealt with in great detail, the practical procedures being accompanied by a wealth of literature data such as cannot be found in any other review of this nature. Thus for information on any properties of these enzymes, these chapters offer a fine source. Other enzymes are dealt with much more briefly, the discussion being confined to practical procedures, as would be expected in a book on methods; this is the case with succinate dehydrogenase (*Slater*, 5 pp.), the copper enzymes (*Schirrmacher-Göllner*, 19 pp.) (uricase also is a copper enzyme!), "malic enzymes" (*Rutter*, 10 pp.) (the name "malic enzymes" should no longer be used!), and the "yellow enzymes" (*Nygaard*, 34 pp.). It is surprising to find that the flavin enzymes are accorded only about 50 pages (nitrate reductase is discussed in a single page, while no mention is made of the other enzymes that act on other N compounds and inorganic S compounds, or of *e.g.* dehydroorotic acid dehydrogenase), whereas the pyridine nucleotide dehydrogenases are spread over about 500 pages. Disparities exist between the various chapters, which suggest that the authors were allowed to decide for themselves how much detail to include in their own contributions.

In view of the high price of this book, it is regrettable that much of the literature cited extends only to 1960 or 1961, so that by the time of publication (November 1964), some chapters were largely out of date. This is particularly true for glucose 6-phosphate dehydrogenase (the enzymes from yeast and from bovine mammary glands were crystallized in 1961) and glutamic acid dehydrogenase. It is advantageous when the dates of the latest publications considered are given, as is done on pages 423 and 917.

Apart from these criticisms, the present volume will be a valuable aid to the enzyme chemist, and will provide him with a wealth of information. In many cases, he will be able to carry out estimations and preparations without recourse to the original publications. The usefulness of this volume will be greatly increased when the index, planned for Volume C, becomes available. It is to be hoped that it will then be possible to report on the hemin enzymes. The print (on yellow paper!) and layout of the book are excellent. *H. Sund* [NB 426/296 IE]

**Advances in Drug Research**, Vol. 1. Edited by *N. J. Harper* and *Alma B. Simmonds*. Academic Press, London-New York 1964. 1st Edit. X + 209 pp., numerous tables and several illustrations, £ 2.10.0.

In the first chapter, *Doyle* and *Nayler* review the chemical structure and action of penicillins and related compounds. This review is competent and up-to-date, and even includes a discussion of the new cephalosporins. The pharmacology of therapeutically interesting compounds, on the other hand, is dealt with rather briefly.

The chapter by *L. S. Schlanker* on the physiological transport of drugs contains fundamental observations on passive transport and on the possibilities of resorption in the gastrointestinal tract in relation to the physical conditions. Short sections are also devoted to transport processes in the various organs of mammals. The review as a whole is well organized and very informative.

The chapter on antitussives by *Doyle* and *Mehta* begins with a description of the coughing reflex and methods of testing the inhibition of coughing. The many cough-inhibiting compounds are considered from the chemical point of view, but the pharmacological aspects are also taken into account. The result is a comprehensive review.

*S. C. Copp* reviews adrenergic neuron blocking agents. A brief description of the methods used for the detection of pharmacological action is followed by a discussion of the active substances discovered so far. This chapter also is written largely from the point of view of structure and action. Most of the substances discussed are related to bretylium or guanethedine. The beta-receptor blocking substances are not considered. This chapter provides a particularly good picture for the chemist. *M. Kramer* [NB 411/283 IE]

**Purines, Pyrimidines, and Nucleotides, and the Chemistry of Nucleic Acids.** A Course in Organic Chemistry. Edited by *R. Robinson*. Advanced Section Vol. XXV. By *T. L. V. Ulbricht*. The Commonwealth and International Library. Edited by *R. Maxwell*. The Macmillan Company, New York, and Pergamon Press, Oxford-London-Edinburgh-Paris-Frankfurt 1964. 1st Edit., VII + 79 pp., 1 illustration, £ 0.12.6.

It is no easy undertaking to condense the chemistry of the purines, pyrimidines, and nucleotides into a 75-page monograph in such a way as to produce a well-rounded and easily understandable review. The purpose of the present monograph is to provide an introduction to the fundamentals of the chemistry of purines and pyrimidines, since this is dealt with only very briefly in most text-books of organic chemistry, particularly those written in English. The author, himself a well-known worker in this field, manages to present an excellent survey in only 60 pages and references to original papers are given at the end of each chapter for those who wish to make a deeper study. It is questionable, however, whether the chapter on nucleic acids (10 pages) should have been included in this short monograph.

*F. Cramer* [NB 423/294 IE]

**Nucleotides and Coenzymes.** By *D. W. Hutchinson*. Methuen's Monographs on Biological Subjects. Edited by *R. Peters* and *F. G. Young*, Methuen & Co., London, J. Wiley & Sons, Inc., New York, 1964. 1st Edit., VIII + 136 pp. £ 0.18.0.

This booklet is intended as a chemical supplement to the widely-read "Biochemistry of Nucleic Acids" by *J. N. Davidson* ("The Child's Guide to the Nucleic Acids"), with particular reference to low-molecular weight compounds. The discussions cover nucleosides, nucleotides, oligonucleotides, and polynucleotides, as well as the nucleotide coenzymes, pyridoxal phosphate and thiamine pyrophosphate. A wealth of data is presented in a well-organized manner and supported by extensive bibliographies at the ends of the chapters. Biochemical aspects are taken into account but the emphasis is placed on the chemical viewpoint.

A number of inaccuracies will undoubtedly be corrected in a second edition. For example, the biosynthesis of pseudouridine can by no means be regarded as having been generally elucidated, and the model for the secondary structure of sRNA has now been revised. Formulae of the nucleosides are not given in the usual, stereochemically unambigous notation. In spite of these minor short-comings, the book undoubtedly offers a good introduction to the nucleotide field.

*H. G. Zachau* [NB 413/285 IE]

**Topics in Phosphorus Chemistry,** Vol. 1. Edited by *M. Grayson* and *E. Griffith*. Interscience Publishers, a Division of J. Wiley & Sons, New York-London-Sydney 1964. 1st Edit., VII + 262 pp., numerous illustrations and tables, £ 4.10.0.

Owing to the constant increase in the number of publications in the phosphorus field, hand-books such as "Kosolapoff" very quickly become outdated. It is therefore gratifying to find that this series, the first volume of which is now available, presents a condensed review of each of the various topics.

The first three contributions deal with the organic chemistry of phosphorus, *i.e.* the preparation of organophosphorus compounds from elementary phosphorus, nucleophilic substitutions on phosphorus halides and esters by Grignard and organolithium compounds, and the Michaelis-Arbuzov and related reactions. The next two chapters are devoted to the following inorganic topics: acids of trivalent phosphorus and their salts, and condensed phosphates containing other oxyacids. The authors of the various chapters have all published papers on the topics in question, so that the problems really have been critically evaluated by specialists. Comprehensive lists of references enable the reader to make a more profound study of the subject. However, the earliest publications should at least have been mentioned. For example, the rearrangement of anhydrous $\overset{4}{P}-\overset{4}{P}$- acid was first observed by *Nylén*, whereas the preparation of salts of this acid from red phosphorus and chlorous acid was first described by *Leininger* and *Chulski*.

This book will be of value not only to the specialist, but also to chemists working in other fields. The presentation is fluid and clear, and the book nowhere gives the impression of being a reference work. *K.-H. Worms* [NB 418/290 IE]

**Boron, Metallo-Boron Compounds, and Boranes.** Edited by *R. M. Adams*. Interscience Publishers, a Division of John Wiley & Sons, New York-London-Sydney 1964. 1st Edit., XXIII + 765 pp., several illustrations and tables, £ 10.7.0.

Knowledge of the chemistry of boron compounds has greatly increased over the last few years. This is reflected in the large number of articles that, like the present book, present a condensed report of a part of the field.

Two contributions on the discovery, occurrence, and technology of the borate minerals and on the behavior of borates in aqueous solutions (*W. A. Gale*) are followed by a longer chapter on the structures, properties, and reactions of inorganic compounds of boron and oxygen (*N. P. Niess* and *G. W. Campbell*). *A. E. Newkirk* presents a very detailed account of the preparation and properties of elementary boron. *B. Post* contributes an excellent section on the refractory binary borides and their chemical and electrical properties. This is followed by two comprehensive chapters (320 pp.) on boron-hydrogen compounds (boranates by *R. M. Adams* and *R. A. Seidle*; boranes by *R. M. Adams*).

Simple metal and onium monoboranates are described in detail, organoboranates and oligo- and polyboranates also being taken into account. The text is supplemented by several illustrations and tables relating to the physical properties of the compounds (infrared spectra, $^{11}$B-NMR spectra, mass spectra). The last chapter (*G. J. Levinkas*) deals with the toxicity of boron compounds (BO, BH, and BC compounds, among others).

The chapters are subdivided in such a way that the reader can quickly find any given topic. The book has a formula index and a subject index, but no author index. The English language literature has been taken fairly fully into account up to 1962, and in some cases even up to 1964. Misprints (*e.g.* pp. 554, 562) and incorrect references (*e.g.* p. 571) are not serious. In many instances the reviewer felt that a summing-up would have been welcome. The editor should have dealt with nomenclature in a general chapter, instead of including it in the individual discussions (pp. 54, 373, 508, 706). Once again, however, the need for standardization of the nomenclature of boron compounds becomes obvious.

This well presented, but unfortunately very expensive book is a valuable synopsis and should be included in the library of anyone working in this field. It can be recommended to anyone wishing to familiarize himself with the chemistry of boron. It is to be hoped that the series which is intended to cover the "Entire Scope of Boron Chemistry" will very soon be continued in the form of good monographic chapters of the same type. *R. Köster* [NB 415/287 IE]

**New Methods of Analytical Chemistry.** By *R. Belcher* and *C. L. Wilson*, with the collaboration of *T. S. West*. Chapman and Hall Ltd., London 1964, 2nd Edit., XV + 366 pp., numerous tables, £ 3.0.0.

The "new" methods described in the first edition (1956) have now become common knowledge or have been found to be of little value. In order to justify its title, therefore, the second

edition had to be virtually a new book. It deals wholly with new reagents and new applications in conventional analysis.

In the volumetric field, many new indicators are described, in particular selective metal indicators. Gravimetric analysis, partition methods, and spectrophotometry are also enriched by new selective reagents, most of which are organic.

The new reagents and m thods are critically compared on the basis of their analytical use and their advantages and disadvantages. Although a selection of this nature must necessa ily be subjective, so that the reader may not agree with the author as to the best method, the book nevertheless fulfils the function of bringing useful new developments to the attention of the analys. This book is even more welcome in that the many progress reports on instrumental analysis often blind us to the fact that there have been just as many important new developments in conventional analytical methods.

A systematic literature search for new methods appears to have been carried out only for the period up to 1959, but a number of publications in English, particularly in the authors' own field, published up to 1963 have also been reviewed.

*F. Umland* [NB 414/286 IE]

**The Electronic Structure of Molecules. A New Approach.** By *J. W. Linnett*. Methuen & Co. Ltd., London and J. Wiley & Sons Inc., New York, 1964. 1st Edit., VII + 167 pp., 7 tables, 25 illustrations, £ 1.5.0.

This book is evidently intended for undergraduate chemistry students, and gives a very clear and easily understandable introduction to the theory of the electronic structure of molecules. Starting with sections on electrons and atoms, and on the chemical bond, it deals with diatomic and other small molecules, organic molecules and reactions, free radicals, inorganic compounds containing elements of the higher periods, and electronically excited states.

However, the reviewer would hesitate to recommend this fine booklet to the beginner, simply because the approach is very personal and one-sided. It is based on *J. W. Linnett*'s suggestion that the Lewis octet should be regarded as a double quartet, *i.e.* the electrons with $\alpha$ spin should be reg ded as practically independent of those with $\beta$ spin. This hypothesis is presented with striking consistency and with surprisingly good results, but the connection with conventional methods of quantum chemistry (the MO and VB methods) remains unclear. However, those who are familiar with these methods will benefit greatly by perusal of this book. The only regret is that the possibility of a mathematical formulation of wave functions on the basis of the qualitative ideas discussed is only touched upon in the closing paragraphs of the last chapter. *M. Klessinger* [NB 416/288 IE]

**Electrons and Chemical Bonding.** By *H. B. Gray*. W. A. Benjamin Inc., New York-Amsterdam, 1964. 1st Edit., XIV + 223 pp., numerous illustrations and tables, paper $ 4.35, cloth $ 8.80.

The quantum-mechanical treatment of atoms and molecules has led to the development of ideas that are extremely helpful to the chemist in the discussion of the structures and reactivities of compounds, and which are indispensable for the interpretation of the results obtained by the physical methods that are becoming increasingly important in chemistry. It is also becoming increasingly important, therefore, that the chemist should familiarize himself with these ideas right at the beginning of his training.

This is the purpose of *H. B. Gray*'s book, which is based on a course of lectures for beginners. This book, with its 132 two-color illustrations and 31 tables, gives an extremely lucid introduction to the electronic theory of the chemical bond. It contains nine chapters, and covers atoms, diatomic, linear triatomic, planar trigonal, tetrahedral trigonal, pyramidal and angular triatomic molecules, organic $\pi$-electron systems, and bonds involving d-electrons. The purely qualitative discussion is based mainly on the MO theory, which is used consistently, even for molecules such as $CH_4$ and inorganic complexes. For this reason concepts such as "hybridization" and "lone pairs of electrons" are only touched upon, and it is not clear why the overlap can be used as a measure of the strength of a bond, even though it is neglected in all of the derivations. No differentiation is made between VB structures and localized molecular orbitals. A particularly good chapter, on the other hand, is that dealing with bonds involving d-electrons, which provides a good introduction to the theory of inorganic coordination compounds. The book contains very few printing errors or instances of vagueness in the text.

*M. Klessinger* [NB 417/289 IE]

**Acid-Base Equilibria.** By *E. J. King*. The International Encyclopedia of Physical Chemistry and Chemical Physics. Edited by *E. A. Guggenheim, J. E. Mayer*, and *F. C. Tompkins*. Volume 4/15. Pergamon Press, Oxford-London-Edinburgh-New York-Paris-Frankfurt 1965. 1st Edit., XI + 341 pp., £ 6.0.0.

"Acid-Base Equilibria" is published as part of the "International Encyclopedia of Physical Chemistry and Chemical Physics", which comprises about 100 volumes. However, the present volume is complete in itself, and may be used independently of the other volumes. A more fitting title might have been "The Physical Chemistry of Acid-Base Equilibria".

The volume is intended for the reader who wishes to make an extensive study of acid-base equilibria, and presupposes a certain knowledge of thermodynamics and of the theory of electrolytes. In five chapters the author gives an excellent introduction to the theoretical principles of the determination of acidity constants (arranged according to the method of determination). In the course of a comprehensive discussion of the pH concept, he rightly points out that in spite of notable advances in instrumentation, the pH value remains an essentially empirical parameter. The relationships between structure and acidity are dealt with rather briefly. The author evidently recognizes that the data available at present cannot be explained by a few neat thermodynamical equations. Subsequent chapters are concerned with the effect of pressure and temperature, the behavior of polyfunctional compounds, and equilibria in non-aqueous solvent systems. The author deliberately omits any discussion of analytical aspects or of acid-base equilibria in melts.

The author has succeeded in giving a very readable account of the physical chemistry of acid-base equilibria, taking into account data from the literature up to 1963.

*W. Simon* [NB 419/291 IE]

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# Automation of Structure Analysis

## Part II. Automation of the Evaluation[*]

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*The extent to which it is possible to automate the determination of a structure from the data collected with automatic measuring equipment is discussed. The development of the automatic evaluation is synchronous with that of digital computer programs. – Even the simple calculation of structure factors from the intensities (i.e. the analysis of the geometrical and physical intensity factors) takes several weeks when the many thousand reflections are processed "manually", i.e. with a desk calculator. A large electronic computer, on the other hand, executes these calculations in a few seconds. Nevertheless, even the largest computers available at present are too small for many of the complex steps in the calculation and for the quantity of data involved. Evaluation methods which, owing to long computing times, can at present only be tested on relatively simple structures will become more attractive with the advent of machines with computing times in the nanosecond range.*

## Introduction

The development of methods for the evaluation of X-ray structural data can be divided into three steps:

### 1. Individual Programs for Routine Calculations

The primary aim of the crystallographer was to simplify the routine work, in order to be able to concentrate on the important steps of the evaluation. As soon as the first electronic computers made their appearance, programs were developed for the calculation of structure factors from an approximation model or for the calculation of Patterson and Fourier syntheses. It soon became clear, however, that calculation with the aid of these independently compiled programs is laborious, since the input formats are different and so involve time-consuming manual operations (re-punching, short intermediate calculations).

[*] For Part I (Automation of the Measuring Process) see Angew. Chem. 77, 484 (1965); Angew. Chem. internat. Edit. 4, 508 (1965).

### 2. Program Systems

The next step, therefore, was the establishment of program systems in which a wide variety of routine programs could be carried out and combined, the only manipulation required being the insertion of a few control cards. Table 1 shows the programs that can be dealt with at present in a program system developed at our Institute. A system of this type must obviously be flexible, in order that new programs may be introduced at any time. The sub-programs themselves can naturally be obtained from a wide range of sources.

Table 1. Computer programs used in our system.

a) Scaling, Lorentz polarization-correction in various recording methods
b) Wilson statistics
c) Correction for absorption
d) Modification of the structure factors for the Patterson synthesis
e) Patterson and Fourier syntheses
f) Drawing program for Patterson and Fourier syntheses
g) Structure factor and least squares calculations
h) Bond lengths and angles and other characteristics of the structure
i) Convolution calculations
j) Calculation of convolution molecules
k) Scanning the Patterson structure with convolution molecules

## 3. Automatic Evaluation

It will ultimately be asked whether the programs in a system can be linked by other sub-programs in such a way that the structure is worked out automatically from the results of the measurements. At present, however, there is no universal process for the determination of structures by X-ray analysis; there are simply a number of promising processes, as well as beginnings that could lead to one or more universal and direct methods for the determination of structures.

The mathematical problem of the evaluation can be defined by Eq. (1):

$$\rho_{xyz} = (1/v) \sum_{h=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} \sum_{l=0}^{\infty} A_{hkl} \cos 2\pi (hx + ky + lz) + \sum_{h=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} \sum_{l=0}^{\infty} B_{hkl} \sin 2\pi (hx + kxy + lz)$$

$$A_{hkl} = |F_{hkl}| \cos \Phi_{hkl}$$

$$B_{hkl} = |F_{hkl}| \sin \Phi_{hkl} \qquad (1)$$

In this equation [1], $\rho_{xyz}$ is the quantity sought, *i.e.* the electron density in the unit cell. The maxima of the electron-density function mark the positions of the atoms. For the numerical evaluation of this equation (three-dimensional Fourier synthesis), it is possible to measure the values of $|F_{hkl}|$ (absolute values of the structure factors), but not its components $A_{hkl}$ and $B_{hkl}$ (obtained by multiplication by $\cos\Phi$ or $\sin\Phi$) (the "phase problem"; $\Phi$ is the phase difference between primary and scattered waves). In principle, therefore, there are an infinite number of ways in which an electron density $\rho_{xyz}$ can be calculated from a given F distribution. However, only one of these distributions is chemically meaningful, and that is one involving almost spherically symmetrical electron-density peaks with chemically reasonable bond lengths and bond angles [2]. The crystallographer can try to narrow down the diversity of structures by considering only chemically meaningful structures, or alternatively he can measure indirectly some of the ratios A/B by comparing at least two sets of structure factors. Some of the methods of evaluation are quite involved. However, in the cases that show the greatest promise for practical applications, the fundamentals can be understood without calculation, as will be seen below.

It is remarkable that automatic structure determination became feasible only after three-dimensional methods (*i.e.* the calculation of a three-dimensional electron-density distribution, instead of projections of the electron density) had gained general acceptance. This may at first seem paradoxical, since three-dimensional work involves far more calculation than two-dimensional work. It was found, however, that the much larger volume of information available greatly simplifies many of the problems. Structures which, with two-dimensional methods, can be solved (if at all) only with skill and intuition, take an almost predetermined course when tackled with three-dimensional methods.

It is expedient to carry out the structure analysis in three steps:

A. Establishment of an approximation model

B. Development of the final model from the approximation model

C. Refinement of the structure.

The approximation model generally contains only some of the atoms present (*e.g.* only the heavy atoms in the case of the heavy-atom method), and the positions of a few of these may still be wrong. The final model gives a qualitatively correct picture of the complete structure; errors of a few tenths of an Ångstrom in the interatomic distances are permissible.

This division is also useful in the so-called direct methods. The object of these methods is the calculation of the correct A:B ratios (phases) without recourse to intuitive evaluation steps; however, at least in the present form of the methods, the results are so vague that they give at best an "approximation model", the interpretation of which may be rather difficult.

## A. Establishment of an Approximation Model

### 1. Heavy-Atom Method

The determination of structures is greatly facilitated if the unit cell contains one or a few heavy atoms, and the heavy-atom method has for many years been one of the most successful techniques available to X-ray structural analysts. It is only natural, therefore, to base our attempted automation on this method.

The positions of the heavy atoms are easy to find, even in a complex organic structure. This is a consequence of a special property of the so-called Patterson function $P_{xyz}$ [Eq. (2)].

$$P_{xyz} = \sum_{h=-\infty}^{\infty} \sum_{k=-\infty}^{\infty} \sum_{l=0}^{\infty} |F_{xyz}|^2 \cos 2\pi (hx + ky + lz) \qquad (2)$$

The formula for $P_{xyz}$ is very similar to the Fourier-synthesis formula (1) for the electron density $\rho_{xyz}$. Unlike $\rho_{xyz}$, however, $P_{xyz}$ can be calculated directly from the observed results, since Eq. (2) contains only the absolute values of the structure factors $F_{hkl}$. The maxima of the Patterson function $P_{xyz}$ characterize the lengths and directions of the interatomic vectors in the crystal [3]. Since the intensities of the maxima are proportional to the product of the numbers of electrons in the atoms joined by the interatomic vector, the heavy atom-heavy atom maxima must be particularly high. This will be illustrated for *C*-(2,2'-biphenylylene)-

[1] In practice the summation limits of h, k, and l are only of the order of 10 (instead of $\infty$). Owing to the triple summation, however, the range of $F_{h,k,l}$ is of the order of 1000.

[2] We shall not be concerned here with the problems of homometry (different chemically possible structures with the same set of absolute values of the structure factors).

[3] Cf. *W. Hoppe*, Angew. Chem. *69*, 659 (1957).

$N_\beta$-cyano-$N_\alpha$-(*p*-iodophenyl)azomethinimine, the structure of which was determined at our Institute [4, 4a]. The dimensions of the unit cell, the space group, and the density of the crystal showed that the asymmetric unit of the unit cell [5] contains only one molecule, and hence only one iodine atom. Since this iodine atom contains about eight times as many electrons as the light atoms (hydrogen is completely ignored at first, because of its low scattering power), the iodine-iodine maxima should be easily recognizable above the background of light atom-light atom maxima, being 64 times as intense as the latter. However, owing to the presence of heavy atom-light atom maxima (which are eight times as intense as the light atom-light atom maxima) and the overlapping of maxima in the background, the difference in intensity is actually rather smaller: the iodine-iodine maxima, in fact, are 2.5 times as intense as the highest background maximum of the Patterson structure (Table 2).

Table 2. Weights (relative intensities) and parameters (x, y, z) of Patterson maxima in the *C*-(2,2′-biphenylylene)-$N\beta$-cyano-$N_\alpha$-(*p*-iodophenyl)azomethinimine structure, which contains one iodine and 23 light atoms in the asymmetric unit. The maxima marked with an asterisk correspond to interatomic vectors between iodine atoms.

| x | y | z | Height of maximum |
|---|---|---|---|
| 0.500 | 0.415 | 0.000 | 40* |
| 0.286 | 0.500 | -0.935 | 35* |
| 0.219 | 0.088 | 0.919 | 20* |
| 0.010 | 0.000 | 0.725 | 9 |
| 0.000 | 0.000 | 0.267 | 9 |
| 0.037 | 0.500 | 0.900 | 8 |
| 0.017 | 0.075 | 0.800 | 8 |
| 0.030 | 0.500 | 0.667 | 8 |
| 0.000 | 0.082 | 0.183 | 8 |
| 0.487 | 0.500 | 0.192 | 8 |

As an illustration, sections through the three-dimensional Patterson structure in the region of the iodine-iodine maxima are shown in Fig. 1; the intensity of the maxima can again be clearly seen [6]. The parameters of the positions of the iodine atoms in the unit cell are given directly by the positions of these Patterson maxima. However, this "iodine crystal structure" is an approximation to the complete crystal structure, in which the light atoms have been disregarded. The fact that this approximation model giving the positions of the heavy atoms is sufficient in most cases to permit the successful execution of the second step, *i.e.* the development of the final model, is of fundamental importance (cf. the discussion of step B of the evaluation).

[4] In collaboration with *R. Huisgen*, Organisch-Chemisches Institut der Universität München.

[4a] *F. Brandl*, Dissertation, Universität München, *1965*.

[5] The asymmetric unit of a unit cell is its smallest part that cannot be further reduced by the symmetry elements of the space group. It can be shown that the determination of the positions of the heavy atoms from the heavy atom-heavy atom maxima becomes particularly easy if the asymmetric unit contains only one heavy atom. This condition is satisfied in most organic heavy-atom structures (*e.g.* in vitamin $B_{12}$).

[6] The contour maps in this figure were drawn by an automatic function plotter controlled by a digital computer using a program developed at our Institute.

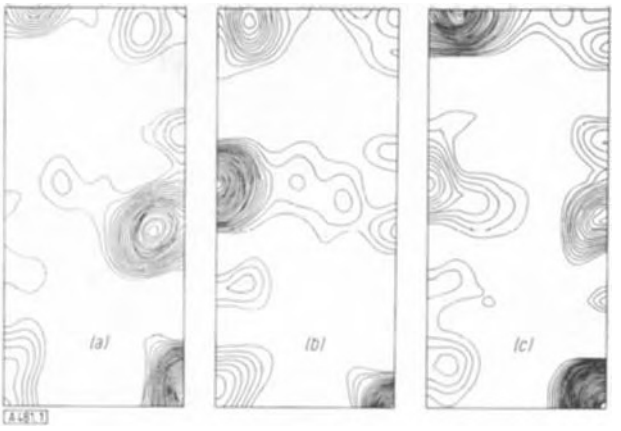



Fig. 1. Three-dimensional Patterson synthesis of *C*-(2,2′-biphenylylene)-$N\beta$-cyano-$N_\alpha$-(*p*-iodophenyl)azomethinimine (cf. Fig. 9). Sections in the neighborhood of the heavy atom-heavy atom maxima. The highest maxima correspond to iodine-iodine vectors. (a) Patterson maximum of iodine in general position (z = 55/60); (b) and (c) Harker maxima of iodine (z = 4/60 and 0).

This example indicates how the automation of step A by the heavy-atom method may by tackled. It is necessary to develop a computer program which will determine the positions of the maxima of the function $P_{xyz}$ and classify these maxima according to their intensities. In another subprogram, which takes into account the symmetry of the space group, the parameters of the positions of the intense Patterson maxima are reduced to the heavy-atom parameters. There are various ways in which this can be done, but these cannot be discussed in the present paper. Computer programs of this type are being developed in our laboratory.

We have discussed this example at some length in order to show that an approach to automatic evaluation can be achieved by simply translating the operations carried out by the crystallographer into computer language. However, since the machine does not develop "intuition", a process of this type can be successful only if no ambiguities that are difficult to resolve are encountered. The logical principle of the process described for the determination of the heavy-atom parameters clearly depends on the condition that the heavy atom-heavy atom maxima are sufficiently intense in comparison with the light atom-light atom maxima. In our next example we shall consider a case in which (for the two-dimensional calculation) this condition is not satisfied. This example will also show how it becomes possible to solve the problem when we turn from two-dimensional to three-dimensional methods.

Fig. 2a shows a Patterson projection of potassium *p*-nitrophenyl-*anti*-diazotate. Potassium contains about three times as many electrons as any of the light atoms. The potassium-potassium maxima should therefore be nine times as high as the light atom-light atom maxima, and three times as high as the light atom-potassium maxima. Although the dominance of the heavy atom-heavy atom maxima is not so pronounced as in the last example, they should be easily recognizable in the Patterson synthesis, and it should therefore be possible to determine the positions of the potassium atoms (determination of the approximation model).

However, the situation is complicated by the superposition of non-potassium-potassium maxima in this Patterson projection, so that the weight of the heavy

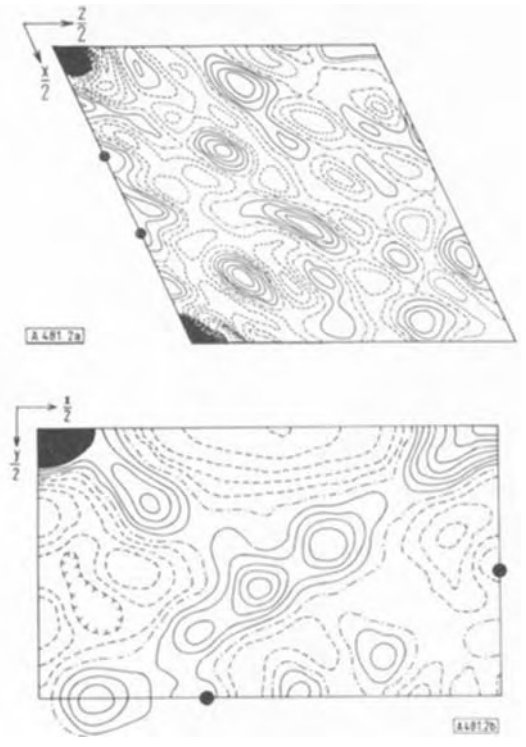


Fig. 2. Two-dimensional Patterson synthesis for potassium *p*-nitrophenyl-*anti*-diazotate (cf. Fig. 9).

(a): b-projection; (b): c-projection. The positions of the heavy atom-heavy atom maxima are indicated by dots.

atom-heavy atom maxima is only a fraction of that of the superimposed maxima. The black dots in the diagram indicate the potassium-potassium maxima. The contour lines show clearly the presence of "false" superposition maxima, which are three to four times as high. The situation is even worse in another Patterson projection of the same crystal (cf. Fig. 2b). It is clear that the heavy-atom method in projections cannot be used in this case, since neither a crystallographer nor a computer would be able to find the potassium-potassium maxima. A skilled crystallographer might be able to determine the structure by an indirect method, *e.g.* by first establishing the orientation of a benzene ring, but this would involve a great deal of effort. An entirely different situation is found when we consider the three-dimensional Patterson structure.

The left-hand column of Table 3 shows the weights of the potassium-potassium maxima, the remainder of the Table those of the highest non-heavy-atom maxima. In this case the symmetry of the crystal gives rise to so-called Harker heavy-atom maxima[7], which have double weights. These maxima are clearly also the highest maxima in the Patterson structure. However, the non-Harker heavy-atom maximum is again of the same order of magnitude as twelve other non-heavy-atom maxima, owing to certain internal symmetries of the structure in question. In other words, difficulties are encountered even in a three-dimensional evaluation if there are no Harker maxima. If (*e.g.* in the absence of Harker maxima in otherwise similar cases) there are a definite number of possibilities, an attempt can be made to resolve the ambiguity by testing the various possibilities in turn with the aid of a computer. Only the correct assumption will give a chemically meaningful structure.

Table 3. Weights of the highest maxima in a Patterson synthesis of potassium *p*-nitrophenyl-*anti*-diazotate (Harker maxima are indicated by an asterisk).

| Potassium-potassium maxima | Non-heavy-atom maxima | |
|---|---|---|
| * 5132 | 2135 | 1825 |
| * 4448 | 2117 | 1814 |
| 1959 | 2099 | 1695 |
| | 2067 | 1665 |
| | 1908 | 1626 |
| | 1889 | 1608 |

[7] Harker maxima are Patterson maxima (with double or fourfold weight) on particular planes or lines. They do not occur in all space groups.

## 2. The Convolution-Molecule Method

The convolution-molecule method[8] can to some extent be regarded as an extension of the heavy-atom method. In the latter, the approximation for an organic molecule is a heavy atom present in this molecule. In the convolution-molecule method, this function is taken over by a molecular fragment having a known steric configuration (*e.g.* an aromatic ring system). The position and orientation of this portion of the molecule in the unit cell are found from the Patterson structure. This "molecular-fragment crystal structure" (as opposed to the "heavy-atom crystal structure") then forms the basis for the next step of the structural analysis.

The convolution-molecule method makes use of certain structural properties of the Patterson function $P_{xyz}$. It can be shown that a molecular fragment having a known steric configuration gives Patterson maxima with definite structures. From the mathematical point of view, these structures are convolution products of the molecular fragments (convolution molecules). Systematic unravelling of these structures from the Patterson structure, taking into consideration the symmetry of the space group, yields the orientation and position of the molecular fragments in the unit cell. The process is similar in some respects to a jigsaw puzzle. The "picture" is the Patterson structure, and the "pieces" are the convolution molecules, of which there are two types.

The structure of the first type (convolution molecule with like indices) depends only on the molecular-fragment structure, and can therefore be calculated when this is at least approximately known. By fitting this convolution molecule into the Patterson structure, we find the orientation parameters of the molecular fragments which are required for the determination of the second type of convolution molecule (convolution molecule with mixed indices). If this convolution molecule can also be fitted correctly into the Patterson structure, we obtain the translation parameters of the molecular fragments, and since we know the orientation parameters, we can now find the complete crystal structure of the molecular fragments. This therefore concludes step A of the evaluation (cf. Fig. 3).

[8] *W. Hoppe*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *61*, 1076 (1957).

These operations can be carried out graphically in projections[9,10]. The use of three-dimensional convolution molecules, however, is very inconvenient. For this reason, the operations involved in the three-dimensional convolution-molecule method have recently been automated[11]. The rotation and displacement of the convolution molecules (which are calculated by means of Fourier series, in order to allow for the finite size of the convolution-molecule maxima) is carried out systematically by the computer. An interesting point is the criterion by which the computer judges the fit. For each orientation and for each translation the convolution molecules are subtracted at all points in the Patterson space[12] from the overall Patterson function. The sums of the negative and of the positive differences (or their squares) are then calculated separately. A large negative sum is unacceptable, since it would mean that the structure in question lacked the required Patterson maxima. On the other hand, a large positive sum is permissible, since this would simply mean that other Patterson maxima were present. This could be due to unknown molecular components, which were not taken into account in the convolution-molecule evaluation.

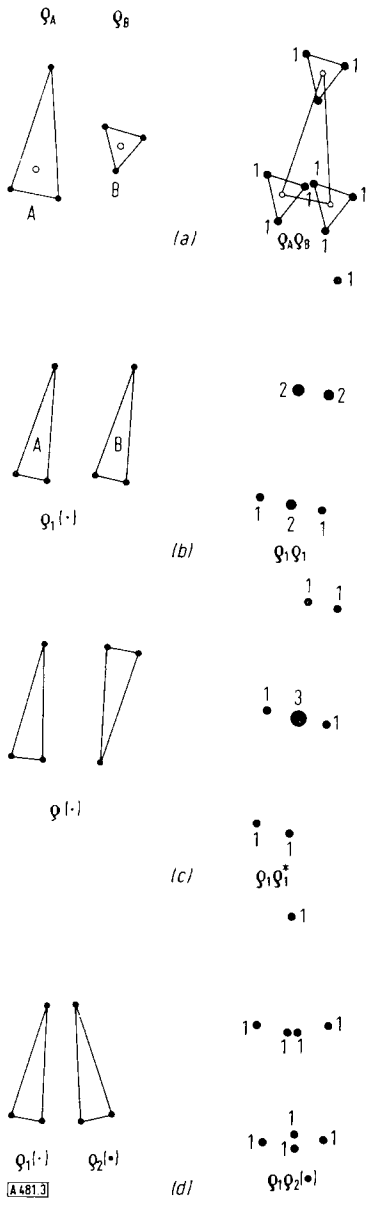



Fig. 3. The convolution method.

Convolution molecules result from the "convolution" of two molecules. The principle is shown in Fig. 3a.

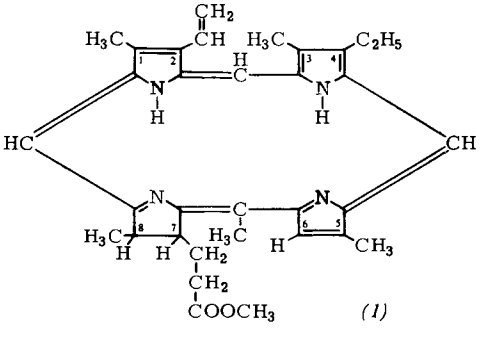
The molecule B is subjected to a parallel displacement to bring it over each of the vertices of molecule A in return, and the positions of the atoms of B are marked (black dots in the drawing). The weight of a point in the convolution molecule is the product of the weight of the vertex of A in question and the weight of the corresponding point of B. The molecules in the unit cell of a crystal are generally identical, but their positions have frequently been altered by symmetry operations.

Figs. 3b to 3d show convolution molecules of two molecules which are identical (3b), linked by a center of symmetry (3c), or linked by a mirror plane (3d). The numbers indicate the multiplicity of coincident points. In Figs. 3b and 3c, rotation of one molecule causes a similar rotation of the other, and hence leads to rotation of the convolution molecule with no change in the structure (convolution molecule with like indices). In Fig. 3d, on the other hand, rotation of the molecule leads to a change in the structure of the convolution molecule (convolution molecule with mixed indices).

As we have shown, the convolution-molecule method (particularly in the automated three-dimensional form) can deal with structures of similar complexity to those studied by the heavy-atom method. In the discussion of the method of successive Fourier synthesis we shall describe one of the structures [phyllochlorin ester *(I)*] solved by the convolution-molecule method.

This method can also be used for the constitutional analysis of organic molecules containing no heavy atoms, as has been shown[13] by the analysis of the crystal structure of ecdysone, the hormone that controls the pupation of insects. This analysis is remarkable in that the "molecular fragment" used was a sterol skeleton, the folding of which was partly incorrect. In spite of this the analysis was successful, and the complete chemical constitution, with all the oxygen functions, was found by X-ray analysis. Since the analysis was carried out on a compound containing no heavy atoms, the positions of all the atoms were found with high accuracy, and it was even possible to locate many of the hydrogen atoms.

Evidently if the "molecular fragment" used in the convolution-molecule method is a heavy atom, this method becomes the heavy-atom method. In this case the convolution molecules are very simple: they give rise to single spherically symmetrical maxima. There is no need to determine an orientation. The programs for the convolution-molecule method can therefore also be used to find the positions of heavy atoms. If, for the purposes of the analysis, the heavy atom has been introduced into the molecule by means of some large organic group (*e.g.*




*(I)*

[9] *W. Hoppe* and *G. Will*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *113*, 104 (1960).

[10] *W. Hoppe* and *R. Rauch*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *115*, 141 (1961).

[11] *R. Huber*, Acta crystallogr. *19*, 353 (1965).

[12] In order to reduce the computing time, however, the existing programs are confined to the maxima of the convolution-molecule functions.

[13] *R. Huber* and *W. Hoppe*, Chem. Ber. *98*, 2403 (1965).

introduction of bromine by esterification of a hydroxy group with bromobenzoic acid), it is expedient to use the convolution-molecule technique instead of the heavy-atom method. The approximation model will then contain the positions of the light atoms of the organic residue, as well as the position of the heavy atom, and the prospects for the second stage of the evaluation will be improved by the improved approximation model.

Another combination of the convolution-molecule method with the heavy-atom method may be useful when the asymmetric unit contains several heavy atoms, and when the geometrical coordination of some heavy atoms is known. In the structural analysis of 2,3,4,4-tetrachloro-1-oxo-1,4-dihydronaphthalene, the convolution-molecule evaluation is based on the known configuration of the four chlorine atoms [14].

A more complicated example is shown in Fig. 4a. In the structure analysis of the cyclopentadienyl-cyclooctatetraene-Co complex $\mu$-$C_8H_8(CoC_5H_5)_2$ [15], it was found that this compound (triclinic, space group $P\bar{1}$) crystallizes with three molecules in the asymmetric unit. The unit cell therefore contains 12 heavy atoms, so that the determination of the heavy-atom structure from the 102 heavy-atom maxima in the Patterson function presents a considerable problem. The problem was solved by regarding the two cobalt atoms as forming a diatomic molecule, in which, on chemical grounds and on the basis of a preliminary examination of the Patterson synthesis, the distance between these two atoms must be between 3.5 and 4 Å. Evaluation on this basis by the convolution-molecule method led to the correct heavy-atom structure (Fig. 5a), and hence, *via* several successive Fourier syntheses (cf. Section B.2), to the complete structure containing the 60 atoms of the asymmetric unit. The analysis showed that the cyclooctatetraene ring is in the boat form with alternating double bonds (cf. Fig. 4b).

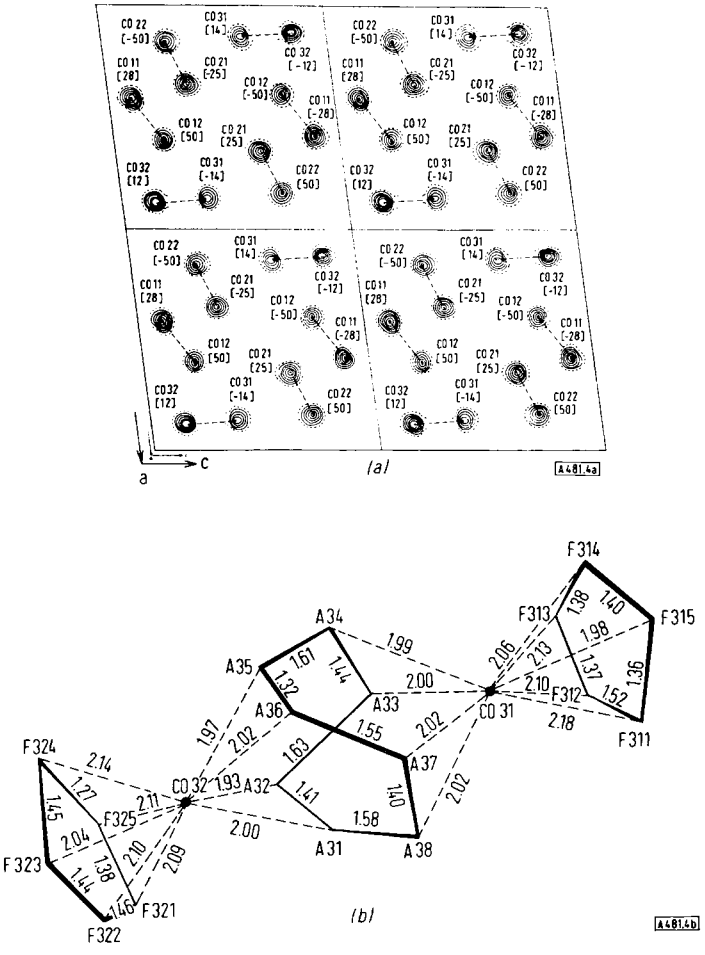



Fig. 4. The convolution-molecule method in structures with a known heavy-atom configuration. Fig. 4a shows the structure of the "$Co_2$ molecules" in $\mu$-$C_8H_8(CoC_5H_5)_2$ in the three-dimensional Fourier synthesis of the heavy atoms in a projection along the b-axis. The lines joining the ends of the "$Co_2$ molecules" are dotted.

Fig. 4b shows the molecular model of $\mu$-$C_8H_8(CoC_5H_5)_2$. State of refinement $R_1 \approx 20\,\%$; 4500 independent reflections.

[14] *W. Hoppe* and *R. Rauch*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *115*, 141 (1961). – The three-dimensional refinement of the structure ($R \approx 15\,\%$) has not yet been published.

[15] *E. F. Paulus*, Dissertation, Universität München, 1965.

### 3. The Fourier-Transform Method and the Diffuse-Scattering Method

The Fourier-transform method is related in some respects to the convolution-molecule method. If the molecular structure is known, it is possible to calculate the scattering diagram of the molecule, and then to try to match this with the intensity distribution of the X-ray reflections [16]. This leads to orientation parameters and (in a somewhat more complicated procedure) to translation parameters. Difficulties are encountered in the analysis of molecular fragments, since, in contrast to the convolution-molecule method, the influence of atoms that are neglected cannot be compensated. This method is therefore less suitable for constitutional analysis.

In a recent variant, the Fourier-transform method is used in the evaluation of thermal diffuse scattering from molecular crystals [17]. Whereas the crystal reflections form a discontinuous distribution, the diffuse scattering gives rise to a continuous blackening on the X-ray photographs (background scattering component). It has been shown that the diffuse scattering in molecular crystals is modulated approximately in accordance with a superposition of the scattering diagrams of the molecules in the unit cell. We can therefore try to match the scattering diagrams of the molecules with the distribution of the diffuse scattering instead of with the reflection distribution. Since the distribution is continuous, the information obtained is more comprehensive. It is possible, for example, to estimate the sizes and shapes of molecules before the structural analysis is commenced. No details can be given in the present paper [17]. It is naturally also possible to combine the Fourier-transform method with the convolution-molecule method.

[16] *A. Hettich*, Z. Kristallogr., Mineralog. Petrogr., Abt. A, *90*, 483 (1935); *P. P. Ewald*, *ibid. 90*, 493 (1935).

[17] Cf. *W. Hoppe* in *R. Brill*: Fortschritte der Strukturforschung mit Beugungsmethoden. Friedr. Vieweg, Braunschweig 1964, pp. 90–166.

Since the diffuse scattering provides additional experimental data, a combination of this kind can often make an analysis much easier (cf. the evaluation of the diffuse scattering in ecdysone [18]).

## 4. Image-Seeking Methods

In the convolution-molecule method, the Patterson structure is broken down into sub-structures, which depend on, but are not identical with, the molecular structure. Taking an entirely different approach, we can also regard the Patterson structure as being composed of $n$ images of the crystal structure which have been mutually displaced [19]. It would obviously be possible to recognize the crystal structure directly from the Patterson structure, if the Patterson maxima of such an image could be marked (cf. Fig. 5). This can be easily done for the Patterson structure of a crystal with a

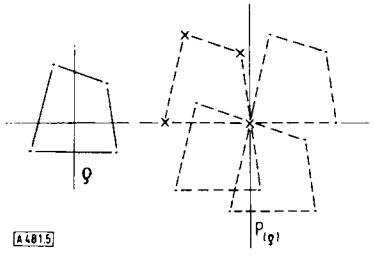



Fig. 5. Image seeking in the Patterson function.

The Patterson function P(ρ) of the structure ρ can be regarded as resulting from the superposition of identical images of the structure ρ. In the image-seeking method, all the Patterson maxima in the Patterson structure that belong to any image of the structure (marked by crosses) are sought.

center of symmetry, if two Patterson structures, which are mutually displaced by an interatomic vector that occurs only once (unique), are superimposed [20]. Patterson maxima that coincide belong to the same "image" of the crystal structure. In the case of acentric structures, however, we first obtain a double image consisting of the structure and its centrosymmetric image. Superposition of this double image on another Patterson function, followed by marking of coincident maxima again gives the structure (or its centrosymmetric image). The process described is independent of model considerations; its use obviously does not even require a knowledge of the empirical formula. This is therefore a direct method, which combines steps 1 and 2 of the evaluation, and which leads directly to the complete structure.

Unfortunately, however, this is applicable only to structures containing small numbers of atoms. If we consider an organic structure consisting of light atoms, and with about 100 atoms in the unit cell, it is necessary to unravel a Patterson structure containing about 10000 Patterson maxima. Since the Patterson maxima have a finite volume, it is hopeless to try to separate these 10000 maxima in the small volume of the unit cell.

[18] *W. Hoppe* and *R. Huber*, Chem. Ber. *98*, 2353 (1965).

[19] $n$ is the number of atoms in the unit cell.

[20] In centrosymmetric structures these are vectors between atoms which are linked by a center of symmetry.

It is not possible to find unique Patterson maxima [21] (required at the beginning of the method), nor can unique Patterson maxima be marked by coincidence as the positions of atoms in the multiple superpositions. The situation changes, however, when the structure contains one or more heavy atoms. The maxima in the Patterson structure then fall into the height classes (heavy atom-heavy atom maxima, heavy atom-light atom maxima, light atom-light atom maxima) discussed earlier. If single Patterson maxima corresponding to distance vectors between heavy atoms can be used for the interpretation of the Patterson structure, it can be shown that the crystal structure can be found from the heavy atom-light atom maxima alone [22].

Evaluation by this method has two advantages. First, it is possible to find the heavy atom-heavy atom vectors even in complex structures, owing to their great weight, and second, the number of heavy atom-light atom Patterson maxima is proportional to the number, $n$, of light atoms. Since the heavy atom-light atom maxima are higher than the light atom-light atom maxima, and since their number is of the same order as the number of light atom maxima, they should be visible separately, even in a complex structure, against a diffuse background of the very numerous light atom-light atom maxima. As we have already mentioned, separability of the Patterson maxima is essential to the success of superposition methods. Many relatively complicated heavy-atom structures have been resolved by this method.

It is admittedly desirable, even in these cases, to determine the positions of the heavy atoms before analysis in the same manner as in the heavy-atom method. Only then is it possible, for example, to decide in limiting cases which Patterson maxima correspond to heavy atom-heavy atom vectors; this is done by means of the Harker maxima (cf. Table 3). In cases of this type, however, the superposition method may be regarded simply as a special case of the heavy-atom method, in which the determination of the approximation model again consists in the determination of the heavy-atom structure.

Since the reliability of evaluation by superposition increases with the number of superpositions (as has been pointed out, at least two superpositions are required in the case of an acentric structure), the use of this method for structures consisting entirely of light atoms is more reliable when a large number of unique light atom-light atom vectors are known. If the structure of a part of the molecule is known, the positions of the light atoms can be found by the convolution-molecule method. Unique light atom-light atom vectors can then be calculated from these positions, and an attempt can be made to use these as a basis for a structural analysis by the superposition technique.

To summarize, the use of the superposition method for complex structures is likely to be successful if the re-

[21] Multiple Patterson maxima occur when a crystal structure includes several interatomic vectors of identical length and direction. Only superpositions on single Patterson maxima lead to coincidence-marking of double or single images of the structure.

[22] This condition must be satisfied for each stage of the evaluation. For example, if an acentric structure contains only two heavy atoms, there is only a single heavy atom-heavy atom vector. Only the first superposition to obtain the double image over the heavy atom-light atom maxima can then be carried out. The same ambiguity is found in the calculation of a Fourier synthesis phased with the two heavy atoms. "Phased" means that the phase shift $\Phi$ is taken into account in the structure factor.

quired unique Patterson vectors are deduced from a previous determination of an approximation model (by the heavy-atom or folded-molecule methods). The superposition method is then used to find the final model, and will therefore be discussed once more in Section B.

## 5. "Direct" Methods

The special form of the electron-density function of the crystal (positivity, separability into atomic electron-density functions) gives rise to relationships between structure factors, which lead directly to the phases of the structure. The methods are therefore automatic in themselves, since the structure can be directly calculated and interpreted by a Fourier synthesis of the phased absolute values of the structure factors. Owing to the unavoidable error in the calculation of the phases, however, this "electron-density synthesis" is often not very clear. As was pointed out in the introduction it provides at best the positions of some of the atoms ("approximation structure"). A structure determination by a direct method must therefore be followed by step B of the evaluation, although this should not really be necessary. Relatively little experience has been gained so far with direct methods. They have mostly been used in projections, and were successful with relatively simple structures. It is possible that more recent work [23–25] and programming in three dimensions will extend the scope of the method to include more complex structures.

## 6. Indirect Phase-Measurement Methods

The difficulties in the evaluation due to the fact that the phases are unknown could, of course, best be eliminated by measurement of the phases. If a direct measurement with X-rays, based on interference effects, does not seem to be possible, the phases can be determined indirectly if additional scattering centers are introduced into the unit cell. It is often not too difficult to introduce an additional scattering center. For example, it may be possible to prepare a chlorine derivative and a bromine derivative in the case of an organic compound. If the two derivatives crystallize in the same lattice (isomorphism), the scattering factor of the "additional scattering center" (in the bromine derivative) corresponds to the difference between the scattering factors of bromine and chlorine.

If the positions of these differentiating atoms in the unit cell are known, it is possible to calculate the structure factors $f_o$ of this "differentiating-atom approximation structure". The phases of the structure factors of the isomorphous crystals can then be obtained by construction, as shown in Fig. 6. The construction is based on the fact that the structure factors of the differentiating-atom approximation structure and of the two isomorphous crystals must form a vector triangle. As can be seen from Fig. 6, there are two possible solutions. This embiguity can be eliminated by preparation of a third aomorphous derivative and repetition of the same visaluation.

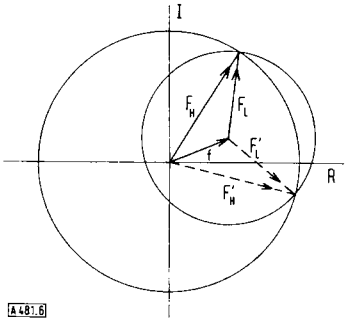



Fig. 6. Indirect phase-measurement by isomorphous replacement.
Construction of the vector characterizing the amplitude $|F_H|$ and the phase $\Phi_H$ of a structure factor $F_H$ of the isomorphous heavy-atom derivative, using the vector triangle of the structure factor of the heavy-atom approximation structure f and of the two measured absolute values $|F_L|$ and $|F_H|$ of the structure factors of the two isomorphous derivatives. The intersection of the circles drawn through the two end-points of f with radii $|F_L|$ and $|F_H|$ represents the solution.

The method of isomorphous replacement was first applied to centrosymmetric structures, in which only one isomorphous replacement is required. In the case of acentric structures, isomorphous replacement has so far been used only in the structure analysis of protein crystals. The successful analysis of these extremely large and complex structures was made possible by indirect phase-measurement by multiple isomorphous replacement.

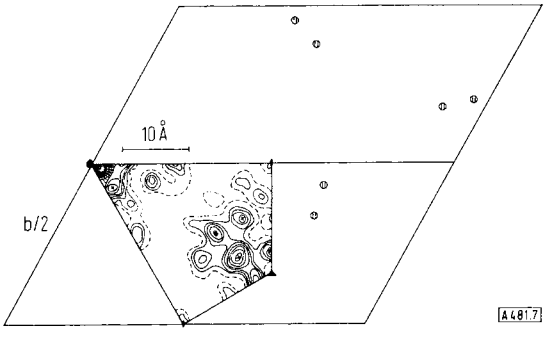



Fig. 7. Determination of the differentiating atoms in isomorphous protein derivatives. Protein [26, 27]: erythrocruorin from *Chironomus thummi*; molecular weight 16000; space group P $3_1$.

The Figure shows the "Patterson projection of the differences" in the direction of the trigonal axis, calculated from the squares of the differences between the absolute values of the structure factors $|F_S|$ of the protein-$HgCl_2$ compound (obtained by diffusion of $HgCl_2$ into the protein crystals) and the absolute values of the structure factors $|F|$ of the protein with no heavy atom. This Patterson synthesis of the differences (one asymmetric unit is shown) shows the Patterson structure of the heavy atoms in the protein (apart from a background that depends on the protein). Each protein molecule is bonded to two heavy atoms in definite positions. The Patterson point-structure of the heavy atom-heavy atom maxima is also shown (crosses) for comparison. The circles indicate the arrangement of the heavy atoms; note the threefold repetition.

[23] *P. Main* and *M. M. Woolfson*, Acta crystallogr. *16*, 1056 (1963).

[24] *W. Hoppe, K. Anzenhofer*, and *R. Huber*: Crystallography and Crystal Perfection – Proceedings of the Symposium held in Madras, January 14th–18th, 1963. Academic Press, London-New York 1963, p. 51.

[25] *W. Hoppe*, Acta crystallogr. *16*, 1056 (1963).

[26] *R. Huber, H. Formanek, V. Braun, G. Braunitzer*, and *W. Hoppe*, Ber. Bunsenges. physik. Chem. *68*, 818 (1964).

[27] *R. Huber, H. Formanek*, and *O. Epp*, unpublished work.

The simple geometrical relationships of Fig. 6 can be easily programmed for each reflection, so that "automatic phase-measurement" in accordance with Fig. 6 raises no fundamental difficulties. The determination of the approximation structure of the differentiating atoms is not quite so simple; however, this evaluation can be largely automated. The real problem with the isomorphous replacement method is chemical in nature: thus it is necessary to prepare isomorphous heavy-atom derivatives in which not only the isomorphously substituted atoms are correctly located in the unit cell, but there must be no disturbance of the isomorphism owing to small displacements of the unsubstituted atoms. Fortunately, the large holes in protein structures, which are filled with solvent molecules, can accommodate quite large heavy-atom groups without disturbance of the crystal structure (cf. Fig. 7). Nevertheless, the preparation of suitable derivatives is often very difficult, even in the case of proteins.

Lack of isomorphism generally prevents the determination of phases with a resolution of better than 2 Å [28]. Although a Fourier synthesis based on these data, in principle, shows all the atoms, this synthesis cannot be interpreted directly, owing to the low resolution and the unavoidable phase error. As in the direct methods, it is necessary to include an evaluation step which, on the one hand, leads to the Fourier synthesis with all the absolute values of the structure factors that can be found by experiment [29], and on the other, eliminates the effect of the phase error (determination of the final model).

The method of anomalous scattering is related in some respects to the isomorphic replacement method. It can be shown that the scattering power of heavy atoms in a structure can be altered by variation of the wavelength of the primary beam. This change in scattering power has the same effect as the replacement of the atom by another atom. To bring about this change, it is necessary to use radiation having a wavelength close to that of an absorption edge of the heavy atom. In acentric structures the change in scattering power is accompanied by a phase change, which provides a possible method for indirect phase measurement. The measurement is made difficult by the fact that the effects are small, so that the measurements must be very accurate. The anomalous-scattering method can be automated by a system fundamentally similar to that used for the indirect phase measurement with multiple isomorphous replacement.

Since both the multiple isomorphous replacement method and the anomalous-scattering method involve measurements on heavy-atom derivatives, these may be included among the heavy-atom methods in the wider sense.

## B. Determination of the Final Model

### 1. Image-Seeking Functions

In the discussion of step A of the evaluation, we showed that the image-seeking functions permit the determination (at least in principle) of the positions of all the atoms. The method used to check for coincidence of superimposed Patterson maxima in the two mutually displaced Patterson structures is important in practice (cf. Fig. 5). The simplest method is to add the superimposed Patterson functions. Coincident Patterson maxima then appear to be intensified ("marked") in the picture obtained by superposition (additive image-seeking function).

Another method is to multiply the Patterson functions. When a Patterson maximum is situated over the background (non-coincidence), one of the factors in the multiplication is zero, and the Patterson maximum disappears in the picture obtained by superposition. In the case of coincident Patterson maxima, both factors are finite, and a maximum therefore apperas in the picture obtained by superposition. It is easy to see that, in the second of these methods, the background of non-coincident Patterson maxima is eliminated, at least in principle (product function). A third method is simply to note the lower of the two values of the superimposed Patterson functions. In this case the background is again eliminated, since non-coincident Patterson maxima lie on the background, the value for which is zero, so that the value recorded in the picture obtained by superposition is equal to zero (minimum function). All three methods can be easily programmed for electronic computers. There are therefore no obstacles to their use in routine work.

It should again be noted that in the case of complex structures, image-seeking methods are likely to be successful only if heavy atoms are present, owing to the overlapping of Patterson maxima.

### 2. Successive Fourier Syntheses

If we calculate a Fourier synthesis with the absolute values of the measured structure factors, together with the phases of an incomplete structural model (an approximation model) – *e.g.* in the case of a heavy-atom structure, the phases of a structure in which all the light atoms are neglected – the Fourier synthesis includes not only the electron-density maxima corresponding to the atoms inserted, but also maxima corresponding to some of the atoms that were neglected in the phase calculation. These atoms can then be included in the next phase calculation (improved approximation model), and a further Fourier synthesis should yield the maxima due to more new atoms. This operation is repeated until

[28] Definition of resolution: The smallest interplanar distance down to which reflections are to be measured. It can be shown that this limitation of the range of reflections measured limits the sharpness of the Fourier electron-density synthesis. In protein crystals, owing to defects in the crystal structure (small displacements of the atoms of the protein molecule) reflections can only be measured down to an interplanar distance of about 1.5 Å. An electron-density synthesis calculated with the aid of these reflection data does not lead to clear resolution of the electron-density maxima of light atoms linked by covalent bonds; it does, however, permit an unambiguous assignment of the amino-acid residues.

[29] Cf. *W. Hoppe* and *J. Gaßmann*, Ber. Bunsenges. physik. Chem. *68*, 808 (1964).

the positions of all the atoms have been found. Clearly, the better the phases of the first approximation model, the more rapidly will this procedure converge.

It is also obvious without calculation that the more atoms an approximation model contains, or – in the heavy-atom method – the higher the scattering power of the heavy atoms, the better is the model. As an illustration, Fig. 8 shows the maxima found in a Fourier

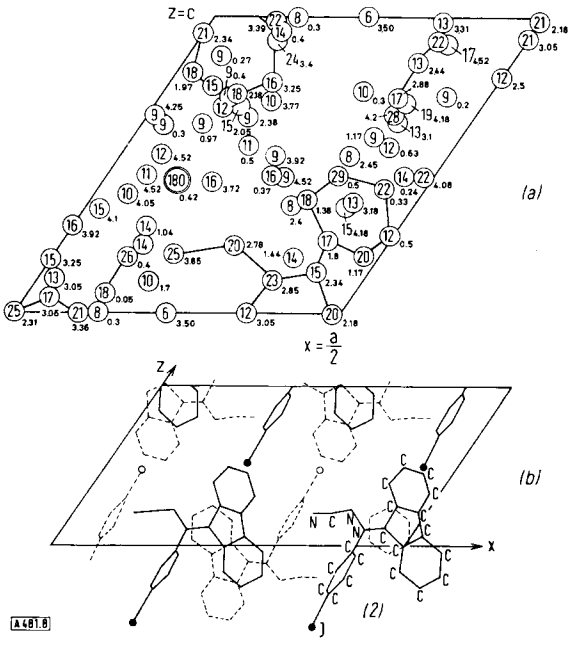
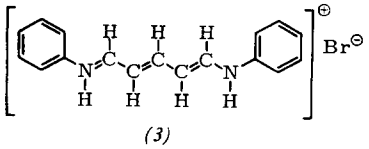



Fig. 8. *C*-(2,2'-biphenylylene)-*N*β-cyano-*N*α-(*p*-iodophenyl)azomethinimine *(2)*.

Fig. 8a shows maxima of a three-dimensional Fourier synthesis calculated with the phases of the iodine-atom approximation structure. The numbers in circles give the relative heights of the maxima; those outside the circles are the y parameters. Note the low "ghost maxima" and the deformation of the structure. Fig. 8 b shows the structure obtained when the analysis was completed.

synthesis of *C*-(2,2'-biphenylylene)-$N_\beta$-cyano-$N_\alpha$-(*p*-iodophenyl)azomethinimine phased only with the iodine atoms (cf. also Fig. 1). Since iodine has a high scattering power, this synthesis already contains the positions of all the atoms. The diagram contains a few extra "ghosts" and break-off maxima, but these can be readily distinguished on chemical grounds. Besides the maxima in Fig. 8, figures are given to indicate their heights.

For an organic structure of approximately the same size, *viz.* 5-anilinopenta-2,4-dien-1-ylideneanilinium bromide *(3)* [30], but containing the less strongly scattering bromine, the Fourier synthesis phased only with bromine did not contain the maxima for all the atoms. However, insertion of the light-atom maxima already found into the calculation of the




*(3)*

next Fourier synthesis gave the complete solution. The phase-determining power of a heavy atom depends not only on its scattering power, but also on the size of the light-atom structure. Thus the scattering power of potassium, for example, is sufficient to give the positions of all the light atoms in potassium *p*-nitrophenyl-*anti*-diazotate [31] by a single Fourier synthesis (cf. Fig. 9).

In structural analyses by the convolution-molecule method, the basis for the calculation of the first phases is the approximation structure of the known molecular

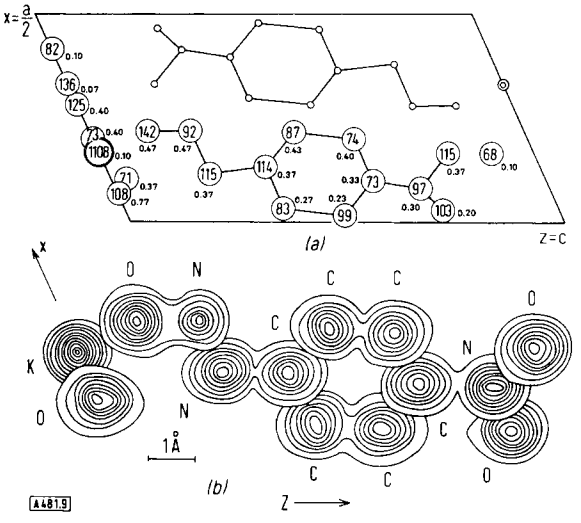



Fig. 9. Potassium *p*-nitrophenyl-*anti*-diazotate.

Fig. 9a shows maxima of a three-dimensional Fourier synthesis phased with potassium (representation as in Fig. 8). Fig. 9b shows the three-dimensional Fourier synthesis obtained when the analysis was completed. The diazotate group in *anti*-configuration is planar (cf. [32]).

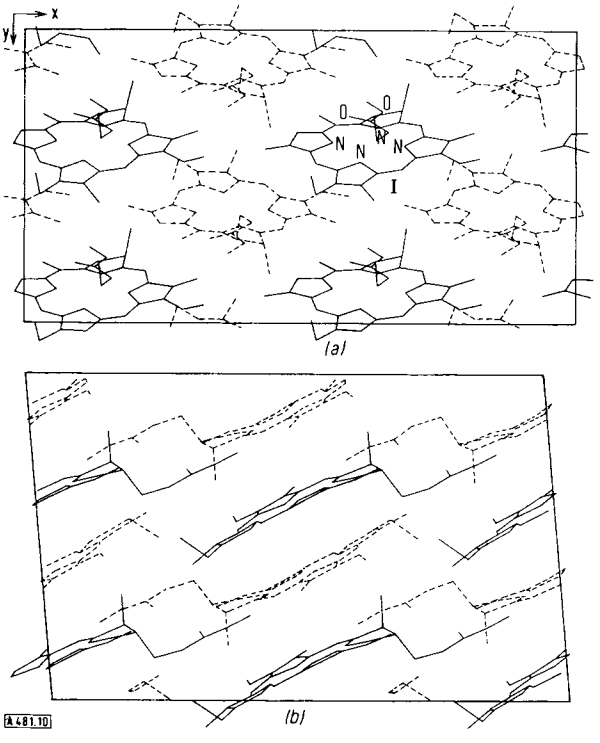



Fig. 10. Molecular model of phyllochlorine ester in c-projection (a) and in b-projection (b), derived from a three-dimensional Fourier synthesis; refined structure, $R_1$ = 15 %. Note the marked difference between the chlorine ring and the idealized planar configuration with four-fold symmetry (not shown) used in the convolution-molecule evaluation.

[30] *H.-J. Springer*, Dissertation, Technische Hochschule München, 1965.

[31] *O. Epp*, Diploma Thesis, Technische Hochschule München, 1965.

[32] *R. Huber*, *R. Langer*, and *W. Hoppe*, Acta crystallogr. *18*, 467 (1965).

fragment. Successive Fourier analysis, apart from giving the positions of new atoms, also leads to a better picture of the molecular fragment, the stereochemistry of which is generally not accurately known. Fig. 10 illustrates this effect for the structure analysis of phyllochlorine ester [33]. The "molecular fragment" used in the convolution-molecule evaluation was a planar chlorine ring with four-fold symmetry. The chlorine ring is obviously anything but planar: apart from a slight curvature of the large ring system, the two tetrahedral carbon atoms in positions 7 and 8 are strongly displaced from the average plane.

In the determination of the structure of ecdysone *(4)* (cf. Section A.2), the coprostane skeleton used was improved so far that the position and orientation of the double bond of an α,β-unsaturated ketone could be discerned. The case of ecdysone is particularly typical, since a sterol skeleton that was wrongly convoluted at first was subsequently corrected by the convolution-model method, and since the unknown constitution of the molecule could be established (with differentiation between C atoms and O atoms) by three successive Fourier syntheses without the aid of chemical information. Fig. 11 shows the three-dimensional Fourier synthesis of ecdysone.

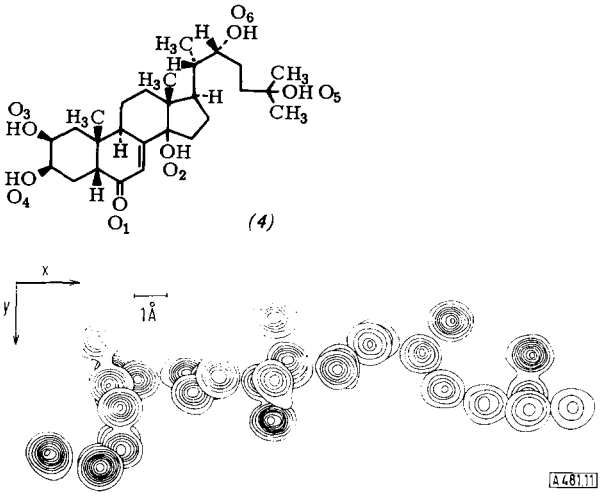



Fig. 11. Three-dimensional Fourier synthesis of the molecular model of ecdysone.

As in step A of the evaluation, the replacement of two-dimensional by three-dimensional methods greatly increases the reliability. This is due not only to the avoidance of undesirable coincident projections of atoms, but also to the large quantity of information, which leads to a partial averaging of the phase error. It must be pointed out, however, that certain positions of the heavy atoms can sometimes give rise to a false symmetry in the Fourier synthesis, which can be very difffcult to eliminate.

The automation of successive Fourier syntheses requires programs that permit the location of maxima in the electron-density functions. Programs of this type are relatively easy to develop, and have recently been introduced into our program system. In order to be complete, an iteration program must also include selection programs, the function of which is to decide which of the maxima obtained are to be interpreted as atoms. This decision can be made by neglecting maxima with intensities lower than a certain value. It has been found useful, however, to introduce an apparent occupation density of the atoms, assumed to be proportional to the height of the maximum. A variation process applied to successive calculation cycles involving least squares [34] not only leads to an improvement in the position parameters of the true atoms, but also brings the occupation densities of these atoms to unity (occupation by a single atom). The occupation densities of maxima that do not correspond to atoms, on the other hand, become zero. The new positions found in this way are used by the computer in the calculation of a new Fourier synthesis, which is interpreted in a new series of cycles. Successes achieved by this method have already been reported [35]. The interpretation of Fourier maxima by the computer may also include the use of stereochemical criteria in the selection of maxima that correspond to atoms. It is interesting to note that the trend in these programming tasks show a steady drift away from classic calculations. Programs of this type are also known as pattern-recognition programs. A non-crystallographic example of such a program is the recognition of hand-written characters. The same characters written by different persons can differ quite markedly. However, they have certain features in common, which permit the reader to read a very wide range of scripts. In this case the computer must imitate decisions that the reader generally makes subconsciuously. A distorted image of a group of atoms in a Fourier synthesis containing phase errors can also be regarded as such a "character".

### 3. Improvement of Phases by Modification of the Electron Density

Some time ago we reported methods by which the inaccurate phases derived from an approximation model could be improved without the use of model constructions in the Fourier space. We sought a function which, when operating on an approximate electron-density function, would improve the approximation to the true electron-density function [36]. The phases and absolute values of the Fourier coefficients of the improved electron-density synthesis can then be determined by a Fourier transformation. Consider a structure in which all the atoms have the same weight. A better approximation is then obtained by replacement of the absolute values of the Fourier coefficients by the measured absolute structure factors, since any deviation from the measured (and hence correct) absolute values of the structure factors indicates an error. The process is then applied to this new set of structure factors, and iteration over several cycles ultimately gives the final structure. Fig. 12 shows how such functions can be built up. In principle, the specially constructed function appraises an electron-density synthesis in the same way as a crystallographer does: new maxima with heights greater than a certain value are regarded as "probable" atoms, while maxima below this limit are regarded as "ghosts". However, the simple yes-no decision is replaced by the more cautious continuous function. Thus the modified electron-density function contains the new "probable"

[33] *W. Hoppe, G. Will, J. Gaßmann,* and *H. Weichselgartner,* unpublished work.

[34] See refinement by means of least squares.

[35] *J. D. Rollett* and *L. J. Hodgson*: Automatic Methods for Heavy Atom Phase Determination. Lecture at the Laue Symposium, Munich 1962.

[36] *W. Hoppe, R. Huber,* and *J. Gaßmann,* Acta crystallogr. *16,* A 4 (1963).

atom maxima as somewhat higher (but still too low) maxima, and the "probable" ghost maxima as somewhat lower (but still present) maxima. The relationship with the method of successive Fourier syntheses is readily apparent.

The function represented in Fig. 12 has the further advantage that it can be readily transformed into reciprocal space. It is therefore possible to modify the structure factors directly in order to improve their phases in successive cycles without intermediate calculation of electron density syntheses. Fig. 13 shows how well the method works for structures in which all the atoms are identical. Fairly small planar test structures have been chosen in order to minimize the extent of calculations required.

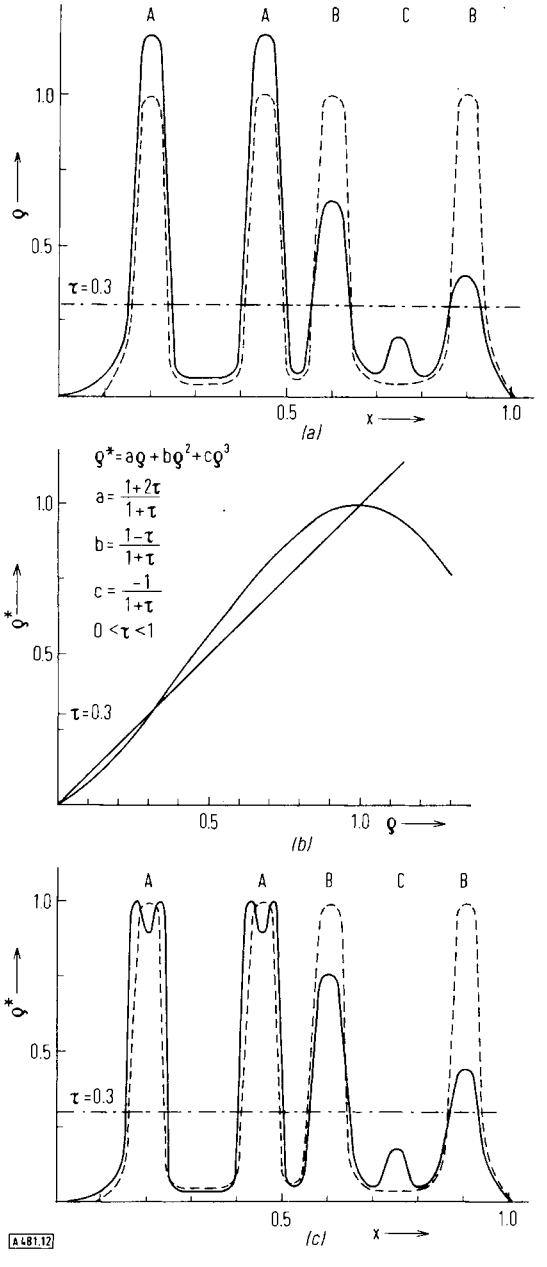



Fig. 12. Phase improvement by modification of the electron density. (a) The result of a Fourier synthesis phased with only some of the atoms present is shown in the one-dimensional example. The atoms used (A) appear to be excessively high, while the atoms (B) omitted are too low. There is also a background present (C) (the correct structure is shown). (b) A function $\varrho^*$ suitable for improvement of the structure. (c) The modified Fourier synthesis obtained on conversion of $\varrho$ into $\varrho^*$. It can be seen that the excessively high maxima (A) have been lowered, the low maxima (B) have been raised, and the background (C) has been reduced. It is to be expected that the phases of the structure in Fig. 12c will be better than those of the structure in Fig. 12a. The corresponding calculations can be carried out automatically in iterated cycles by the convolution process, without intermediate calculation of the Fourier synthesis.

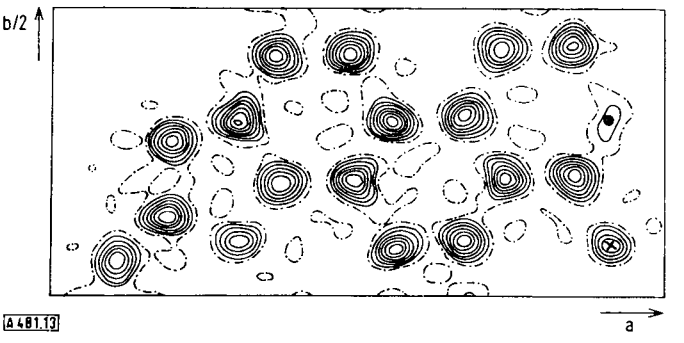



Fig. 13. Two-dimensional hypothetical test structure (a "methylated cyclopentadienophenanthrene") phased with all the atoms, but with qualitatively incorrect positioning of one of the eighteen atoms. The false maximum (cross) appears to be appreciably higher than the true one (dot). The process of Fig. 10 led to convergence in eight cycles, with complete elimination of the false maximum, and with development of the true maximum to the correct height.

The hypothetical test structure in Fig. 13 was phased with a model in which one out of the eighteen atoms given was in an entirely wrong position. As can be seen in the diagram, the maximum corresponding to the false atom is appreciably higher than the one at the position of the correct atom, which can scarcely be distinguished from the background. In considering this Fourier synthesis, the analyst would be inclined to assume that the structure is correct, and that the only errors are phase errors due to lack of accuracy of the coordinates. Only after vain attempts to refine the model would he realise that his structure must contain a qualitative error. Even in this case, however, the new phase-improvement process converges.

The programs, originally designed for two-dimensional calculations, were subsequently extended to three dimensions. It was found that even much poorer approximation models lead to convergence in three-dimensional calculations. In one case convergence was obtained with a structure phased with only four out of ten identical atoms. Moreover, the four given atoms were displaced by about 0.2 Å from their true positions. Investigations on a similar process for heavy-atom structures are in progress.

### C. Refinement of the Structure

The result of a successful Fourier synthesis is a set of atomic coordinates which still contain slight errors. Methods of refining the structure, most of which are regularly used in a semi-automatic form, were developed some time ago. We shall deal here only with those that are particularly suitable for automatic calculation, in which the experimental values are fitted by the method of least squares.

### 1. Least-Squares Refinement of Atomic Parameters

The equation for the structure factor is:

$$F_{\vec{h}} = \sum_{j=1}^{N} f_j \exp 2\pi i (\vec{h}, \vec{r_j} + \Delta \vec{r_j}) \quad (3)$$

After this equation has been linearized by the method of least squares, the $\Delta\vec{r_j}$ can be found by solution of a system of linear equations, and the difference between $(F_h)_{exp}$ and $(F_h)_{calc}$ can then be minimized.

The atomic coordinates, the scaling factor, and the thermal factors of the individual atoms may be used as parameters. Anisotropic thermal vibrations can be readily taken into account, and the method of least squares has the advantage that the residual error of the varied coordinates can be determined in a satisfactory manner. The process and the associated computing programs have for some time been an essential part of structural analysis.

### 2. Refinement of Phases

This process has only recently been described [37], and like the method of phase correction by modification of the electron density (Section B.3), has so far been successfully tested only for structures consisting of identical atoms. In structures of this kind, each structure factor

$$F_{\vec{h}} = \sum_{h'} |F_h| \, |F_{h-h'}| \exp (\Phi_{h'} + \Phi_{h-h'} + \Delta\Phi_{h'} + \Delta\Phi_{h-h'}) \quad (4)$$

can be represented as the sum of all the other structure factors, as in Eq. (4). This equation is very similar to that for the structure factor from the contributions of the individual atoms present in the structure (3), with the product $F_h \, F_{h-h'}$ of the structure factors in place of the form factors $f_j$ of the atoms.

A particularly interesting point is that – again purely formally – the coordinate-dependent exponential functions $\exp 2\pi i(hr_j + \Delta r_j)$ are replaced by ones depending on the phases of the structure factors. Owing to the formal similarity of the two equations, it is possible, in principle, to use the same mathematical process based on the method of least squares. This process, however, no longer leads to correction of the error in the atomic coordinates $\Delta r_j$, but to the correction of the phase error $\Delta\Phi$. We have successfully used the new method for a number of simple test structures. It should be noted that phase refinement also leads to the appearance of new atoms and the disappearance of wrong ones in the improved Fourier synthesis. The method gives similar results in this respect to those obtained by the method described in Section B involving modification of the electron density.

[37] *W. Hoppe*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *118*, 122 (1963); *W. Hoppe*, *R. Huber*, and *J. Gaßmann*, Acta crystallogr. *16*, A 4 (1963).

### 3. Other Methods of Refinement

It has been shown that the refinement methods of difference Fourier synthesis and the method of steepest descent are related to the refinement of the atomic coordinates using the method of least squares. The difference Fourier synthesis method is often used in structure analysis. In this method the differences between the calculated and experimental structure factors are used to calculate a Fourier synthesis, the course of which in the vicinity of the atom maxima gives an indication of the corrections to be applied. In principle, the method of least squares is completely analogous, but in this case the gradients of the Fourier synthesis are considered instead of the atom maxima. It cannot be said whether a gradient of this kind is subject to any disturbing effects. In the difference Fourier synthesis, however, the course of a function is considered over the entire space. It may therefore be possible to recognize any abnormalities in the course of the function. For example, if an atom is omitted in the calculation of the structure factors, the missing atom appears in the correct place in the difference Fourier synthesis. A qualitatively wrong atom gives a deep minimum at the wrong position and a Fourier maximum in the correct position. Like the phase-refinement method, therefore, difference Fourier synthesis can also lead to qualitative corrections. No attempt has yet been made to carry out an automated difference Fourier synthesis, but this is possible with the aid of principles similar to those discussed in connection with the automatic evaluation of Fourier syntheses.

## D. Closing Remarks

Crystal-structure analysis has not yet become an automatic process, and it may take some time before structures will be solved by simply running off a computer program. It is also likely that only some of the structural problems that arise will be capable of being solved automatically. However, X-ray analysis will undoubtedly become more important in chemistry, and particularly in constitutional analysis. A constitutional formula will then frequently form the starting point of an investigation instead of the end result. It will also be possible, as is the case in absorption spectroscopy, to carry out parallel studies on related compounds in a reasonable time, and so base conclusions not only on the absolute values of the bond lenghts and bond angles, but also on changes in these parameters.

## E. Appendix

Since completion of the manuscript new results have been obtained, particularly in phase correction by modification of the electron density [38]. Fig. 14 shows the Fourier synthesis of an acentric, two-dimensional test structure comprising 22 carbon and 2 phosphorus atoms calculated from the phases of the P atoms. After 30 cycles of phase correction the Fourier synthesis shown in Fig. 15 was obtained, in which the arrangement of atoms can be clearly seen (the electron densities due to the phosphorus atoms have been subtracted).

[38] *J. Gaßmann*, Dissertation, Technische Hochschule München, 1966.

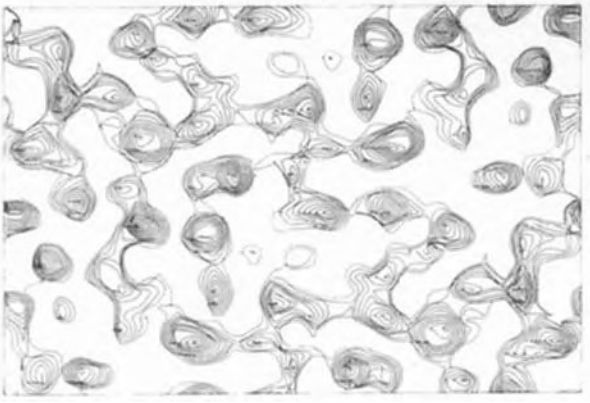


Fig. 14. Two-dimensional Fourier synthesis of a hypothetical 24-atom test structure (a naphthalene-type ring system connected by a carbon chain to a five-membered ring; short side chains) phased with two phosphorus atoms. Plane space group pg. The distorted form of the diagram makes chemical interpretation very difficult.

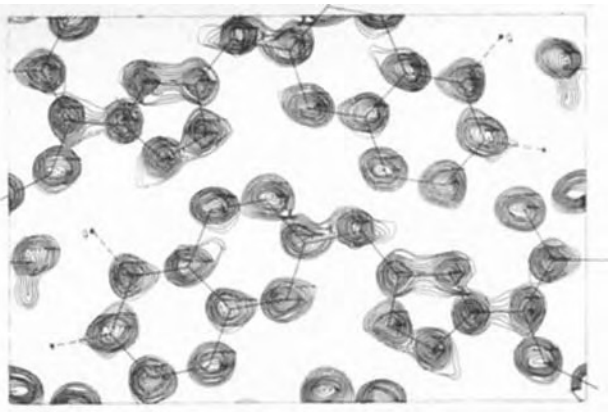


Fig. 15. Two-dimensional Fourier synthesis of the same structure as in Fig. 14 after 30 phase-correction cycles. The locations of the two phosphorus atoms used for initial phasing are marked by asterisks.

Three-dimensional phase correction was successfully tested on two real organic structures: Firstly, on phyllochlorine ester, $C_{33}N_4O_2H_{38}$, where intitial phasing was made on the basis of an idealized, plane chlorine ring model, the orientation and position of which had been determined by the convolution molecule method (cf. also Fig. 10). Secondly, on the rubidium salt of the "sulfolipid" $RbSC_9O_{10}H_{17}$ [39] (initial phasing by the heavy-atom technique with Rb and S). In both cases strong, spurious maxima were introduced into the initial Fourier syntheses on account of symmetry elements; in the course of the phase correction these maxima disappeared.

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Translated by Express Translation Service, London

[39] *Y. Okaya*, Acta crystallogr. *17*, 1276 (1964).

# Some Advances in the Inorganic Chemistry of Bromine [*]

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*Recent advances in the chemistry of bromine and its inorganic compounds are covered under the headings of technology, properties and reactions, liquid bromine as an inorganic solvent, analysis, and new or newly studied compounds. Much of what is new in bromine chemistry is characteristic also of what is new in inorganic chemistry as a whole. That is, more detailed information about compounds and reactions is becoming available from the application of new instrumental and theoretical techniques.*

## Technology

Bromine is obtained from ocean water and natural brines, and to a lesser extent as a by-product in the processing of sodium and potassium chlorides from salt deposits. Some attention has been given to new ways of isolating bromine, including ion exchange [1] and solvent extraction [2], but these have not come into commercial use. Practically all of the current production from ocean water is made by chlorination and volatilization, followed by the collection of bromine either in sodium carbonate or sulfurous acid solution [3, 4]. From the latter, bromine is recovered by rechlorination and distillation. It may be possible to avoid the need for chlorine in this step by a new process [5] in which a trace of butyl nitrite or an alkali metal nitrite in an acidic medium serves as a catalyst for oxidation by oxygen or air at 0 to 200 °C and pressures of 1 to 4 atmospheres.

[*] Presented in part at a symposium on the inorganic chemistry of the halogens, held by the Chemical Society (London) at its anniversary meeting at the University of Birmingham, England, April 7th, 1964.

[1] *R. F. Hein*, US.-Pat. 3037845 (June 5th, 1962); 3174828 (March 23rd, 1965); *F. J. Gradishar* and *R. F. Hein*, US.-Pat. 3098716 (July 23rd, 1963); *L. C. Schoenbeck*, US.-Pat. 3075830 (Jan. 29th, 1963); 3101250 (Aug. 20th, 1963), E. I. duPont de Nemours.

[2] *M. Israel, A. Baniel*, and *O. Schachter*, Israel Pat. 15408 (Oct. 25th, 1962).

[3] *A. G. Sharpe* in *J. W. Mellor*: Comprehensive Treatise on Inorganic and Theoretical Chemistry. Longmans, Green and Co., London 1956, Vol. 2, Suppl. 2, p. 689.

[4] *V. A. Stenger* in *Kirk-Othmer*: Encyclopedia of Chemical Technology. 2nd Ed., Wiley, New York 1964, Vol. 3, p. 759.

[5] *W. A. Harding* and *S. G. Hindin*, US.-Pat. 3179498 (April 20th, 1965), Air Products and Chemicals, Inc., and Northern Natural Gas Co.

Table 1. A typical analysis of high-purity commercial bromine.

| | |
|---|---|
| Assay as $Br_2$ | >99.98 % |
| Moisture | 0.003 % |
| Non-volatile matter | 0.0008 % |
| Chlorine plus chloride | 0.0005 % |
| Sulfate as $SO_4$ | <0.0010 % |
| Chloroform | <0.0005 % |
| Carbon tetrachloride | <0.0005 % |
| Bromoform | <0.0005 % |
| Carbonyl bromide | <0.0005 % |

The purity of commercial bromine has recently been increased markedly. A typical analysis is shown in Table 1. Whereas the various producers have their own methods for obtaining such purity, some processes have been described in the literature. Chlorine is generally removed by distillation in the presence of an excess of bromide. In a modification [6] of this step, a 5 to 30 % solution of an inorganic bromide in water is saturated with crude bromine. The undissolved liquid bromine (not over 10 % of the total) retains most of the organic matter and is removed. The dissolved bromine is distilled out, condensed, and dried, being reported then to contain less than 10 ppm of organic impurities. *Codell* and *Norwitz* [7] remove organic matter from bromine completely by passage with oxygen at 1000 °C through a furnace packed with fragmented quartz or high-silica glass (Vycor). In our experience this works well, but must be followed by a chlorine-removal step as chlorine is produced by the oxidation of chloroform or other organic chloro compounds. Drying must also be done after the oxidation. Purification by low temperature-low pressure sublimation [8] is suited only for small-scale use.

Evaluation of purity in the range shown demands improved analytical techniques. In our laboratories an infrared-spectroscopic method has been used [9]. Pure bromine is transparent throughout the usual infrared region [10]. Moisture and most of the probable organic impurities can be detected very sensitively in a half-inch cell with rock-salt windows. Figure 1 shows the infrared spectrum of typical high-purity bromine, along with the locations of bands of possible impurities.

*Chao* and *Stenger* [11] purified high-quality bromine further for use in the determination of various properties. Moisture and acidity are the critical impurities which must be removed prior to determinations of electrical conductivity. Pure, dry bromine is an extremely poor conductor and considerable difficulty surrounds the measurements. Minimum values were obtained after about ten distillations over barium oxide in a sealed apparatus. The bromine so prepared had a purity estimated as better than 99.999 mole-%, none of the impurities listed in Table 1 being detectable. The following values were obtained at 25.0 °C: Specific conductivity, $9.10 \times 10^{-12}$ ohm$^{-1}$ cm$^{-1}$; thermal conductivity, $2.93 \times 10^{-4}$ cal cm$^{-1}$ sec$^{-1}$ deg$^{-1}$; surface tension 40.9 dyne cm$^{-1}$.

Moisture is also an important factor in the corrosion of metals by bromine. When its moisture content is below about 40 ppm, bromine can be transported in nickel vessels [12]. Dry bromine also fails to react with such active metals as sodium and magnesium. *Stull et al.* [13] used a magnesium calorimeter in their work on the heat capacity of bromine, which is 0.113 cal/g at 25.0 °C.

Mass-spectrometric measurements have been made on the volatile products obtained on reaction of bromine with nickel at temperatures up to 1300 °C and at bromine pressures between $10^{-4}$ and $10^{-7}$ mm Hg. It was found [14] that bromine dissociates on the nickel surface at a temperature-dependent rate. $NiBr_2$ is formed between 300 and 900 °C with a maximum in the rate at about 600 °C. Above 900 °C, NiBr is formed at a rate increasing with nickel temperature. Both products are formed in surface reactions at rates proportional to the bromine pressure. On the basis of the volatilization rates and energy considerations, the reaction scheme shown in Table 2 was suggested. It appears that below about 880 °C (but probably above 600 °C), the nickel is covered with a monolayer of NiBr. Below 600 °C, the monolayer is more likely $NiBr_2$.

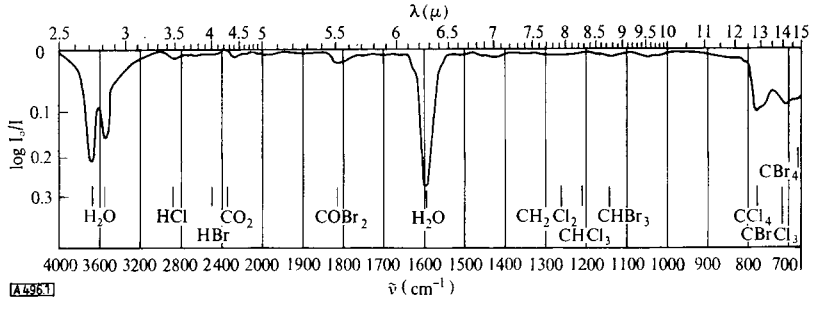


Fig. 1. Infrared spectrum of highly purified bromine.

It has long been known [15] that bromine forms lamellar compounds with graphite by penetrating between the carbon planes. Two types of such compounds are known [16].

[6] *L. R. Belohlav*, US.-Pat. 3145084 (Aug. 18th, 1964), Great Lakes Chemical Corp.

[7] *M. Codell* and *G. Norwitz*, Analytic. Chem. *29*, 967 (1957); US.-Pat. 2929686 (March 22nd, 1960).

[8] *K. Matauschek*, Naturwissenschaften *50*, 223 (1963); Z. anorg. allg. Chem. *337*, 48 (1965).

[9] *R. B. Duvall* and *L. R. Kiley*, Analytic.Chem.*30*,549,1470 (1958).

[10] *H. Wagner*, Naturwissenschaften *50*, 224 (1963); Z. anorg. allg. Chem. *337*, 54 (1965).

[11] *M. S. Chao* and *V. A. Stenger*, Talanta *11*, 271 (1964).

[12] *D. E. Lake* and *A. A. Gunkler*, Chem. Engng. *67*, 136 (1960).

[13] *D. L. Hildenbrand*, *W. R. Kramer*, *R. A. MacDonald*, and *D. R. Stull*, J. Amer. chem. Soc. *80*, 4129 (1958).

[14] *J. D. McKinley*, J. chem. Physics *40*, 576 (1964).

[15] *W. Rüdorff*, Z. anorg. allg. Chem. *245*, 383 (1941).

[16] *J. Maire* and *J. Mering*: Proceedings of the Third Conference on Carbon. Pergamon Press, London 1959, p. 337.

Table 2. Reactions of bromine with heated nickel.

| | | |
|---|---|---|
| $Br_2$ (g) + Ni (surface) | → 2 NiBr | |
| $Br_2$ (g) | → 2 Br | on a NiBr monolayer |
| Br | → Br (g) | |
| NiBr + Br | → $NiBr_2$ | |
| $NiBr_2$ | → $NiBr_2$ (g) | |
| NiBr | → Ni + Br (g) | |
| NiBr | → NiBr (g) | |

In those with a bromine content up to that corresponding to the composition $C_{16}Br$ (Type I), the bromine has penetrated only between some of the carbon planes and the crystallographic order is two-dimensional. On introduction of further bromine, compounds (Type II) up to composition $C_8Br$ are obtained in which there is one bromine layer for every two carbon layers; the crystallographic order is three-dimensional, and the distance between two carbon layers with an intercalated bromine layer is 3.70 Å. The crystallographic radius of a bromine atom, or the length of a carbon-bromine bond of an aromatic bromo-compound (such as might be expected from graphite and bromine) is slightly less than half as great. Only some of the bromine is ionic. The compound $C_8Br$ decomposes above 50 °C. Hysteresis is observed upon vapor-pressure change, part of the bromine being held irreversibly. For example, an intercalation compound of natural graphite at 30 °C at an atomic ratio Br/C of 0.082 has a vapor pressure of 0.49 $p_0$, where $p_0$ is the vapor pressure of pure bromine at the same temperature. After evacuation for one hour in series with a liquid nitrogen trap, 18 % of the bromine remains on the graphite.

The rate and extent of bromination [17] of natural graphite depends on the grain size. Large crystals (0.02-2 mm) form $C_8Br$ over a range of bromine partial pressures from 0.5 to 0.9 mm Hg at 20 °C. The bromine contents of small crystals (0.002-0.01 mm) increase with partial pressure. Between −12 and −20 °C, the initial activation energy was found to be 2.4 kcal/mole.

*Aronson* [18] has investigated the exchange of radioactive $^{82}Br$ with graphite-bromine compounds at 30–50 °C. The rates of exchange appear to agree with the concept that the exchange process is one of volume diffusion rather than a surface effect. The diffusion coefficients were found to increase with increasing bromine content and the reversibly absorbed bromine showed a higher rate of exchange than the "residual" bromine. The activation energy for diffusion, about 11–14 kcal/mole at 30 °C, is considerably greater than that for the initial bromination.

## Liquid Bromine as an Inorganic Solvent

Solubilities of various alkali bromides in liquid bromine were determined by *Kramer* and *Stenger* (Table 3) a number of years ago, and a process for the separation of

Table 3. Solubilities of alkali halides in liquid bromine (grams per 100 grams of solution at 25 °C).

| Alkali metal | Chloride | Bromide |
|---|---|---|
| Lithium | 0.0037 | 0.005 |
| Sodium | 0.001 | 0.010 |
| Potassium | 0.0055 | 0.0185 |
| Rubidium | 0.015 | 0.058 |
| Cesium | 0.175 | 19.3 |

cesium bromide from the other alkali bromides was based on the results [19]. During the last few years metallic cesium has been in increasing demand as the active element in ion propulsion and in thermionic converters. Purity is of great importance in these applications. The purest cesium commercially available up to the present was prepared from cesium bromide purified through the bromine extraction process. Rubidium and other alkalies are the common impurities to be removed. As can be seen from the data in Table 3, extraction of a mixture of cesium and rubidium bromides with bromine can yield after evaporation a cesium bromide product that contains only about 0.3 per cent RbBr. Subsequent crystallizations from water lower the rubidium content by about two-thirds at each step. Removal of the other alkalies is even more efficient.

*Kramer* has subsequently made approximate determinations of the solubilities of several other chlorides and bromides in liquid bromine (Table 4). No other striking solubilities such as that of cesium bromide have been encountered. It is known, of course, that several inorganic liquids, such as titanium tetrachloride, are miscible with bromine.

Table 4. Solubilities of bromides in liquid bromine (grams per 100 grams of solution at 25 °C).

| Element | Solubility of bromide |
|---|---|
| Aluminum | quite soluble (anhydrous)<br>0.002 (hydrated) |
| Iron(III) | 0.324 (anhydrous)<br>slightly soluble (hydrated) |
| Nickel(II) | 0.0003 |
| Copper(II) | 0.0001 |
| Manganese(II) | 0.0002 |
| Zinc | 0.0146 |
| Cadmium | 0.001 |
| Magnesium | 0.002 |
| Calcium | 0.003 |
| Strontium | 0.002 |
| Barium | 0.005 |

The equivalent conductance of solutions of tetrabutylammonium bromide and trimethylamine hydrochloride in bromine *increases* with increasing concentration [20]. For example, the equivalent conductance of the tetrabutyl compound at 25 °C is 1.43 $ohm^{-1}$ $cm^2$ $eq.^{-1}$ at 0.092 M and 3.04 at 0.165 M. It was postulated that this behavior is characteristic of a solution of a liquid in a supercooled fused salt. *Stenger* and *Chao* [20a] have observed the same effect with solutions of cesium bromide in bromine.

[17] *J. G. Hooley*, Canad. J. Chem. *40*, 745 (1962). See also *B. Bach, M. Bagouin, F. Bloc*, and *A. Herold*, C. R. hebd. Séances Acad. Sci. *257* (3), 681 (1963); *E. Stumpp*, Z. anorg. allg. Chem. *337*, 285 (1965).

[18] *S. Aronson*, J. inorg. nucl. Chem. *25*, 907 (1963).

[19] *W. R. Kramer* and *V. A. Stenger*, unpublished; *V. A. Stenger*, US.-Pat. 2481455 (Sept. 6th, 1949), Dow Chemical Company.

[20] *G. W. Moessens* and *C. A. Kraus*, Proc. nat. Acad. Sci. U.S.A. *38*, 1023 (1952).

[20a] *V. A. Stenger* and *M. S. Chao*, US.-Pat. 3 236 649 (Feb. 22nd, 1966), Dow Chemical Comp.

*Gorenbein* and *Kaplan*[21] have described concentration cells based on platinum electrodes in bromine containing phosphorus(V) bromide, chloride, or oxide chloride. The EMF values obtained were relatively low (about 0.03 volt). *Chao* and *Stenger* have carried out preliminary studies [20a] on batteries employing dissimilar metals in a bromine-cesium bromide electrolyte. The potential difference between magnesium and tungsten electrodes in this system is 1.9 volt. Because of rapid polarization, however, such cells have limited practical utility.

The structure of liquid bromine at 23 °C has been investigated by *Cagliotti* and *Ricci*[22], using neutron diffraction. The intensities of neutron beams scattered after impinging upon the bromine surface at various angles were measured, corrected for background, and plotted against angle. Two strong and several subsidiary maxima were observed. From a mathematical treatment of the data they conclude that the bromine molecules do not rotate freely, but that some of the structural features of crystalline bromine are preserved in the liquid.

*Waddington* and *White*[23] studied liquid hydrogen bromide as an ionizing solvent and used it as a medium for the preparation of several substituted ammonium, phosphonium, and arsonium tetrabromoborates. In general, hydrogen bromide, with a dielectric constant $\varepsilon$ of 7.0, is a poorer solvent than hydrogen chloride ($\varepsilon$ = 10.6). Upon dissolving tetramethylammonium bromide in hydrogen bromide at −83 °C, two liquid layers are formed when a concentration of 0.06 M is reached, the upper one having the greater conductivity.

## Analytical

For the detection of bromide ion in mixtures, several modifications of the Baubigny-Hahn fluorescein test[24] are known. *Haba* and *Wilson*[25] have devised a new version in which samples are treated by the Weisz ring oven technique. The disk obtained is sprayed with a 1:5 mixture of acetic acid and 30 % hydrogen peroxide, followed by 0.5 % fluorescein in ethanol. A red line of eosin in the dried sample indicates bromide. A procedure is also given by these authors for differentiating between iodide and bromide by use of a palladous nitrate reagent. *Somerville* and *Campbell*[26], working with the Hahn test in dilute solutions, recommend obtaining the proper buffer pH of 5.4 by adding an excess of pure calcium carbonate to the solution containing acetic acid. This simplifies the neutralization.

A test similar in principle but employing phenol red rather than fluorescein was developed by the author with *I. M. Kolthoff* some time ago. A spectrophotometric modification, recently revised and improved by *Goldman* and *Byles*[27], in which chloramine-T replaces the original hypochlorite, has been included with the Standard Methods of the American Public Health Association (1960).

Perhaps the most sensitive determination of bromide ion yet described[28] makes use of the fact that the oxidation of iodine to iodate by permanganate in acidic solution is catalysed by a trace of bromide. The extent of reaction unter given conditions can be followed by extracting the remaining iodine with carbon tetrachloride and comparing its color intensity with that of a control solution free from bromide. The reaction is carried out for ten minutes at 0 °C. The more bromide is present, the more iodine is converted to iodate by the permanganate and the lower is the color intensity of the extract. Sensitivity to as little as one microgram of bromide per liter of natural water is reported.

The qualitative identification of bromate was studied by *Miller*, *Philip*, and *Underwood*[29] by infrared spectrometry in potassium bromide disks. Potassium bromate shows absorption bands at 12.5 and 23.3 μ. The former band encounters interference from iodate, which has a band at 13.2 μ with a shoulder at 12.5, but the 23.3 μ band appears to be specific for bromate. *Haba* and *Wilson*[30] have also used the infrared method, but preceded it by an anion separation scheme[30a], so that only silicate, bromate, and iodate are present in the mixture to be tested. If the infrared spectrometer available does not permit measurements at 23.3 μ, interference is encountered between bromate and iodate. For such a case, a polarographic method can be recommended, as the waves of iodate and bromate are well separated in a solution buffered on the alkaline side[30b].

*Feigl* and *Pollak*[31] have reported a spot test sensitive to 0.8 μg of bromate. The bromate is reduced by sulfosalicylic acid in the presence of molybdophosphoric acid, forming molybdenum blue.

A volumetric method for the analysis of hypobromite-bromite-bromate mixtures is given by *Hashmi* and *Ayaz*[32]. The total oxidizing power is determined iodometrically in acidic solution by titration with standard thiosulfate. The sum of hypobromite and bromite is found by allowing another portion to stand for 5 minutes with an excess of standard arsenite in alkaline solution, after which the mixture is buffered with sodium bicarbonate and acetic acid and the excess of arsenite is titrated with standard iodine to a starch endpoint. To a third portion sodium bicarbonate and an excess of ammonium sulfate are added to reduce hypobromite selectively, the sum of bromite and bromate then being determined iodometrically after acidification. However, *Andersen* and *Madsen*[33] have pointed out that bromite

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[29] *M. W. Miller*, *R. H. Philip Jr.*, and *A. L. Underwood*, Talanta *10*, 763 (1963).

[30] *F. R. Haba* and *C. L. Wilson*, Talanta *11*, 21 (1964).

[30a] Qualitative Inorganic Analysis Tables. 3rd Ed., Midlands Qualitative Analysis Committee, 1958; cf. *R. Belcher* and *H. Weisz*, Mikrochim. Acta *1958*, 571; *1956*, 1847.

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[33] *T. Andersen* and *H. E. L. Madsen*, Analytic. Chem. *37*, 49 (1965).

also reacts to some extent with ammonium sulfate. They proposed a method in which hypobromite is titrated potentiometrically with standard ferrocyanide at pH 8–9.

An apparatus has been described [34] for the analysis of corrosive halogen compounds by gas chromatography. It makes use of a nickel introduction device and a nickel column packed with Voltalef 300 LD, a fluorinated resin, impregnated with Kel-F oil, a fluorocarbon. Tested for the analysis of hydrofluoric acid and chlorine trifluoride, it should also be suitable for hydrobromic acid and the bromine fluorides.

## Bromine Compounds

A number of new or unusual inorganic compounds containing bromine have been described recently. Two which could not have been prepared at all a few years ago are technetium oxide tribromide, $TcOBr_3$ [35], and potassium bromotechnetate, $K_2TcBr_6$ [36].

The oxide tribromide, formed from technetium dioxide and bromine at 350 °C, is a brown solid that sublimes at 400 °C. Potassium hexabromotechnetate(IV) is made by evaporation of the chloro analogue or of potassium pertechnetate with hydrobromic acid. It forms large, dark red, regular octahedral crystals of the potassium chloroplatinate type. Bromides and oxide bromides of rhenium have been studied by *Colton* [37], who reported the following compounds:

$ReBr_3$: dark brown crystals (from heating $ReBr_5$); sublimes at 350 °C in vacuum.

$ReBr_4$: dark solid (?) (from $HReO_4$ + HBr); probably unstable.

$ReBr_5$: blue-green (from Re + $Br_2$ at 650 °C); melts readily; distils upon gentle heating in bromine vapor.

$ReOBr_4$: blue (from Re oxides + $Br_2$ at 150 °C); sublimes readily.

$ReO_3Br$: colorless, volatile, unstable liquid (from $ReBr_4$ + $O_2$ at 120 °C).

Potassium hexabromorhenate has also been described [36]. It is almost identical crystallographically with its technetate analogue.

Sulfur bromide pentafluoride, $SBrF_5$ [38, 39], was prepared by addition of bromine to sulfur pentafluoride at 150–200 °C. Its microwave spectrum shows that the sulfur-bromine bond (2.19 Å) is longer than the sulfur-fluorine bonds (1.597 Å).

Bromine(I) fluorosulfate, $BrOSO_2F$ [40, 41], is formed by the reaction of excess of bromine with peroxydisulfuryl fluoride. It is a red-black liquid boiling at 120.5 °C. With an excess of the peroxy compound one obtains bromine(III) fluorosulfate, $Br(OSO_2F)_3$ [40, 41], an orange, crystalline solid melting at 50 °C. Both products are strongly reactive oxidants. Addition of bromine trifluoride to the Br(III) compound, or of bromine to fluorine fluorosulfate, yields the non-stoichiometric compound $Br_2 \cdot 3SO_3F_2$ [41], a yellow, high-boiling liquid.

Phosphoryl bromide chloride fluoride, POBrClF [42], was studied as one of a series in which it was shown that substitution of bromine for a lighter halogen decreases the PO stretching frequency, the group electronegativity, and the estimated PO force constants. The changes are about 4, 10, and 7 %, respectively, on replacement of fluorine, but only about 0.8, 2, and 1 % for replacement of chlorine.

Bromochromic acid, $HCrO_3Br$ [43], was observed during the extraction of chromic acid from 5 M hydrobromic acid with t-butyl phosphate. Its formula was established from the amounts of hydrogen, chromate, and bromide ions transferred from the aqueous to the organic phase. The extraction of hydrobromic acid alone under similar conditions is negligible. The absorption spectrum in the organic phase was also shown to differ from that of solvated dichromic acid, which is obtained when hydrobromic acid in the aqueous phase is replaced by nitric, sulfuric, or perchloric acid.

Boron dibromide azide, $(BBr_2N_3)_3$ [44], is prepared by slowly bubbling nitrogen through bromine, passage of the vapors over phosphorus pentoxide for drying and then through a glass tube loosely packed with sodium azide to yield vapors of bromine azide, which in turn are passed through boron tribromide:

$$Br_2 + NaN_3 \rightarrow NaBr + BrN_3$$
$$BrN_3 + BBr_3 \rightarrow BBr_2N_3 + Br_2$$

Precautions must be taken to avoid explosions. The compound is deposited as colorless crystals when excess of boron bromide and bromine are removed by vacuum. It dissolves in benzene as the trimer, according to determinations of molecular weight. After recrystallization from carefully purified carbon tetrachloride, the product showed a melting point of 94.5 °C with very little decomposition.

Tetrafluorobromates of the higher alkali metals, as well as the corresponding products in which bromine is replaced by chlorine or iodine, result from the direct addition of fluorine to the appropriate alkali halide at 15 to 250 °C [45, 46]:

$$CsBr + 2\,F_2 \rightarrow CsBrF_4$$

At 350–400 °C the compounds dissociate into alkali fluoride and halogen trifluoride:

$$CsBrF_4 \rightarrow CsF + BrF_3$$

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[35] *K. Schwochau*, Angew. Chem. *76*, 15 (1964).

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[37] *R. Colton*, J. chem. Soc. (London) *1962*, 2078; *R. Colton* and *G. Wilkinson*, Chem. and Ind. *1959*, 1314.

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The compounds are white, low-melting (100–200 °C), and strong oxidants. They oxidize an excess of iodide to iodine and liberate oxygen from water. Based on violence of reaction, the order of reactivity with water in respect to the different fluorohalates is Cl > Br > I. In the case of the chloro compounds, chlorate is formed, whereas the fluorobromates are reported to yield both bromate and hypobromite. In respect to salts of the various alkali elements, the order of thermal stability is Cs > Rb > K. Potassium, silver, and barium fluorobromates had been prepared earlier [47] by the addition of excess bromine trifluoride to the corresponding chlorides.

Following the pioneer work of *Kraus* and *Moore* [48] there has been great interest in the adsorption of metal halide complex ions by anion-exchange resins of the strong base type. Differences in the acid concentrations at which various ions are adsorbed or eluted from a resin permit useful separations in some cases, and furnish information about the relative stabilities of complexes. Thus iron(III) in 6 M HCl is strongly held on a resin column, while aluminum passes through readily. The iron complex dissociates in more dilute acid, so that the iron may be eluted from the resin with 0.1 M HCl. Among the transition metals the indicated order of increasing stability of the complexes is Ni < Mn < Co < Cu < Fe(III) < Zn. This is the reverse of the order of acid concentrations required to hold the metal on a column. That is, nickel passes through even in 12 M HCl, while zinc is held tightly at any concentration above 0.005 M. The adsorbed ions are assumed to have the general formula $MX_4^{2-}$ where M denotes a divalent metal and X a halogen, or $MX_4^-$ where M is trivalent. The same order of stability applies in hydrobromic acid solutions [49], though generally the bromide complexes are bound somewhat less strongly than their chloride analogues. For example, *Horne et al.* [50], in comparing the adsorption of zinc in various concentrations of hydrochloric and hydrobromic acids, found maximum adsorption at 2.1 M in HCl as against 2.9 M in HBr. However, it should be remembered that the complex ions must compete with halide ions for positions on the resin, and that the resin holds bromide more strongly than chloride [51]. True complex dissociation constants cannot be obtained from ion-exchange data alone.

That it is primarily the halide ion concentration rather than the acidity that influences adsorbability, but that there is also a secondary cation effect, was shown by the work of *Kraus et al.* [52] and *Horne* [53]. Greater adsorption is obtained from a lithium halide solution than from the equivalent concentration of halogen hydracid. The other alkali metals appear to lose effectiveness in this respect in the order of increasing atomic number, and the same is true of the alkaline earth elements. *Lindenbaum* and *Boyd* [54] substituted a liquid anion-exchange system for the solid resin, studying the distribution of transition metal halides between solutions of trioctylammonium halides in toluene, and of HCl, HBr, or LiCl in water. The organic phase was found to extract metal halide complexes in accordance with the halide concentrations in the aqueous phase and the relative order of complex stability (above). Spectrophotometric examination of the organic phase showed the extracted species to be $MX_4^{2-}$ or $MX_4^-$. No such complex ion was found for nickel, which is not extracted.

Contrary to expectations, some of the metal halide complexes are also taken up by a cation-exchange resin [55]. Those which are [gold, gallium, iron(III)] can also be extracted from HCl solutions with ether. Indium is not significantly adsorbed either from HCl or LiCl solution. The order of adsorbability of indium halides from the corresponding acids by Dowex 50 was found to be Cl < Br < I [56]. Iron(III) in HBr or LiBr solutions is adsorbed by Dowex 50 or extracted by a cation-exchange type solution of dinonylnaphthalenesulfonic acid in toluene [57]. Spectrophotometry and analysis of the latter solution revealed that the extracted complex ion is $FeBr_4^-$, accompanied by the equivalent quantity of $H^+$ or $Li^+$. The authors concluded that in the case of cation exchange media the phenomenon is not one of ion exchange, but a salting out of ion pairs ($H^+ \cdot FeBr_4^-$) from the concentrated aqueous phase.

Many elements, including aluminum, alkaline earths, rare earths, iron(III), chromium(III), and manganese(II), are held tightly by Dowex 50 and cannot be eluted with a moderate volume (300 ml) of dilute acid. According to *Fritz et al.* [58], however, some of the heavy metals can be eluted with 0.6 M HBr because of the soluble complexes which they form. Mercury(II), cadmium, bismuth(III) and lead are eluted in that order; the separation is improved by eluting with gradually increasing concentrations of HBr. Zinc follows lead, before most other elements break through, but would probably encounter interference from copper(II) or magnesium.

Double salts of alkali metal and heavy metal halides can usually be prepared easily by dissolving stoichiometric quantities of the appropriate salts in water and allowing crystals to form by slow evaporation. They can be recrystallized from water in the same way (or, in the case of a pseudo-alkali tetraalkylammonium complex, from an alcohol). The structures of the cesium tetrahalocuprates $Cs_2CuX_4$ have been elucidated [59] with the aid

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[59] *B. Morosin* and *K. Lawson*, J. molecular Spectroscopy *12*, 98 (1964).

of ultraviolet, visible, and infrared spectra. The tetrachloro- and tetrabromocuprate ions are slightly distorted from a regular tetrahedral arrangement. *Sabatini* and *Saconni*[60] prepared a series of tetraalkylammonium tetrahalometallate complexes of divalent manganese, iron, cobalt, copper, zinc, and nickel, all having the general formula $(R_4N)_2MX_4$. Far infrared spectra showed the halogen atoms to have a regular tetrahedral configuration in all cases except those of the copper compounds.

All the bromine atoms in the bromoselenates of cesium and ammonium are crystallographically equivalent. Potassium bromoselenate differs from the others in this respect. It also has at least three low-temperature transition points (−33, −52, and −64 °C) as revealed by a plot of quadrupole resonance frequency against temperature[61]. The nature of the transitions has not been determined; at 25 °C the crystals are cubic[61a].

Equilibrium constants for aqueous systems of potassium bromide and zinc or cadmium bromide have been determined through shifts in the Raman spectra[62]. With zinc bromide several species are formed: $ZnBr_4^{2-}$, $ZnBr^+$, and hydrated $ZnBr_2$; with cadmium bromide only $CdBr_4^{2-}$ was found. The constant for the formation of bromocadmate is considerably larger than that for bromozincate:

$$[ZnBr_4^{2-}]/[ZnBr_2]\,[Br^-]^2 = 0.2$$

$$[CdBr_4^{2-}]/[Cd^{2+}]\,[Br^-]^4 > 1$$

The above constants help to clarify the behavior of zinc and cadmium bromides on an anion-exchange resin of the quaternary ammonium base type. Both metals are adsorbed strongly by the resin from 1 M HBr. Upon elution with water or 0.005 M HBr both come off very slowly, but cadmium much more slowly than zinc. Apparently the resin may be regarded as equivalent to an insoluble but ionizable alkali bromide, which retains the metal bromide in complex form when bromide ion is present.

A problem of long standing in inorganic chemistry involves the instability of the oxygen acids of bromine. Before 1959 bromous acid and bromite ion, $BrO_2^-$, were known only in solution. In that year *Kircher* and *Periat*[63–65] prepared crystalline barium bromite, $Ba(BrO_2)_2 \cdot H_2O$.

A suspension of 270 g of barium hydroxide in a liter of water is treated with bromine equivalent to 97 % of the theoretical requirement to form barium hypobromite. The mixture is cooled to 0 °C and kept for 70 min while the reaction

$$2\,Ba(OBr)_2 \rightarrow BaBr_2 + Ba(BrO_2)_2$$

takes place. Then 16 g of barium hydroxide is added and the suspension is cooled to −5 °C. Ammonium hydroxide is added cautiously to reduce the remaining hypobromite. An excess must be avoided. Bromate crystals are filtered out and the filtrate is partially evaporated *in vacuo* at 30 °C. Barium bromite monohydrate precipitates upon cooling to 0 °C and may be recrystallized from water.

Bromites of sodium, lithium, potassium, and calcium can be prepared by appropriate modifications of the procedure. Sodium bromite trihydrate is a yellow, crystalline compound which can be dehydrated *in vacuo*. An X-ray powder pattern showed the anhydrous sodium bromite to be a distinct species. Bromite solutions, reported to be useful in the desizing of textiles[66], are now commercially available in Europe[33].

The use of a precipitation reaction, such as that of barium bromate with the equivalent amount of sulfuric acid, for the preparation of bromic acid solutions free from impurities can now be avoided by using a cation-exchange resin[67]. A potassium bromate solution (about 0.5 M) is passed through the resin in hydrogen form; with a column of suitable length, complete removal of potassium can be achieved. The acid solution can be concentrated *in vacuo* to about 50 % $HBrO_3$.

Perbromic acid and perbromates have never been prepared in either the solid state or in solution, although perchlorates and periodates are well-known.

A solution of bromine dioxide, $BrO_2$, in trichlorofluoromethane has been prepared by *Schmeisser* and *Joerger*[68] by oxidizing a bromine solution at −50 °C with ozone. The gaseous products of reaction of potassium bromate with sulfuric acid in a shock wave[69] contain various bromine oxides. Small amounts of bromite and hypobromite are formed[70] by exposure of solid alkali bromates to γ-rays from $^{60}Co$.

## Applications of Bromine and Its Compounds

Current western world production of bromine in all forms is in excess of 250 million pounds annually. Whereas forty years ago nearly all of the bromine produced went into inorganic bromides and bromates, today only about 3 % is sold in inorganic form. By far the largest portion goes into motor fuels as ethylene bromide; here the end use may be considered as inorganic, for the bromine serves to convert lead (from the tetraalkyl-lead antiknock compound) to lead bromide. The latter is volatile at cylinder combustion temperatures and is swept out with the exhaust.

Considerable amounts of bromine are used as methyl bromide, ethylene bromide, and bromochloropropanes for insect control and soil sterilization. In this use the reactivity and the volatility of the compound are both

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[65] *J. Meybeck*, *R. Kircher*, and *J. Leclerc*, German Pat. 1069123 (Nov. 19th, 1959); U.S.-Pat. 3085854 (April 16th, 1963), Soc. d'Etudes Chimiques Ind. Agr.

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[70] *G. E. Boyd*, *E. W. Graham*, and *Q. V. Larson*, J. physic. Chem. *66*, 300 (1962).

of importance. Methyl bromide, for example, has a boiling point of 3.7 °C and acts as a methylating agent. It penetrates stored grain or baled cotton or tobacco readily, killing insects at any stage of their life cycle. The excess of fumigant is easily dissipated by exposure to air.

Almost the only large, purely inorganic use of bromine is in the photographic industry, where alkali bromides are allowed to react with silver nitrate to produce a light-sensitive emulsion of silver bromide. The other applications of inorganic bromides and bromates are likely to be organic or biological in nature: much of the alkali bromide goes into pharmaceuticals as a mild sedative, while bromates are used as oxidants for improving the baking quality of wheat flour and for reacting with sulfur compounds in hair-wave preparations. Liquid bromine is used in organic syntheses, bleaching, and as a bactericide to purify water in swimming pools.

A few applications of bromine compounds are based on their relatively high density. Several compounds are employed as gauge fluids and some offer promise of commercial use in mineral separation by sink-float processes. In the latter application the efficiency of recovery is of great importance. Thus in the separation of potassium chloride (density 1.984) from sodium chloride (density 2.165), formulations containing bromochloromethane and dibromomethane are of interest because of their moderate boiling points. Table 5 gives the properties of some of these heavy liquids.

Table 5. Liquid bromine compounds of high density.

| Compound | Density at 25 °C | M.p. (°C) | B.p. (°C) |
|---|---|---|---|
| Bromoethylbenzene | 1.335 | −65 | 200 |
| Bromobenzene | 1.495 | −30.6 | 156.1 |
| 1-Bromo-2-chloroethane | 1.739 | −16.5 | 108.6 |
| Bromochloromethane | 1.923 | −88 | 67.8 |
| Bromodichloromethane | 1.995 | −57.1 | 90.1 |
| 1,2-Dibromoethane | 2.179 | 9.9 | 131.4 |
| Dibromomethane | 2.497 | −52.7 | 96.9 |
| Tribromomethane | 2.891 | 7.7 | 149.5 |
| 1,1,2,2-Tetrabromoethane | 2.964 | 0.1 | 151/44 mm Hg |

Some of the most useful and growing applications of bromine compounds are in the fields of fire extinguishing and prevention. Bromine vapor itself has the property of extinguishing a flame from the combustion of gas or wood when introduced even in quite small amounts into the air supply. Apparently the bromine exerts a chain-stopping effect upon the flame propagation reaction [71]. Various bromine-containing liquids have been proposed for use in fire extinguishers. Bromochloromethane is very effective on a weight basis and has a relatively low toxicity. Some effective fluorine-containing bromoethanes have still lower toxicities, but are more expensive.

In the field of fire prevention, progress is being made on the incorporation of halogen compounds into plastics to render them self-extinguishing. Some of the materials that have been found useful for formulation with vinyl polymers such as polystyrene are tetrabromobutane, 1,2-dibromotetrachloroethane, pentabromochlorocyclohexane, and tetrabromoisopropylidenebisphenol. On a weight basis, bromine derivatives are more effective than their chlorine counterparts. This is significant in decreasing the proportion of additives required, because with too great a proportion some other property of the plastic may be affected adversely. A further reduction in the quantity required has been made possible by the discovery [72] that substances capable of free-radical initiation operate synergistically with the bromine compounds, making the latter effective at considerably lower concentrations. As an example, the self-extinguishing effect of 5 % tetrabromoethane in polystyrene can be equalled by that of only 0.5 % if an equal amount of dicumyl peroxide is also present.

There is virtually no limit to the quantity of bromine available, as the oceans represent an essentially inexhaustable source. Organic chemists have been diligent in using bromine compounds in syntheses, as well as describing their properties. Inorganic chemists have prepared and characterized many compounds, but generally have not found many applications for them. Research in new uses for bromine and its compounds should be encouraged.

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[71] *C. P. Fenimore* and *G. W. Jones*, Combustion and Flame 7, 323 (1963); *C. F. Cullis*, *A. Fish*, and *R. B. Ward*, Proc. Roy. Soc. (London) *276*, 527 (1963).

[72] *J. Eichhorn*, J. appl. Polymer Sci. *8*, 2497 (1964); *A. K. Jahn*, and *J. W. Vanderhoff*, *ibid.* *8*, 2525 (1964).

# Advances in Molecular Diamagnetism

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*At the present state of instrumentation and quantum-mechanical approximations, diamagnetic measurements can supply information on chemical structure which complements the results of other approaches, such as infrared and NMR spectroscopy. General applicability and relatively low cost of equipment are among the advantages of this technique. There is growing interest in the relation to chemical shifts in NMR spectra and in the possibility offered by this technique for testing quantum-chemical approximations.*

## I. Introduction

Diamagnetism, a virtually universal phenomenon, has recently evoked increasing interest in structural chemistry. This can be attributed particularly to the development of NMR spectroscopy, to improvements in the accuracy of susceptibility measurements, and not least to new, better quantum-mechanical approximations for calculating the diamagnetism of localized and delocalized electrons in atoms, molecules, and crystals. The close correlation between diamagnetism and the chemical shift of nuclear resonance signals has greatly contributed to interest in the former. The importance of reliable diamagnetism parameters is further enhanced by the fact that these parameters are often used for testing quantum-mechanical approximations. Diamagnetism therefore plays a significant part in quantum chemistry, especially in electron correlation methods.

An attempt is made here to summarize present knowledge of intramolecular magnetic fields and the information on chemical structure obtainable therefrom. Diamagnetism of crystals is treated by a separate theory (*Landau* and *Peierls*), forming a special branch of solid-state physics, and will not be discussed here. Since the diamagnetic aspect of magnetochemistry was dominated for a long time by *Pascal*'s incremental system, the scope and the limitations of this method will first be outlined.

The atomic incremental system introduced by *Pascal*[1] and improved by *Pacault*[2] is based on resolution of the molar susceptibility $\chi_M$ into terms for the constituent atoms:

$$\chi_M = x_1 \chi_1 + x_2 \chi_2 + x_3 \chi_3 + \cdots \qquad (1)$$

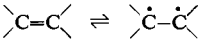
where the $x_i$ and $\chi_i$ represent the numbers of atoms of kind i in the molecule and their atomic susceptibility, respectively.

*Pascal* obtained the atomic susceptibilities of hydrogen and carbon from the susceptibilities of monochlorinated hydrocarbons and of liquid chlorine. As in the case of molar refraction, it was necessary to account for deviations ("exaltations") by the introduction of structural increments $\lambda$ according to Eq. (2):

$$\chi_M = \sum_i \chi_{A_i} + \sum_i \lambda_i \qquad (2)$$

The value of this system (cf. Table 1) has been manifested in the following applications:

1. Pascal increments can be used to calculate the correction for diamagnetism in paramagnetic materials.
2. Comparison between observed and calculated susceptibilities reveals the presence of paramagnetic impurities.
3. Structural investigations based on the incremental system were of interest particularly in organic chemistry, although they did not find wide application on account of the high demands placed on experimental accuracy. With increasing precision of magnetic measurements, the number of specific molecular structural increments needed in *Pascal*'s method became so great that finally one had to be introduced for practically every type of molecule. It was discouraging that most structural terms could not be satisfactorily explained. We may mention, as an example, the positive exaltation of double bonds (see lower half of Table 1), which was believed to result from a paramagnetic component due to the equilibrium



*E. Müller*[3] showed this assumption to be incorrect by investigating the temperature-dependence of the diamagnetism of compounds containing double bonds. This problem has been solved by quantum mechanics (cf. Section II).

One of the most important advances in the theory of magnetism was *van Vleck*'s proof[4] of the inadequacy of *Langevin*'s classical theory of molecular diamagnetism, which expresses the susceptibility as the sum of a temperature-dependent "paramagnetic" term, applicable only when the molecule has a permanent magnetic moment, and a general temeprature-independent term, given by Eq. (3), for the diamagnetic susceptibility:

$$\chi_M = -\frac{e^2 \cdot N_A}{6mc^2} \sum_i \overline{r_i^2} \qquad (3)$$

[1] *P. Pascal*, Ann. Chim. Physique *19*, 5 (1910).

[2] *A. Pacault*, Rev. sci. *86*, 38 (1948).

[3] *E. Müller*, Z. Elektrochem. angew. physik. Chem. *45*, 593 (1939).

[4] *J. H. van Vleck*: The Theory of Electric and Magnetic Susceptibilities. University Press, Oxford 1932.

Table 1. Diamagnetic increments according to *Pascal* [1] and *Pacault* [2].

| Atoms or groups | χ [*] |
|---|---|
| $CH_2$ | 11.36 |
| H | 2 |
| C | 7.36 |
| O (Alcohols) | 5.3 |
| C=O (Aldehydes; ketones) | 6.4 |
| C(=O)O (Acids) | 15.15 |
| S | 16.9 |
| N | 9 |
| Cl | 18.5 |
| Br | 27.8 |
| I | 42.2 |
| **Structural increments** | **λ** |
| C=C | + 5.5 |
| $CH_3$ | − 0.85 |
| C≡C | + 0.8 |
| C=C−C=C | +10.6 |
| N=N | + 0.8 |
| Benzene ring | −15.1 |
| Furan ring | −10.92 |
| Thiophene ring | −14.22 |

[*] All values of χ and λ are given here and in the following text in units of $-10^{-6}$ EMU per mole.

where e and m are, respectively, the charge and mass of the electron, c the speed of light, $N_A$ Avogadro's number, and $\overline{r_i^2}$ the mean square distance of the i-th electron from the nucleus.

*Van Vleck* showed on a quantum-mechanical basis that a temperature-*in*dependent "paramagnetic" term $\chi_P$ exists in addition to the temperature-independent diamagnetic term $\chi_D$. These two phenomena always occur together, and cannot be determined separately by direct susceptibility measurements.

The difficulties encountered in the application of the Pascal increment system are caused at least partly by the $\chi_P$ term, which varies appreciably with the symmetry of the electron system. This fact strongly restricts the additivity of atomic susceptibilities, as was first shown by *Guy* and *Tillieu* [5] and by *Dorfman* [6].

Further, it is now known that an atomic incremental system is not suitable for assigning the contributions to diamagnetism in a molecule. For example, in methane the k electrons of carbon contribute about 1 % of the molar susceptibility, the remaining 99 % being due to the four pairs of bonding electrons. Therefore empirical bond increments have been proposed [7,8] (see Table 2).

Table 2. Empirical bond increments according to *Pascal* [1], *Pacault* [2], and *Pascal, Gallais*, and *Labarre* [8].

| Bond | $\chi_M$ | Bond | $\chi_M$ |
|---|---|---|---|
| C–C | 3.7 | C–Cl | 20.35 |
| C–H | 3.85 | C–Br | 29.65 |
| C–O | 4.5 | C–I | 44.05 |
| O–H | 4.65 | C=C | 1.9 |
| C–S | 10.3 | C=O | 2.7 |
| S–H | 10.45 | C–C | 2.9 [8] |
| C–N | 4.85 | C–H | 4.2 [8] |
| N–H | 5.00 | | |

[5] *J. Tillieu*, Ann. Physics *2*, 631 (1957).

[6] *J. G. Dorfman*: Diamagnetismus und chemische Struktur. Teubner, Leipzig 1964.

[7] *A. Pacault, J. Hoarau*, and *A. Marchand*: Advances in Chemical Physics. Interscience Publishers, New York 1961, Vol. 3, p. 171.

The quantum-mechanical theory of diamagnetism was to be of great importance for the further development of the incremental system.

## II. Theoretical Basis

### 1. Quantum-Mechanical Approximations, van Vleck Paramagnetism, and Gauge Invariance

Quantum-mechanical approximations for the calculation of molecular diamagnetism were first introduced for localized electrons by *van Vleck* [4] (perturbation method) and by *Gans* and *Mrowka* [9] (variation method), and for delocalized electrons (molecular ring currents in aromatic compounds) by *London* [10] (HMO method).

The motion of electrons with momentum $\mathbf{p}$ in an external electromagnetic field of vector potential $\mathfrak{A}$ ($\mathfrak{H}$ = curl $\mathfrak{A}$) and mean electrostatic potential energy V is described classically by the Hamiltonian (4):

$$\mathbf{H} = \sum_i \frac{1}{2m}\left(\mathbf{p}_i - \frac{e}{c}\mathfrak{A}_i\right)^2 + V \qquad (4)$$

Using $\mathbf{H}_0$ for the Hamiltonian in the absence of an external field and $\mathbf{H}_1$ for denoting the perturbed state, and assuming a constant magnetic field $\mathfrak{H}$ acting along the z-axis (x, y, and z are Cartesian coordinates), we obtain

$$\mathbf{H} = \mathbf{H}_0 - \sum_i \left[\frac{e\mathfrak{H}}{2mc}(x_i \mathbf{p}_{y_i} - y_i \mathbf{p}_{x_i}) - \frac{e^2\mathfrak{H}^2}{8mc^2}(x_i^2 + y_i^2)\right] \qquad (5)$$

Moreover, since the component of the magnetic moment in the direction of the field, $M_z$, is given by

$$M_z = -\partial \mathbf{H} / \partial \mathfrak{H} \qquad (6)$$

we obtain

$$M_z = \sum_i \left[\frac{e}{2mc}(x_i \mathbf{p}_{y_i} - y_i \mathbf{p}_{x_i}) - \frac{e^2\mathfrak{H}}{4mc^2}(x_i^2 + y_i^2)\right]. \qquad (7)$$

$M_z$ is thus the sum of two terms: one depends on $\mathfrak{H}$, the other does not vanish even when $\mathfrak{H} = 0$ (provided that the orbital angular momentum of the electron is not zero). The former represents diamagnetism, the latter paramagnetism. Since $\chi = M/\mathfrak{H}$ and $(\overline{x^2} + \overline{y^2})/\overline{r^2} = 2/3$, the second term in Eq. (7) leads to Eq. (3), due to *Langevin*. On applying quantum-mechanical methods, Eq. (5) becomes

$$\mathbf{H} = \mathbf{H}_0 - \sum_i \left[\frac{e\,h}{4\pi mc}\left(\mathbf{X}_i \frac{\partial}{\partial y_i} - \mathbf{Y}_i \frac{\partial}{\partial x_i}\right)\mathfrak{H} - \frac{e^2}{8mc^2}(\mathbf{X}_i^2 + \mathbf{Y}_i^2)\mathfrak{H}^2\right] \qquad (8)$$

It appears at first sight that, similarly to the classical expression (7), Eq. (8) gives, in the absence of an orbital magnetic moment, a relationship for $M_z$ in the

[8] *P. Pascal, F. Gallais*, and *S. F. Labarre*, C. R. hebd. Séances Acad. Sci. *252*, 2644 (1961).

[9] *R. Gans* and *B. Mrowka*, Königsberger gelehrte Ges., Nachr. *12*, 1 (1935).

[10] *F. London*, J. Physique Radium *8*, 397 (1937).

magnetic field $\mathfrak{H}$ containing only the term $\mu_i$ for the classical Langevin diamagnetism, as given by Eq. (9):

$$\mu_i = -\frac{e^2 \mathfrak{H}}{4mc^2}(x^2 + y^2) \tag{9}$$

However, the advances brought about by the quantum-mechanical theory lie in the fact that it does lead to a different result. For electron systems that are not spherically symmetrical, the perturbation method results in a temperature-*in*dependent paramagnetism, even in the absence of orbital angular momentum. This paramagnetism, of great importance in magnetochemistry, is not understandable on the classical theory. Taking into account second-order terms, we obtain for the energy $E_M$ of a system in a magnetic field:

$$\begin{aligned} E_M &= E_n^o - \mathfrak{H}(n \mid \mathbf{M}_z^o \mid n) - \mathfrak{H}^2 \sum_{n \neq m} \frac{(n \mid \mathbf{M}_z^o \mid m)^2}{E_n^o - E_m^o} \\ &+ \mathfrak{H}^2 \frac{e^2}{8mc^2} \sum (n \mid \mathbf{X}^2 + \mathbf{Y}^2 \mid n) \\ &= E_o - \frac{1}{2}\mathfrak{H}^2 \chi \end{aligned} \tag{10}$$

where m and n denote two different eigenstates, the superscript o signifies the absence of applied field, and $E_0$ is the energy in the absence of a field.

From Eq. (10) we obtain for the magnetic moment $m_z$:

$$\begin{aligned} m_z &= (n \mid \mathbf{M}_z^o \mid n) + 2\mathfrak{H} \sum_{n \neq m} \frac{(n \mid \mathbf{M}_z^o \mid m)^2}{E_m^o - E_n^o} \\ &-2\mathfrak{H} \frac{e^2}{8mc^2} \sum (n \mid \mathbf{X}^2 + \mathbf{Y}^2 \mid n) \end{aligned} \tag{11}$$

This expression is the quantum-mechanical counterpart of the classical relationship (7). The first term is the diagonal matrix element of the magnetic moment along the z-axis (*i.e.* the quantum-mechanical mean value); it corresponds to the classical orbital paramagnetism. The third term is the diagonal matrix element of the space operator $(\mathbf{X}^2 + \mathbf{Y}^2)$ [*i.e.* the quantum-mechanical average of $(x^2 + y^2)$]; it corresponds to the classical diamagnetism $\chi_d$. The second term is positive and non-classical, and represents a paramagnetic component. A more detailed treatment using Maxwell-Boltzmann statistics reveals that this paramagnetism $\chi_p$ is temperature-independent, and therefore cannot be separated from diamagnetism by carrying out measurements at various temperatures. Quantum-mechanical calculation of this term is very difficult; it requires a knowledge of the non-diagonal matrix elements in the numerator and the energies of the excited states in the denominator.

Apart from the well-known problems of electronic interaction, solution of the Schrödinger equation for molecules with the Hamiltonian operator given by Eq. (8) is associated with difficulties connected with gauging for Eq. (4) the vector potential according to Eq. (12).

$$\mathfrak{A} = -\frac{1}{2}\mathfrak{r} \times \mathfrak{H} \tag{12}$$

where $\mathfrak{H}$ is the magnetic field.

*London*[10] first attempted to eliminate these difficulties using the MO method and introducing gauge-invariant[*] atomic wave functions (see Fig. 1).

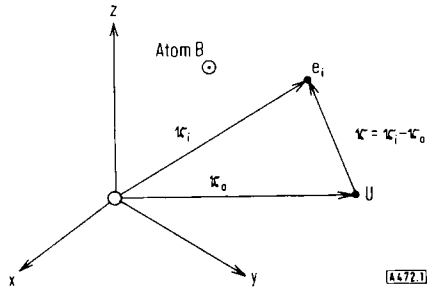



Fig. 1. Coordinates and vectors used in the construction of gauge-invariant atomic orbitals. (U is the origin of the vector potential, $\mathfrak{r}_0$ is the vector connecting the origin of the coordinate system and that of the vector potential, $\mathfrak{r}_i$ is the position vector of electron $e_i$.) If the center of atom B is taken as the new origin of the vector potential $\mathfrak{A} = -1/2\mathfrak{r} \times \mathfrak{H}$, then $\mathfrak{A} - \mathfrak{A}_0 = -1/2(\mathfrak{r}_i - \mathfrak{r}_B) \times \mathfrak{H}$ *i.e.* the new vector potential is independent of $\mathfrak{r}_0$.

The final result (sum of $\chi_d$ and $\chi_p$) of Eqs. (10) and (11) does not depend on the origin of the vector potential and is therefore gauge-invariant. However, this is not true of the absolute values of $\chi_d$ and $\chi_p$. Fig. 2 shows that, when taken separately, $\chi_d$ and $\chi_p$ vary greatly with the origin of the vector potential, $\chi_p$ reaching its minimum value when the origin is chosen as the centroid of the electronic charge distribution. Since the

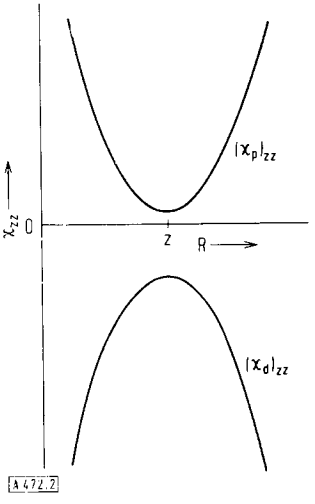



Fig. 2. The variation in the z-component of $\chi_p$ and $\chi_d$ with the distance R of the origin of the vector potential along the x-axis from the centroid, Z, of the electron charge distribution (cf. *Chan* and *Das* [119]). The abscissa and the ordinate are expressed in arbitrary units of $\chi$ and R.

series expansion of the $\chi_p$ term cannot generally be completed, the accuracy of the $\chi_p$ approximation depends considerably on the gauging and improves with increasing applicability of the condition

$$|\chi_d| \gg |\chi_p| \tag{13}$$

It must be remembered in the construction of molecular wave functions that the validity of the linear combination of atomic orbitals (LCAO) is affected by the origin of the vector

[*] A physical relationship is called gauge-invariant when it is unchanged by a gauge transformation. When the vector potential $\mathfrak{A}_i$ of the electromagnetic field is subjected to the transformation $\mathfrak{A}_i' = \mathfrak{A}_i + \frac{\partial \sigma}{\partial x_i}$ (where $\sigma$ is any function of time and space), the magnetic field, which can be represented by the rotation of the vector potential, remains unchanged. Since *Maxwell*'s equations are gauge-invariant, the origin of the vector potential can be chosen freely.

potential. For this reason, *London*[10] introduced the following atomic orbitals $\Phi_B$ which depend on the magnetic field and on the gauge:

$$\Phi_B = \Psi_B \exp\left\{-\frac{2\pi i e}{hc}\mathfrak{A}_B \cdot r\right\} \tag{14}$$

where $\mathfrak{A}_B$ is the vector potential at the center of atom B and $\Psi_B$ is the unperturbed eigenfunction belonging to atom B.

$$\Psi_i = \sum_i c_i \Phi_i \tag{15}$$

The coefficients of the linear combination (15) are determined

$$\left(\mathbf{p} + \frac{e\mathfrak{A}}{c}\right)^2 \Phi_B = \exp\left\{-\frac{2\pi i e}{hc}\mathfrak{A}_B \cdot r\right\}\left[\mathbf{p} + \frac{e}{c}(\mathfrak{A} - \mathfrak{A}_B)\right]^2 \Psi_B \tag{16}$$

as usual by a variation method. Since Eq. (16) applies, the difficulties of gauging have thus been eliminated and the Schrödinger equation has become gauge-invariant (the term in braces is a scalar, and that in the brackets a vector independent of $r_o$ as shown by Fig. 1).

One-electron variation methods have proved particularly suitable for the calculation of the diamagnetic effect of localized pairs of bonding electrons[5]. In this method, developed by *Gans* and *Mrowka*[9], the relation

$$\Psi = \Psi_o e^{\Phi} \tag{17}$$

is used for the eigenfunction $\Psi$ perturbed by the magnetic field. This relationship had previously been employed in the form

$$\Psi = \Psi_o (1 + \Phi) \tag{18}$$

by *Slater* and *Kirkwood*[11] as a first approximation. The variation involved is carried out by the Ritz method. *Tillieu*, using Eq. (10) and the field-dependent wave function

$$\Psi = \Psi_o (1 + iG_z \mathfrak{H}) \tag{19}$$

obtained the expression

$$E = E_o + \frac{e^2\mathfrak{H}^2}{8mc^2}(\Psi_o | X^2 + Y^2 | \Psi_o) - 4i\mathfrak{H}^2(\Psi_o | G_z M_z^o | \Psi_o) - \frac{h^2\mathfrak{H}^2}{4\pi^2 m}(\Psi_o | \operatorname{grad} G_z | \Psi_o) \tag{20}$$

When the bond axis A–B is normal to the z-axis, we have the simple relationship (21) for $G_z$, which is the correction function of the unperturbed wave function

$$G_z \approx ax + bxy \tag{21}$$

calculated for minimum energy. The variation method gives the following conditions of minimization:

$$\frac{\partial E}{\partial a} = 0 \text{ and } \frac{\partial E}{\partial b} = 0, \tag{22}$$

whence a = 0, and

$$b = \frac{\pi e}{hc} \cdot \frac{(\Psi_o | X^2 - Y^2 | \Psi_o)}{(\Psi_o | X^2 + Y^2 | \Psi_o)} \tag{23}$$

[11] *J. C. Slater* and *J. G. Kirkwood*, Physic. Rev. *37*, 682 (1931).

Using Eqs. (20) and (23), we obtain for the susceptibility along the three axes (the bars over $x^2$, $y^2$, and $z^2$ show that these parameters represent quantum-mechanical mean values):

$$\left.\begin{aligned}\chi_x &= C\left[\overline{y^2} + \overline{z^2} - \frac{(\overline{y^2} - \overline{z^2})^2}{\overline{y^2} + \overline{z^2}}\right] \\ \chi_y &= C\left[\overline{z^2} + \overline{x^2} - \frac{(\overline{z^2} - \overline{x^2})^2}{\overline{z^2} + \overline{x^2}}\right] \\ \chi_z &= C\left[\overline{x^2} + \overline{y^2} - \frac{(\overline{x^2} - \overline{y^2})^2}{\overline{x^2} + \overline{y^2}}\right]\end{aligned}\right\} \tag{24}$$

$$C = -\frac{N_A e^2}{4mc^2} \tag{25}$$

Eq. (24) shows the connection between $\chi_p$ (the third term in the brackets) and the asymmetry of the charge distribution.

The connections between the Tillieu wave functions (17) and the London-type gauge-invariant atomic orbitals (GIAO) (15) have been discussed by *Raychaudhuri* and *Sinha*[12]. *Hameka*[13] and *Karplus*[14] have recently developed some SCF–GIAO methods, representing today the most accurate approximations for the calculation of diamagnetism.

In the case of the noble gases (see Table 3), the spherical symmetry of whose electron configuration obviates the difficulties concerning $\chi_p$, the calculated values may now be more accurate than the best observed values. Using a twenty-term Hylleraas wave function, *Glick*[20] obtained $\chi_M = 1.8914 \pm 0.0002$ for helium, and suggested this value as a standard in the measurement of the susceptibility of gases.

Table 3. Experimental and calculated values of $\chi_M$ for the rare gases.

| | He | Ne | Ar | Kr | Xe |
|---|---|---|---|---|---|
| exp. [15] | 2.02 ± 0.08 | 6.96 ± 0.14 | 19.32 | 29.0 ± 0.4 | 45.5 ± 0.7 |
| calc. acc. to: | | | | | |
| *Hartree* and *Stoner* [16] | 1.90 | 8.6 | 24.8 | — | — |
| *Angus* [17] | 1.68 | 5.07 | 16.65 | 29.3 | 44.8 |
| *Kirkwood* [18] | 1.92 | 6.15 | 17.0 | 29.3 | 45.7 |
| *Courty* [19] | 1.913 | 7.167 | 20.218 | 30.005 | 44.600 |

The most accurate empirical value available for $H_2$ is $\chi_M = 4.0051$[21]. Using various wave functions, *Wick*[22], *Hirschfelder*[23], *Steensholt*[24], and *Witmer*[25] carried out calculations on this molecule, the best approximations being obtained by *Ishiguro* and *Koide* (4.0689)[26] and by *Hameka*


[12] *A. K. Raychaudhuri* and *S. K. Sinha*, Molecular Physics *7*, 473 (1964).

[13] *H. F. Hameka*, Physica *25*, 625 (1959).

[14] *N. Karplus* and *H. J. Kolker*, J. chem. Physics *38*, 1263 (1963).

[15] *C. Barter*, *R. G. Meisenheimer*, and *D. P. Stevenson*, J. physic. Chem. *64*, 1312 (1960).

[16] *E. C. Stoner*, Proc. Leeds philos. lit. Soc., sci. Sect. *1*, 484 (1929).

[17] *W. R. Angus* and *W. H. Hill*, Trans. Faraday Soc. *31*, 1491 (1935).

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[19] *C. Courty*, J. Physique Radium *21*, 233 (1960).

[20] *R. E. Glick*, J. physic. Chem. *65*, 1552 (1961).

[21] *G. G. Havens*, Physic. Rev. *31*, 579 (1928).

[22] *G. C. Wick*, Z. Physik *85*, 25 (1933).

[23] *J. O. Hirschfelder*, J. chem. Physics *3*, 555 (1935).

[24] *G. Steensholt*, Philos. Mag. *38*, 748 (1947).

[25] *E. E. Witmer*, Physic. Rev. *50*, 1094 (1936).

[26] *E. Ishiguro* and *S. Koide*, Physic. Rev. *94*, 350 (1954).

(4.045)[27]. Very good approximations were also obtained by *Karplus* and *Kolker*[27a] and by *Hoyland*[27b].

Calculations have also been carried out on $N_2$ by *Bonet* and *Bushkovitch*[28], and on $NH_4^+$ by *Hartmann* [29] and by *Venkatachalam* and *Kabadi*[30]. The calculations for $CH_4$ are collected in Table 4. The great discrepancy between theoretical and experimental values shows that $\chi_p$ is by no means merely a correction factor. *Eschbach* and *Strandberg*[33b], *Wick*[22], and *Ramsay*[33c] recently discussed experimental methods for determining $\chi_p$ for diatomic $\Sigma$ molecules, based on determination of the magnetic moment of molecular rotation, *e.g.* by the microwave Zeeman effect. *Weltner*[34] obtained $\chi_p = 9.3$ for $CH_4$, this value being approximately equal to the difference between the calculated and the observed value of $\chi_M$.

Table 4. Theoretical values, $\chi_d$, of the diamagnetism, and experimental value, $\chi_M$, for the total magnetic susceptibility effect of methane.

| Author | Method | $\chi_d$ |
|---|---|---|
| *Banyard* [31] | Central-field wave function with exchange | 26.3 |
| *Coulson* [32] | MO | 26.6 |
| *Coulson* [32] | Heitler-London | 27.7 |
| *Buckingham, Massey,* and *Tibbs* [33] | Hartree self-consistent field | 33.2 |
| *Venkatachalam* and *Kabadi* [30] | Heitler-London with ionic contributions | 21.11 |
| *Mills* [33a] | Hartree-Fock central-field electron density | 28.4 |
| *Mills* [33a] | Modified Hartree-Fock distribution | 29.0 |
| | | $\chi_M$ |
| *Barter, Meisenheimer,* and *Stevenson* [15] | Experiment | 17.4 ± 0.8 |

A different empirical method has been described by *Dorfman*[6]. Assuming that $\chi_d$ is the same as the susceptibility derived from the refractive index[*] *via Kirkwood*'s equation (26), then the difference between this value and the experimental susceptibility $\chi_M$ directly represents the quantity $\chi_p$.

$$\alpha = -\frac{4}{9}\frac{a_0^3}{N_e}(\Sigma\bar{r^2})^2 \qquad (26)$$

where $\alpha$ is the electric polarizability, $N_e$ the number of electrons, and r is in units of $a_0 = h^2/(4\pi^2 me^2)$.

[27] *H. F. Hameka*, Rev. mod. Physics *34*, 87 (1962).

[27a] *H. S. Kolker* and *M. Karplus*, J. chem. Physics *39*, 2011 (1963).

[27b] *J. R. Hoyland*, J. chem. Physics *41*, 3153 (1964).

[28] *J. V. Bonet* and *A. V. Bushkovitch*, Physic. Rev. *85*, 707 (1952).

[29] *H. Hartmann*, Z. Naturforsch. *2a*, 489 (1947).

[30] *K. A. Venkatachalam* and *M. Kabadi*, J. physic. Chem. *59*, 740 (1955).

[31] *K. E. Banyard*, J. chem. Physics *33*, 832 (1960).

[32] *C. A. Coulson*, Proc. physic. Soc. Sect. A *54*, 51 (1942).

[33] *R. A. Buckingham, H. S. Massey,* and *S. T. Tibbs*, Proc. Roy. Soc. (London) Ser. A *178*, 119 (1941).

[33a] *I. M. Mills*, Molecular Physics *1*, 99 (1958).

[*] $\alpha$ and $\chi_d$ would then be connected by Eqs. (3) and (26) as follows: $\chi_d = -e^2 N_A (a_0 N_e \alpha)^{1/2}/(4mc^2)$

[33b] *J. R. Eshbach* and *M. W. P. Strandberg*, Physic. Rev. *85*, 24 (1952).

[33c] *U. F. Ramsay*, Physic. Rev. *58*, 226 (1940).

[34] *W. Weltner*, J. chem. Physics *28*, 478 (1958).

## 2. Diamagnetic Increments due to Localized Electron Pairs

Using the principles of the Guy-Tillieu method, *Baudet*[35] was the first to give a comprehensive treatment of electrons localized at atoms and bonds, arriving at an incremental system. He obtained the eigenfunctions of an electron-pair bond A–B from the atomic wave functions of the atoms A and B by means of Eq. (27)

$$\Psi_o = N(\Psi_{oA} + \lambda\Psi_{oB}) \qquad (27)$$

where N is a normalizing factor, and $\lambda$ is a coefficient expressing the difference between the electronegativities of A and B.

The integrals in Eq. (24) can be calculated relatively easily with the aid of good approximations to the atomic wave functions (*e.g.* by *Slater* or *Coulson*) and experimental values for the averages of the coordinates. Table 5 shows the susceptibilities of the inner-shell electrons of closed s-, p-, and d-orbitals in various atoms. The data in Table 6 refer to the susceptibilities of lone electron pairs in various states of hybridization, the

Table 5. Total susceptibilities of inner electrons of filled s-, p-, and d-orbitals in some atoms [35].

| Atom | $\chi = \chi_d + \chi_p$ | | | | | | $\Sigma\chi$ |
|---|---|---|---|---|---|---|---|
| | $1s^2$ | $2s^2$ | $2p^6$ | $3s^2$ | $3p^6$ | $3d^{10}$ | |
| C | 0.15 | | | | | | 0.15 |
| N | 0.105 | | | | | | 0.105 |
| O | 0.08 | | | | | | 0.08 |
| Cl | 0.017 | 0.29 | 0.46 | | | | 0.77 |
| Br | 0.004 | 0.05 | 0.08 | 0.35 | 0.54 | 3.07 | 4.10 |

Table 6. Susceptibilities of lone electron pairs of some atoms in different states of hybridization [35] ($\mu$ shows the degree of hybridization).

| Atom | $\mu$ | $\chi = \chi_d - \chi_p$ |
|---|---|---|
| N | 1 | 2.22 |
| | 1.732 | 2.43 |
| O | 1.414 | 1.73 |
| | 1.732 | 1.78 |
| Cl | 0 | 5.37 |
| | 1.732 | 4.13 |
| | | 2.58 |
| Br | 0 | 8.45 |
| | 1.732 | 7.46 |

Table 7. Total susceptibilities of bonding electron pairs in A–B bonds [35] ($\mu_A$ and $\mu_B$ give the degrees of hybridization of atoms A and B).

| A–B | $\mu_A$ | $\mu_B$ | $\chi = \chi_\perp - \chi_p$ |
|---|---|---|---|
| C–H | 1 | 0 | 3.33 |
| | 1.414 | 0 | 3.74 |
| | 1.732 | 0 | 4.05 |
| C–C | 1 | 1 | 2.38 |
| | 1.414 | 1 | 2.47 |
| | 1.732 | 1 | 2.91 |
| | 1.414 | 1.414 | 2.60 |
| | 1.732 | 1.414 | 3.01 |
| | 1.732 | 1.732 | 3.10 |
| C–N | 1 | 1 | 2.37 |
| | 1.732 | 1.732 | 3.15 |
| C–O | 1.414 | 1.414 | 2.55 |
| | 1.414 | 1.732 | 2.51 |
| | 1.732 | 1.732 | 2.73 |
| N–H | 1.732 | 0 | 3.63 |
| O–H | 1.732 | 0 | 3.34 |

[35] *J. Baudet*, J. Chim. physique Physico-Chim. biol. *58*, 228 (1961).

susceptibilities of the bonding electron pairs forming A–B bonds being shown in Table 7. Susceptibilities of a π-electron pair in multiple bonds are given in Table 8. The data in Table 9 indicate the accuracy of *Baudet*'s calculations on different types of compounds.

Table 8. Susceptibilities of π-electron pairs in multiple bonds [35].

| Bond | $\chi = \chi_d + \chi_p$ |
|---|---|
| C–C | 3.42 |
| C≡C | 4.94 |
| C–N | 3.44 |
| N–N | 2.35 |
| C–O | 3.05 |

Table 9. Molar susceptibilities of some acyclic organic compounds [35].

| | $(\chi M)_{exp.}$ | $(\chi M)_{calc.}$ |
|---|---|---|
| Hydrocarbons | | |
| n-Hexane | 74.3 | 73.10 |
| n-Heptane | 85.2 | 84.35 |
| Hexene | 65.7 | 66.90 |
| 2,4-Dimethylhexane | 88.5 | 89.6 |
| 1-Heptyne | 77.6 | 76.50 |
| 2-Heptyne | 76.3 | 77.05 |
| n-Butylallene | 73.5 | 71.86 |
| Amines | | |
| n-Butylamine | 58.9 | 59.09 |
| n-Amylamine | 69.4 | 70.44 |
| Alcohols | | |
| Methanol | 21.9 | 22.01 |
| Ethanol | 33.7 | 33.36 |
| Ethers | | |
| Diethyl ether | 55.05 | 56.40 |
| Diisoamyl ether | 128.6 | 124.5 |
| Nitriles | | |
| Acetonitrile | 27.6 | 26.94 |
| Propionitrile | 38.8 | 38.29 |
| Halogen derivatives | | |
| n-Butyl chloride | 66.4 | 63.79 |
| Isoamyl chloride | 78.7 | 75.14 |
| Ethyl bromide | 53.3 | 51.79 |
| n-Propyl bromide | 64.9 | 63.14 |
| n-Butyl bromide | 75.5 | 74.49 |
| Isoamyl bromide | 88.6 | 85.84 |
| Ethyl iodide | 68.2 | 68.04 |
| n-Propyl iodide | 80.45 | 79.39. |
| n-Butyl iodide | 91.8 | 90.74 |
| Silanes | | |
| Diethoxymethylsilane | 92.99 | 96.73 |
| Diethoxydimethylsilane | 104.6 | 108.06 |
| Ketones | | |
| Methyl ethyl ketone | 46.08 | 51.26 |
| Diethyl ketone | 57.32 | 62.60 |

*Pople* has developed a GIAO-MO method attempting resolution into atomic increments on the basis of some considerable simplifications. Using the Hückel and London approximations for the atomic susceptibility, he obtained [36] $\chi_d$ and $\chi_p$ terms containing matrix components of the charge density (in both terms) and of the bond order (in the $\chi_p$ term). The results are unsatisfactory. *Hameka* [37] has pointed out that it is not permissible to neglect the interatomic two-center integrals in the expression for $\chi_p$. This contribution is manifested in practice in "neighboring-bond effects".

### 3. Neighboring-Bond Effects

The discrepancies evident in Table 9 (especially with ketones) show that correlation effects must be taken into account and that one-electron approximations are inadequate. It has been shown by *Haberditzl* [38], in particular for compounds with adamantane-type structure, that these correlation effects are manifested in the following observations.

The diamagnetism of an electron-pair bond between atoms A and B is essentially determined by the nature and the number of other atoms linked to A and B. The "neighboring-bond effect" is not merely a correlation factor, since it is often of the same order of magnitude as the diamagnetism of a bonding electron pair. Thus similar relationships apply as discussed by *Szabo* [38a] for bond dissociation energies.

The neighboring-bond effect was already observed by *Pascal* on chloroalkanes, but he did not recognize its general occurrence. Phenomena due to this effect were later also found in the structural isomers of alkanes (cf. Tables 10). It was taken into account by *Pacault* [2], *Trew* [39], and by *Angus* [40] using empirical structural increments for the $CH_3$, $CH_2$, and the CH groups. Neighboring-bond effects are also exhibited by compounds containing nitrogen and sulfur [41].

Table 10. Molar susceptibilities of some alkanes and alcohols.

| Compound | $(\chi M)_{exp.}$ | $(\chi M)_{calc.}$ [38] |
|---|---|---|
| n-Pentane | 63.05 | 63.15 |
| n-Hexane | 73.3 | 74.5 |
| n-Heptane | 85.38 | 85.85 |
| n-Octane | 96.93 | 97.20 |
| n-Nonane | 108.13 | 108.55 |
| n-Decane | 119.51 | 119.90 |
| n-Undecane | 131.8 | 131.25 |
| 2,2-Dimethylbutane | 76.24 | 76.0 |
| 2-Methylpentane | 75.26 | 75.2 |
| 2-Methylhexane | 86.24 | 86.55 |
| 2,2,3-Trimethylbutane | 88.36 | 88.25 |
| 2,2,4-Trimethylpentane | 99.1 | 99.4 |
| $C_4H_9OH$ | 56.3 | 56.5 |
| $CH_3-CH(CH_3)-CH_2OH$ | 57.8 | 57.6 |
| $C(CH_3)_3OH$ | 57.3 | 57.3 |

*French* and *Harrison* [42] were the first to introduce "bond-interaction" increments. On the basis of SCF calculations, *Hameka* [43] has put forward a theoretical treatment for the neighboring-bond effect in alkanes.

The differences in the $\chi_M$ values between isomers [*] shown in Table 10 can be explained by the neighboring-bond effect in the following manner: the susceptibility due to a C–H or C–C bond, for example, is decreased by other carbon atoms linked to the carbon in question. If primary, secondary, tertiary, and quaternary carbon atoms are denoted respectively by $C_1$, $C_2$, $C_3$ and $C_4$, we have the following sequences for the $(\chi_M)_{total}$ of the isomers:

$$\chi_{C_1-H} > \chi_{C_2-H} > \chi_{C_3-H}$$

and

$$\chi_{C_1-C_2} > \chi_{C_2-C_2} > \chi_{C_3-C_3} > \chi_{C_4-C_4}$$

[36] *J. A. Pople*, J. chem. Physics *37*, 53 (1962).

[37] *H. F. Hameka*, J. chem. Physics *38*, 3008 (1963).

[38] *W. Haberditzl*: Über ein neues Diamagnetismus-Inkrementsystem. Akademie-Verlag, Berlin 1964.

[*] For further examples, see ref. [38], Tables 17–13.

[38a] *Z. G. Szabo*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 1183 (1957).

[39] *V. C. G. Trew*, Trans. Faraday Soc. *49*, 604 (1953).

[40] *W. R. Angus, G. I. W. Llewelyn*, and *G. Scott*, Trans. Faraday Soc. *55*, 887 (1959).

[41] *H. François*, Bull. Soc. chim. France *1962*, 506, 513, 515.

[42] *C. M. French* and *D. Harrison*, J. chem. Soc. (London) *1954*, 1990.

[43] *H. F. Hameka*, J. chem. Physics *34*, 1996 (1961).

In isomeric compounds an increase in $\chi_M = \chi_d + \chi_p$ is brought about primarily by a decrease in $\chi_p$ (at constant $\chi_d$). The terms $\chi_d$ and $\chi_p$ have different signs and the inequality $|\chi_p| < |\chi_d|$ invariably holds. Clearly this could be the basis of a semiempirical increment system taking into account this effect. Table 11 shows a system developed along these lines and based on the following concepts [38]:

Table 11. Survey of new inner-electron and bond increments [38].

Inner-shell increments

| Atom | χ | Atom | χ | Atom | χ |
|---|---|---|---|---|---|
| C | 0.15 | F | 5.0 | Br | 20.0 |
| O | 3.6 | Cl | 12.5 | I | 36.0 |
| N | 2.4 | | | | |

Bond increments [*]:

| Group | χ | Group | χ | Group | χ |
|---|---|---|---|---|---|
| $C_1$—H | 4.2 | $C_1$—$C_1$ | 3.6 | $C_3$—$C_3$ | 3.3 |
| $C_2$—H | 3.8 | $C_1$—$C_2$ | 3.6 | $C_2$—$C_4$ | 3.3 |
| $C_3$—H | 3.5 | $C_1$—$C_3$ | 3.6 | $C_3$—$C_4$ | 3.3 |
| $C_1$—$C_4$ | 3.4 | $C_2$—$C_2$ | 3.6 | $C_4$—$C_4$ | 3.3 |
| $C_2$—$C_3$ | 3.4 | | | | |
| $C_1^*$—H | 3.6 | C—C* | 2.6 | $C_1 \pi C_2$ | 3.4 |
| $C_2^*$—H | 3.2 | C*—C* | 2.4 | $C_2 \pi C_2$ | 2.2 |
| | | | | $C_1 \pi C_3$ | 2.2 |
| $O_0$—H | 4.7 | C—$O_1$ | 1.8 | C—$C_2(O_1)$ | 4.6 |
| $O_1$—H | 2.3 | C—$O_2$ | 1.7 | C—$C_3(O_1)$ | 4.6 |
| | | | | $C(O_1)$—$C(O_1)$ | 5.7 |
| $C_3^*$=O | 0.2 | $C_2^*(O)$=O* | 1.8 | | |
| $C_2^*$=O* | 0.6 | $C_3^*(O)$=O* | 1.8 | | |
| $C_1^*$=O* | 4.3 | | | | |
| O(C=O)-H | 3.6 | C*(O)—O | 4.0 | C*—$O_1$ | 1.5 |
| $C_1$—Cl | 8.1 | $C_1$—Br | 8.1 | $C_1$—I | 8.1 |
| $C_2$—Cl | 8.1 | $C_2$—Br | 8.1 | $C_2$—I | 8.1 |
| $C_2(Cl_2)$—Cl | 6.9 | $C_1$(Cl)—H | 3.8 | C(Cl)—F | 3.1 |
| $C_3(Cl_3)$—Cl | 5.9 | $C_2$(Cl)—$C_2$(Cl) | 2.8 | $C(Cl_2)$—F | 1.5 |
| $C_4(Cl_4)$—Cl | 4.2 | | | | |
| $N_0$—N | 5.3 | $C_1$—$N_1$ | 4.8 | $C_2$—$N_2$ | 2.2 |
| $N_1$—H | 3.5 | $C_2$—$N_1$ | 2.7 | $C_2$—$N_3$ | 2.2 |
| $N_2$—H | 1.8 | | | $C_2(N)$—$C_2(N)$ | 6.6 |

[*] The subscript gives the number of carbon atoms linked to the atom in question. Other atoms or groups thus bonded are shown in parentheses; the asterisk denotes $sp^2$ hybridization and $\pi$ stands for $\pi$-bond electron pair.

1. For inner-shell core electrons (and for the lone electron pairs) we use increments calculated on a quantum-mechanical basis. These data often can be regarded as more accurate than observed values.

2. The bonding-electron increments are determined empirically (taking into account the neighboring-bond effect), with the aid of the incerements calculated in point 1. above. This is made necessary by the fact that one-electron approximations can be calculated with sufficient accuracy for $\chi_d$, but not for $\chi_p$. (Complete calculations have so far been reported only for a few diatomic molecules [44, 45].)

The use of such an incremental system reveals regularities in the neighboring-bond effect and enables us to carry out incremental calculations [38] (see Tables 10, 12, and 13) which reflect conformational differences, solvent effects, hydrogen-bond formation, *etc.* Incremental magnetochemistry could thus join other techniques of structural investigation, such as infrared and NMR spectroscopy, which require a considerably larger expenditure for equipment.

[44] *H. Hamano, H. Kim,* and *H. F. Hameka,* Physica *29,* 111 (1963).

[45] *H. Kim, H. Hamano,* and *H. F. Hameka,* Physica *29,* 117 (1963).

## 4. Diamagnetic Shielding

The bond susceptibilities $\chi_x$, $\chi_y$, $\chi_z$ generally are different [see Eq. (24)]. An electron-pair bond is thus usually magnetically anisotropic. In NMR spectroscopy, the magnetic shielding of the protons, causing the chemical shift, depends also on the spatial distribution of such anisotropic bonds. When a molecule is placed in a magnetic field $\mathfrak{H}$, an additional magnetic field $\mathfrak{H}'$ will be induced at each atomic nucleus.

$$\mathfrak{H}' = -\sigma \cdot \mathfrak{H} \qquad (28)$$

where $\sigma$ is the magnetic shielding constant [46] and can be split up according to

$$\sigma = \sigma_l + \sigma_w \qquad (29)$$

into $\sigma_l$, the local component due to electrons in atom A to which the proton is attached, and $\sigma_w$, the long-range component encompassing all the effects of the electrons in the neighboring atoms. The following approximate relationship holds between $\sigma_l$ and $\chi_A$ of atom A:

$$\sigma_l \approx 2 \sum_i \left( \frac{\chi_A}{r_i^3} \right) \qquad (30)$$

The accurate determination of the relationship between $\sigma_l$ and $\chi$ is, however, very difficult [48]. Empirical values of $\sigma_l$ are tabulated in ref. [49]. In simple cases, $\sigma_w$ can be traced to a mean magnetic anisotropy, $\Delta\chi = \chi_\perp - \chi_\parallel$. We thus obtain [47]:

$$\sigma_w = \Delta\chi\,(1-3\cos^2\vartheta)/3\,R^3 \qquad (31)$$

where R is the distance between the proton and the center of the bond, and $\vartheta$ is the angle formed by the radius vector R and the axis of the dipole.

If several anisotropic (C–C and C–H) bonds are responsible for $\sigma_w$, then only $\sum\Delta\chi_{C-C} - \sum\Delta\chi_{C-H}$ can be obtained. It is generally assumed that $\Delta\chi_{C-C} > \Delta\chi_{C-H}$ [50,51]. There is still only poor agreement among results on bond anisotropy, owing mainly to the sometimes arbitrary division into local and long-range shielding terms and to the uncertain assignment to the different C–C bonds in the molecule.

*Narasimhan* and *Rogers* [52] give $\Delta\chi_{C-C} \approx 1.5$ to 3 for propane. *Zürcher* [53] found $\Delta\chi_{C-C} \approx 2$ for 5α- and 5β-androstane. *Lonsdale* [54] has determined anisotropy in long-chain paraffins and alkylcarboxylic acids. A value of about 25 was obtained for the total C–C anisotropy of a $C_{18}$ chain.

[46] *J. A. Pople, W. G. Schneider,* and *H. J. Bernstein*: High Resolution Nuclear Magnetic Resonance. McGraw-Hill, New York 1959, p. 167.

[47] *H. M. McConnell,* J. chem. Physics *27,* 226 (1957).

[48] *N. F. Ramsey,* Physic. Rev. *78,* 699 (1950); *86,* 243 (1952).

[49] *A. Lösche*: Kerninduktion. Deutscher Verlag der Wissenschaften, Berlin 1957.

[50] *J. I. Musher,* J. chem. Physics *35,* 1159 (1961).

[51] *C. J. Jameson* and *H. S. Gutowsky,* J. chem. Physics *40,* 1714 (1964).

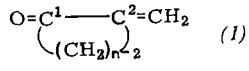
[52] *P. T. Narasimhan* and *M. T. Rogers,* J. physic. Chem. *63,* 1388 (1959).

[53] *R. F. Zürcher,* Helv. chim. Acta *44,* 1755 (1961).

[54] *K. Lonsdale,* Proc. Roy. Soc. (London), Ser. A *171,* 541 (1939).

Using this value and Pascal increments for C–C and C–H bonds, *Davies*[55] obtained $\Delta\chi_{C-C} = 4.0$ and $\Delta\chi_{C-H} = 3.0$. By examining the shielding of axial and equatorial protons in cyclohexane, *Moritz* and *Sheppard*[56] found $\Delta\chi_{C-C} - \Delta\chi_{C-H} = 4.2$. There are some indications[57], however, that other shielding mechanisms must be taken into account in cyclohexanes.

The uncertainty in the molecular parameters R and $\alpha$ are further sources of error in Eq. (31). When R is relatively small (non-aromatic compounds), the $\Delta\chi$ values can be determined with an accuracy of about 20 %. Using the $^{13}C$–H coupling constant of 23 compounds, *Reddy* and *Goldstein*[58] obtained a C–C anisotropy of $10.0 \pm 1.0$, which is considerably greater than the result of any other method. A simpler and more reliable determination of the C–C and C–H anisotropy is possible when the C–C bonds lie in the same plane, as shown for benzene in Section II.5. Reliable values for the bond susceptibility can also be utilized in the reverse manner: for the calculation of $\sigma$ from the anisotropy. Thus the proton shift of the methylene group on $C^2$ in cyclic $\alpha$-methylene ketones



*(1)*

*(1)* (n = 5–10 or 16) has been calculated approximately by *Klose*[59] as a function of the angle of rotation around the $C^1$–$C^2$ bond. Comparison with experimental values shows that the keto-vinylidene group exhibits a fully staggered conformation in compounds with n = 5 to 8 and a fully eclipsed conformation in compounds with n = 9 and 10. Partially free rotation is found when n = 16.

## 5. Molecular Ring Currents

It has long been known that aromatic compounds exhibit two special features of diamagnetism:

1. Aromatic compounds are characterized by strong magnetic anisotropy; the susceptibility $\chi_3$, normal to the plane of the ring, is greater than susceptibilities $\chi_1$ and $\chi_2$ measured in this plane ($\chi_1 \approx \chi_2$).

2. The mean susceptibility as given by Eq. (32) is higher than the value expected on the basis of the incremental system derived theoretically or empirically.

$$\bar{\chi}_M = \frac{1}{3}(\chi_1 + \chi_2 + \chi_3) \qquad (32)$$

The first feature can be demonstrated experimentally only in a few cases, namely when sufficiently large crystals are available. According to *Pauling*[60] and *London*[10], only $\chi_3$ contributes to the high value of the mean diamagnetism, for this term involves the diamagnetic effect of the delocalized $\pi$-electrons which give rise to a molecular ring current in the aromatic system. The quantum-mechanical treatment[10] of this ring current diamagnetism has been developed particularly by *Rebane*[61], *McWeeny*[62], and *Pople*[63].

Using the gauge-invariant wave functions of Eq. (14) and the Hückel approximation, *London* obtained the secular equation

$$\Sigma c_k [\eta_{k,l}\beta \exp\{2\pi i f_{k,l}\} + \delta_{k,l}(\alpha - E)] = 0 \qquad (33)$$

$$\eta_{k,l} = \begin{cases} 1, \text{ when k and } l \text{ adjacent} \\ 0, \text{ when k and } l \text{ not adjacent} \end{cases} \qquad \delta_{k,l} = \begin{cases} 1, \text{ when } k = l \\ 0, \text{ when } k \neq l \end{cases}$$

where $\alpha$ is the Coulomb integral, $\beta$ the exchange integral; k and $l$ denote the atoms of the linear combination; $f_{k,l} = \frac{e}{hc} \Phi S_{k,l}$; $S_{k,l}$ = area of the triangle formed by k, $l$, and the origin of the vector potential.

For various fused aromatic systems, *London*'s method gives only fair approximations. An electron-gas method (the box model) was introduced by *Schmidt*[64] and later also used by *Rebane*[61] (see also [65]). One-electron approximations are again inadequate, and empirical or semi-empirical derivations are unavoidable.

Table 12. Molar susceptibilities of some aromatic compounds. Ring-current diamagnetism was taken into account in the calculations.

| Compound | $(\chi M)_{exp.}$ | $(\chi M)_{calc.}$ [38] |
|---|---|---|
| Toluene | 65.6 | 66.95 |
| *o*-Xylene | 77.8 | 79.1 |
| Phenol | 59.3 | 60.0 |
| Aniline | 62.5 | 62.5 |
| *N*-Ethylaniline | 85.9 | 83.6 |
| *N,N*-Dimethylaniline | 86.0 | 85.6 |
| *o*-Toluidine | 74.4 | 74.7 |
| Diphenylamine | 107.1 | 110.4 |
| Benzidine | 115.2 | 121.0 |
| *o*-Aminophenol | 66.1 | 67.7 |
| *o*-(*N*-Methylamino)phenol | 75.7 | 78.8 |
| *o*-(*N*-Ethylamino)phenol | 88.9 | 90.2 |
| *o*-(*N*-Butylamino)phenol | 112.2 | 112.9 |
| *N,N'*-Ethylene-bis(*o*-aminophenol) | 154.8 | 154.6 |
| *N,N'*-Hexamethylene-bis(*o*-aminophenol) | 198.2 | 196.7 |
| *o*-(*N*-Phenylamino)phenol | 119.3 | 116.9 |
| *o*-(*p*-Tolylamino)phenol | 128.4 | 129.1 |
| *N,N'-o*-Phenylenebis(*o*-aminophenol) | 179.0 | 179.0 |
| Benzonitrile | 65.2 | 65.0 |
| 1-Cyano-2-phenylacetylene | 78.2 | 78.2 |
| Phenylacetonitrile | 76.9 | 77.1 |
| Salicylic acid | 75.98 | 76.0 |
| Methyl salicylate | 86.84 | 86.85 |
| Ethyl salicylate | 98.60 | 98.20 |
| Naphthalene | 91.90 | 91.9 |
| Anthracene | 131.0 | 129.0 |
| Naphthacene | 167.0 | 166.1 |
| Biphenyl | 106.0 | 105.6 |
| Triphenylmethane | 167.6 | 166.25 |

The semi-empirical incremental system shown in Table 11 gives $\chi_M = 41.1$ for benzene (experimental value 54.8). For comparison, the values for 1,3-cyclohexadiene are $(\chi_M)_{calc.} = 49.3$ and $(\chi_M)_{obs.} = 48.6$. Thus the $\pi$-conjugation in benzene results in an excess in $\chi$ of $\chi^E = 13.7$. If this value is used as "benzene increment", the susceptibility of aromatic compounds in general can be calculated. Table 12 shows the agree-

[55] *D. W. Davies*, Molecular Physics *6*, 489 (1963).

[56] *A. G. Moritz* and *N. Sheppard*, Molecular Physics *5*, 361 (1962).

[57] *N. Müller* and *W. C. Tosch*, J. chem. Physics *37*, 1671 (1962).

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[63] *J. A. Pople*, Molecular Physics *1*, 175 (1958).

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ment between observed and calculated values for aromatic systems, this agreement being satisfactory in most cases, despite the expected effect of substituents on the $\pi$-electron system. The agreement is also good for non-condensed polynuclear aromatic systems, and particularly so for fused aromatic compounds in which no separate ring current systems exist in the individual rings. The diamagnetism of a condensed system containing $n$ benzene rings is composed additively of normal bond increments, atomic increments, and $n$ benzene increments. This result suggests a semi-empirical determination of the diamagnetism due to the ring current ("London diamagnetism", $\chi_L$). In accordance with the concepts discussed above under points 1. and 2., and on the basis of a spatial averaging (London diamagnetism is perpendicular to the plane of the benzene ring), we find that $\chi_L = 3\,\chi^E = 41.1$. For a system containing $n$ benzene rings, $\chi_L \approx 3n\chi^E_{benzene}$, indicating approximate additivity of ring currents in individual benzene rings. This result is in agreement with recent modifications of the London theory by *Maddox* and *McWeeny*[66,67], with the aid of which *Memory*[68] showed that approximate additivity of $\chi_L$ holds for the fifteen five-ring systems investigated.

The $\chi_L$ value for benzene (41.1) obtained with the new system exceeds those recently reported by *Davies*[69] and by *Caralp* and *Hoarau*[70] ($\chi_L$ = 33.26 and 33.13 respectively), but is in excellent agreement with *Pople*'s result[71]. The anisotropy caused by the London diamagnetism is increased by the anisotropy of the C–C and C–H single bonds in the plane of the ring. The total magnetic anisotropy of benzene is the sum of the London diamagnetism and the bond anisotropies, *i.e.* $\chi_L + \Sigma\chi^E$.

From measurements on crystalline benzene, *Hoarau*, *Lumbroso*, and *Pacault*[72] obtained: $\chi_1 = 34.9$; $\chi_2 = 34.9$; $\chi_3 = 94.6$[*]. We thus have $\Sigma\chi^E = 18.6$. This value is distributed over the six C–C $\sigma$-bonds, the six C–H $\sigma$-bonds, and the three C–C $\pi$-bonds. As shown above, the anisotropy of the C–C and the C–H $\sigma$-bonds is about 1. *Tillieu*'s calculation gives $\chi^E \approx 2$ for the C–C $\pi$-bond. Accordingly, $\Sigma\chi^E \approx 18$, in good agreement with the estimated value.

Quantum-mechanical calculations show that these considerations cannot be extended to pentalenes and other systems with 4n, instead of (4n + 2), carbon atoms[73,74]. The chemical shift of proton resonance in aromatic systems is particularly suitable for the investigation of ring currents [see, *e.g.*, [46] and Eqs. (29) and (30)].

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[*] In the absence of anisotropy one would have

$\chi_1 = \chi_2 = \chi_3 = (\chi M)_{normal}$

Actually, however

$\chi_3 = (\chi M)_{normal} + \chi_L + \Sigma\chi^E$

## III. Use of Diamagnetism in Structural Investigations

### 1. Compounds with Localized Electrons

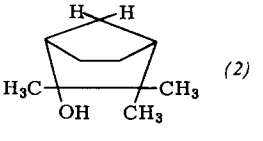
Ample experimental data on diamagnetic susceptibilities are now available for structural investigation; these data have been compiled critically by the International Union of Pure and Applied Chemistry[75].

Some results from our work on complex ring systems are collected in Table 13. They show the applicability of the incremental calculations even to compounds for which this was previously not possible (terpenes, adamantane derivatives).

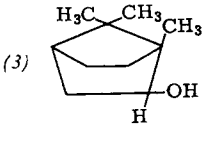
Table 13. Molar susceptibilities of complex ring systems. Experimental values are compared with those calculated with the new increment system [38].

| Compound | $(\chi M)_{exp.}$ | $(\chi M)_{calc.}$ |
|---|---|---|
| Vitamin C | 91.8 | 91.80 |
| Dehydroacetic acid | 75.0 | 75.70 |
| 1,4;5,8-Diethano-1,4,4a,4b,5,8,8a,8b-octahydroanthraquinone | 151.6 | 152.10 |
| Isoborneol *(4)* | 120.3 | 117.10 |
| Camphene hydrate | 115.2 | 115.20 |
| Muscone | 174.8 | 176.30 |
| Tanacetone *(9)* | 109.7 | 104.40 |
| α-Pinene *(5)* | 100.7 | 100.70 |
| β-Pinene *(6)* | 101.9 | 102.20 |
| Menthone | 110.6 | 109.40 |
| 1,8-Cineol *(7)* | 114.5 | 114.33 |
| Fenchol *(8)* | 118.8 | 117.40 |
| (+)-Limonene | 98.0 | 97.20 |
| Dipentene [(±)-Limonene] | 98.6 | 97.20 |
| Adamantane | 94.3 | 94.3 |
| Hexamethylenetetramine | 69.1 | 69.3 |
| Pentamethylenetetraminesulfone *(10a)* | 84.3 | 82.45 |
| Homopentamethylenetetraminesulfone *(10b)* | 94.6 | 93.80 |

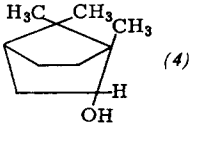
Some bicyclic terpene alcohols, namely camphenol *(2)*, isoborneol *(3)*, and borneol *(4)*, may be selected as examples[38]. The mutual steric hindrance of the OH




*(2)*




*(3)*

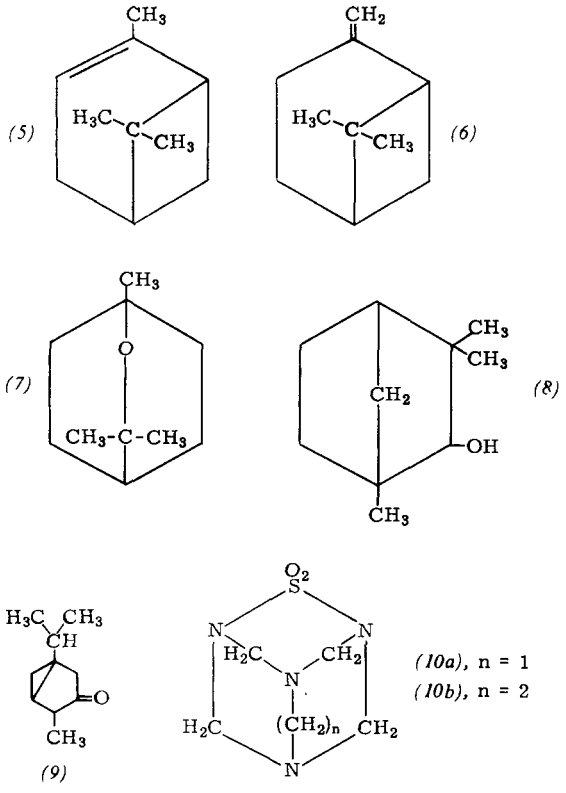



*(4)*

and the $CH_3$ groups decreases from *(2)* to *(4)*, whereas diamagnetism increases in the same direction. Thus diamagnetism reflects also the different molecular conformations caused by steric effects.

Good agreement is also found (see Table 13) between observed values and those calculated by the incremental system for α-pinene *(5)*, β-pinene *(6)*, 1,8-cineol *(7)*, and fenchol *(8)*.

[75] Tables de Constantes selectionnées de diamagnetisme et paramagnetisme. Pergamon Press, Paris 1957.



(5) (6) (7) (8) (9) (10a), n = 1 (10b), n = 2

A similar change in diamagnetism of 1–5 % is observed on formation of betaine structures[76] and hydrogen bonds[38]. The latter can give rise to electron delocalization resulting in $\chi$-anisotropy[77]. The temperature-dependence of this anisotropy leads to a temperature-dependence of diamagnetism, *e.g.* in aliphatic dicarboxylic acids[78]. Similar phenomena are observed in organic sulfur compounds[79]. The diamagnetism of organic compounds of Si, Ge, and Sn has recently been investigated[80,81]. For $XeF_4$, experiment[82] is in good agreement with theory[83].

Much work has been done on the increase of diamagnetism[84] brought about by disappearance of double bonds in addition polymerization. This increase has been observed in polyoxymethylene[85], polyvinyl acetate[86], polymethyl methacrylate[87], polycyclopentadiene, polystyrene[88], and in silicones[89].

$$\chi_{Poly} = \frac{n\chi_{mono} + (n-1)\lambda}{n \cdot M_{mono}} \qquad (34)$$

$\chi_{Poly}$ = weight susceptibility of the polymer; $\chi_{mono}$ = molar susceptibility of the monomer; M = molecular weight; $\lambda$ = diamagnetism of the C–C $\pi$-bond.

Polyethylene oxides have been studied in the liquid, the recrystallized, and in the glassy state, and the change in diamagnetism on melting has been discussed[90]. The magnetic anisotropy of polymers was first measured by *Nilakantan*[91]. Further determinations were carried out on cellulose, silk, keratin, and rubber[92], as well as on polystyrene and polyterephthalate fibers[93].

*Angus* and *Tilston*[94] examined 69 binary mixtures of organic compounds for the validity of *Wiedemann*'s rule [cf. Eq. (1)] for the diamagnetic susceptibility of mixtures. Papers by *Datar* and *Khanolkar*[95], and by *Venkateswarlu* and *Sriraman*[96] may be mentioned among more recent investigations. A comprehensive analysis of the (generally small) deviation from additivity in mixtures is still to be carried out. The largest deviations have been found for the acetone/chloroform[97] and the acetic acid/pyridine[98] systems, caused, in the latter, by salt formation.

### 2. Ring-Current Diamagnetism

*Selwood*[99] has surveyed all aromatic compounds which have been found to exhibit London diamagnetism (see also Table 12). In linearly fused systems, there is a linear relationship between anisotropy and the number of fused rings[100]. It can be shown that hexabenzocoronene is best considered as three fused phenanthrene systems[101]. Several studies[102,103] have been devoted to the effect of *o*-, *m*-, and *p*-substituents on ring-current diamagnetism.

Diamagnetic data have led to the following inferences concerning the aromaticity of pseudo-aromatic compounds. Substituted azulenes exhibit a weaker diamagnetic effect than the corresponding naphthalene derivatives[104–106]. The London diamagnetism of the pyrylium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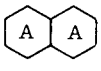
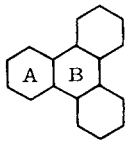
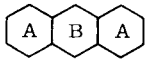
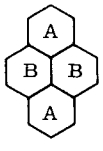
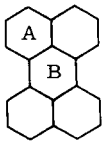
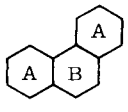
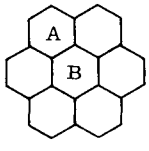
cation is about the same as that of benzene [106]. Dibenzo[*b*:*f*]oxalene behaves magnetically as two benzene rings and two non-aromatic ring systems [106]. Borazole also exhibits London diamagnetism [107].

A connection between anomalous diamagnetism and carcinogenicity has long been suspected [108]. 3,4-Benzopyrene, for example, has an anomalously low diamagnetic susceptibility. Such a connection has not, however, been proved by investigations on hydrocarbons [109–111] and other carcinogenic substances [112]. The diamagnetism of carcinotherapeutic agents has also been studied [113].

Relationships have been found between changes in diamagnetism (±10 %) on formation of charge transfer complexes of aromatic compounds and the stability of the complexes [38].

Particularly accurate investigations of London diamagnetism have recently become possible by means of its resultant magnetic shielding. *Jonathan*, *Gordon*, and *Dailey* [114] obtained information on the ring-current density in the individual rings of fused aromatic systems (see Table 14); *Memory* determined the ring-current densities of 3,4-benzopyrene, 1,2-benzanthracene, and 1,2:5,6-dibenzanthracene [114a].

Table 14. Ring currents, I, of the individual rings in condensed aromatic systems, calculated from the chemical shift ($I_{benzene} = 1$) [114].

| Molecule | Ring | Ring current I | Molecule | Ring | Ring current I |
|---|---|---|---|---|---|
|  | A | 1.093 |  | A<br>B | 1.111<br>0.747 |
|  | A<br>B | 1.085<br>1.280 | | | |
|  | A<br>B | 1.329<br>0.964 |  | A<br>B | 0.979<br>0.247 |
|  | A<br>B | 1.133<br>0.975 |  | A<br>B | 1.460<br>1.038 |

Large conjugated ring systems such as porphyrins and phthalocyanins represent a transition to compounds with "quasi-free" electrons, such as graphite. These systems have the highest diamagnetic susceptibilities of all organic compounds, partly because of their exceptionally high London diamagnetism [115]. The perimeter of the current in the porphyrin ring can be determined from the experimental London diamagnetism [38] (cf. Fig. 3). It coincides with the conjugated system, whose

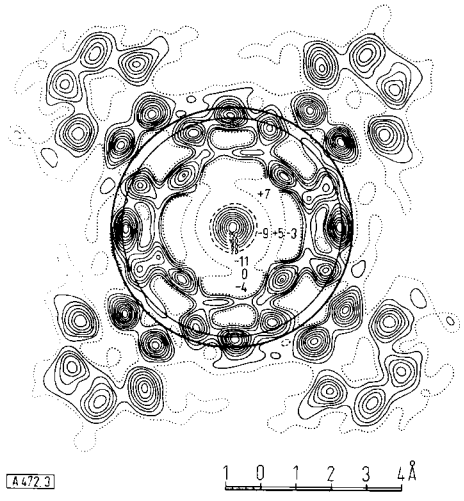



Fig. 3. Electron density contour map of Pt-phthalocyanine [120]. The $\pi$-electron ring current calculated from the diamagnetic effect is drawn to scale. The inner ring is calculated semi-empirically, the outer ring by the Pascal system. The electron densities are given as electrons per Å$^2$; negative values are due to experimental and computational errors.

area has been calculated to be 38 Å$^2$ by *Crute* [116]. Using the radius obtained on the basis of the diamagnetic effect, we find an area of 39 Å$^2$. The diamagnetic ring current of porphyrins and their metal complexes will doubtless attract great biochemical interest, in addition to supplying new information for the theory of diamagnetism of delocalized electrons.

A completely new field of research should be mentioned in conclusion, namely that of orientational and concentration effects in diamagnetic macromolecules in an external field. These have been discussed by *Dorfman* [117] and detected in glutamate dehydrogenase by *Haberditzl* and *K. Müller* [118]. This effect may provide a means of influencing chemical reactions with a magnetic field.

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# The Surface Tension of Solids

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*The surface tension of a solid, unlike that of a liquid, cannot be measured directly. After a discussion of the most important methods used so far, all of which are subject to uncertainty, the determination of the surface tension of solids from the wetting equilibrium is described.*

## I. Introduction

There are more methods for the measurement of the surface tension (specific surface free energy) of a liquid than for that of practically any other physical quantity. If we consider only static and quasi-static methods, there are two reasons for this multiplicity. First, the surface area of a liquid can easily be increased in such a way that the work involved is entirely consumed as surface work, which has the dimensions energy per unit area or force per unit length. This is the basis of, *e.g.* the bubble-pressure method and the ring method, in which the surface tension of the liquid is the force per unit length required to detach the ring from the surface of the liquid [1]. Second, owing to the tendency of liquids to minimize, their surface (or interfacial) area, cohesive and adhesive forces give rise to droplets and menisci, from the forms of which the surface tension can be determined [2].

The situation is different in the case of solids. When a surface area is increased, not all the work supplied can reappear as surface free energy. Moreover, solids do not assume shapes that are determined solely by the work of cohesion per unit area (which is equal to twice the surface tension) [*]. Thus the determination of surface tensions is much more difficult for solids than for liquids, with the result that values reported for a given solid may differ by one or two orders of magnitude.

Some of the terms used in the present paper are defined below.

The term surface denotes the phase boundary between a condensed phase and an uncondensed phase. An interface is a phase boundary between two condensed phases.

The surface tension $\sigma$ or interfacial tension $\gamma$ is the change in Helmholtz free energy F accompanying an increase in a surface or interfacial area $\Omega$ at constant volume V, temperature T, and number of moles $n_i$ of component i.

$$\sigma \text{ or } \gamma = (\partial F/\partial \Omega)_{V,T,n_i}$$

The contact angle $\vartheta$ is the angle formed at the three-phase line solid-liquid-gas between a solid and a liquid in contact with each other.

The equilibrium between a solid and a liquid phase, described by Young's equation (3), is known as the wetting equilibrium.

The specific total surface energy $\Sigma$ and the specific total interfacial energy $\Gamma$ are defined as follows:

$$\Sigma = \sigma - T(d\sigma/dT)$$
$$\Gamma = \gamma - T(d\sigma/dT)$$

The work of cohesion, $\zeta_s$ and $\zeta_l$, is twice the surface tension and the work of adhesion, $\zeta_{sl}$, is the sum of the surface tensions of two phases minus their interfacial tension.

$$\zeta_s = 2\sigma_s;\quad \zeta_l = 2\sigma_l;\quad \zeta_{sl} = \sigma_s + \sigma_l - \gamma_{sl}.$$

## II. Methods for the Determination of the Surface Tension of Crystals

### 1. Calculation from the Surface Tension of the Melt

In view of the difficulty of measuring the surface tensions of solids by the methods used for liquids, an obvious route to such data is measurement of the properties of the melt. On the basis of *Jaeger*'s results [3] on the temperature-dependence of the surface tensions of fused alkali metal halides, *von Engelhardt* and *Haussühl* [4] calculated the surface tensions of the {100} faces of these salts at 25 °C. For sodium chloride they obtained $\sigma_s = 170$ dynes/cm.

It is assumed in this calculation that the temperature coefficient of the surface tension is independent of temperature, and in particular that it is the same for the crystal and for the melt; it is also assumed that the surface tensions of the {100} face and of the melt are equal at the melting point. It is reasonable to assume a constant temperature coefficient for each phase, since the order in the surface both of the crystal and of the melt are not different from those in the interior of the phases, and the surface specific heats therefore probably are zero [1]. It is questionable, however, whether the melt and the {100} face have the same temperature coefficient of surface tension, since the crystal face and the surface of the melt do not necessarily exhibit the same state of order. Since the ratio of the surface tension of the melt to that of the solid is approximately the same as that of the heat of vaporization to the heat of sublimation [1]

[1] For details of such methods, see *e.g. K. L. Wolf*: Physik und Chemie der Grenzflächen. Springer, Heidelberg 1957.

[2] See, *e.g., A. W. Neumann*, Dissertation, Universität Mainz 1962; Z. physik. Chem. NF *41*, 339 (1964); *43*, 71 (1964).

[*] Surface tensions cannot be determined easily even for single crystals, where the crystal's habit (on the basis of the Gibbs-Wulff theorem) possibly is determined by surface energies.

[3] *F. M. Jaeger*, Z. anorg. allg. Chem. *101*, 1 (1917).

[4] *W. v. Engelhardt* and *S. Haussühl*, Kolloid-Z. *173*, 20 (1960).

(provided that melting is not associated with a change in order at the surface) the last of the above assumptions appears uncertain.

### 2. Determination from the Dependence of Solubility on Grain Size

From the dependence of solubility on grain size [5, 6], *van Zeggeren* and *Benson* [7] determined the surface tension of the {100} face of NaCl by use of the Thomson-Gibbs equation. To ensure the approximate validity of Ostwald's dilution law (which is used in the evaluation), the experiments were carried out in alcoholic solution, so that the quantity measured is the interfacial tension $\gamma_{sl}$ between sodium chloride and the alcoholic solution. Surprisingly, however, the value obtained (171 ± 12 dynes/cm at 25 °C) agrees well with that for the cubic faces of NaCl obtained from the surface tension of the melt (see Section II, 1).

### 3. Determination from Supercooling of Melts

The interfacial tension between a supercooled liquid and the crystalline phase can be calculated from the frequency of homogeneous nucleation using a theory developed by *Turnbull* and *Fischer* [8,9]. From this theory the interfacial tension between solid and liquid benzene at −60 °C is found to be 20.4 dynes/cm [10]. This value was confirmed [11] by investigation of the relationship between the equilibrium temperature T and the pressure of curvature of the solid/liquid phase boundary. In capillaries,

$$T = T_m - (T_m \gamma_{sl}/q_l \rho_s)(2/r)$$

where $T_m$ is the melting temperature, $q_l$ the heat of fusion per gram, $\rho_s$ the density of the solid, r the radius of curvature of the interface. Supercooling experiments for the determination of crystal/melt interfacial tensions have recently also been carried out on high polymers [12].

### 4. Determination from Abrasion and Grinding

The mechanical energy required to abrade or grind a solid is consumed not only as heat and as work of deformation, but also as interfacial work. This raises the question of whether the surface free energy of the abraded solid can be determined from abrasion or grinding tests. Experiments of two types have been carried out:

On the assumption that the total energy, the frictional energy, and the work of deformation in abrasion experiments with isotypic crystals are as constant as the shape, particle-size distribution, and the number of abraded particles, *von Engelhardt* and *Haussühl* [3] deduced the relationship

$$\sigma_s = \text{const. } V^{-2/3} \qquad (1)$$

for the specific surface free energy $\sigma_s$, where V is the volume of solid ground off under given conditions.

When the surface tensions of the solids, calculated from data of the melts, are plotted against $V^{-2/3}$, two straight lines are obtained, one for lithium and sodium halides, the other for potassium and rubidium halides. The surface tension of any crystal of the two groups of alkali metal halides can thus be determined.

Instead of grinding crystals individually with an abrasive under standardized conditions, *Kusnezow* [13] ground two different crystals against each other. Partly because of the different method used, different assumptions are made, and different results are obtained. It is assumed that, during the mutual abrasion of two crystals, the energy used to increase the surface area is uniformly distributed over the two crystals and that the particles abraded from each of the two substances are equal in size. It follows from these assumptions that the volumes ground off are inversely proportional to the surface energies:

$$V_1/V_2 = \sigma_{s2}/\sigma_{s1} \qquad (2)$$

Therefore, if the surface tension of one of the crystals is known, those of other solids can be determined by abrasion measurements.

The discrepancy between Equations (1) and (2) is probably due to the fact that *Kusnezow* regards the size, but *von Engelhardt* and *Haussühl* the number, of abraded particles as constant. Both methods involve further difficulties: *Kusnezow* uses the value calculated by *Born* and *Stern* [14] for the surface tension of the cubic face of the ideal NaCl crystal, which is not necessarily valid for the real cubic face (see Section II, 6). *Von Engelhardt* and *Haussühl* also use theoretical values for ideal crystals as reference values, as well as the surface tensions of solids found from solubilities and data of the melt. Since the abrasion experiments are carried out in xylene, a further uncertainty is the effect of the interfacial tension between the crystal and xylene on the result.

### 5. Determination from the Work of Cleavage

At first glance it appears possible to determine the surface tension of crystals from their cleavability, since the cohesive energy per unit length, which is equal to twice the surface tension, must be overcome during cleavage. The following distinctions are made [15], according to the experimental arrangement used:

[5] *J. J. P. Valeton*, Ber. Königl. Sächs. Ges. Wiss., Math.-phys. Kl. *67*, 1 (1915).

[6] *G. A. Hulett*, Z. physik. Chem. A *37*, 385 (1901).

[7] *F. van Zeggeren* and *G. C. Benson*, Canad. J. Chem. *35*, 1150 (1957).

[8] *D. Turnbull* and *J. C. Fischer*, J. chem. Physics *17*, 71 (1949).

[9] *D. Turnbull*, J. appl. Physics *21*, 1022 (1950).

[10] *D. G. Thomas* and *L. A. K. Staveley*, J. chem. Soc. (London) *1952*, 4569.

[11] *A. Skapski*, *R. Billups*, and *A. Rooney*, J. chem. Physics *26*, 1350 (1957); *A. Skapski*, *R. Billups*, and *D. Casavant*, *ibid. 31*, 1431 (1959).

[12] *F. P. Price*, J. Polymer Sci. *42*, 49 (1960).

[13] *W. D. Kusnezow*: Einfluß der Oberflächenenergie auf das Verhalten fester Körper. Berlin 1961. A comprehensive list of references is given.

[14] *M. Born* u. *O. Stern*, Ber. Berliner Akad. *48*, 901 (1919).

[15] *H. Tertsch*: Die Festigkeitserscheinungen der Kristalle. Springer, Vienna 1949.

a) In cleavage by impact, a knife-edge is driven into the crystal by a well-defined blow.

b) In cleavage by pressure, a knife-edge is pressed into the crystal.

c) In cleavage by fracture, a wedge with an apex angle of 60 to 90° is used instead of the knife-edge.

d) Cleavage by tension does not require the use of a tool; the crystal is simply pulled apart.

These methods give different values for the work of cleavage for the same crystal; the values are not related. Sometimes the results differ even qualitatively. Thus cleavage of sodium chloride by pressure or by fracture is easier along the {100} face, whereas cleavage by impact occurs more readily along the {110} face [15]. Evidently it is not generally possible to convert the energy required for cleavage directly into surface energy, since, depending on the experimental conditions, varying proportions of the mechanical work done are consumed for the elastic deformation of the cleavage tool or are dissipated as heat or sound. This seems the only possible explanation for the very high values ($10^4$ to $10^6$ ergs/cm$^2$) obtained [16] by impact cleavage for the cubic face of rock salt. In view of these difficulties, reasonably accurate values of surface or interfacial tensions are most likely to be obtained by measurements on readily cleavable crystals at very low temperatures (cf. the tension cleavage experiments carried out by *Gilman* [17] at −196 °C in liquid nitrogen). The method is suitable for only a few solids, and even with these it can only be used for a single direction. However, the work of cleavage of mica probably is an accurate measure of the surface tension of the solid; a value of 315 ergs/cm$^2$ was recently obtained by *Bailey* [18] by fracture cleavage.

### 6. Theoretical Calculations

The surface tensions of crystals of the NaCl type can be predicted by calculations on models. Thus *Born* and *Stern* [14] treated the Coulomb attraction between the ions and the repulsive forces, assumed exponential, and *Born* and *Göppert-Mayer* [19] refined these results by taking into account dispersion forces.

Further refinements included consideration of the polarization of surface ions and of the deformation of the outer crystal layer under the action of surface forces, as well as quantum-mechanical calculations [20–24]. These calculations relate to ideal crystals and give values of 70 to 180 dynes/cm for the surface tension of rock salt, the most widely studied crystal, at room temperature.

*Benson*, *Schreiber*, and *Patterson* [25] calculated a value of 112 dynes/cm at 0 °K for the real NaCl crystal, whereas *van Zeggeren* and *Benson* obtained a value of approximately 190 dynes/cm at 0 °K both from the classical theory of ionic crystals [26] and on the basis of a simple quantum-mechanical model [24]. It appears, therefore, that the commonly accepted value of 150 to 170 dynes/cm for the surface tension of the {100} plane at room temperature may be correct for ideal crystals, but that the surface tension of real crystals is lower.

## III. Physical Chemistry of Interfaces

### 1. Statement of the Problem

In some cases, information about the surface tension of solids has been obtained by analogy with liquid properties that are readily found by experiment. In others, the interaction between a solid and a liquid was used as a basis for conclusions regarding the unknown surface tension $\sigma_s$ and the interfacial tension $\gamma_{sl}$ between the solid and the liquid. Earlier studies of this nature, *e.g.* [27–29], failed to produce any far-reaching results, mainly because Young's equation

$$\sigma_s - \gamma_{sl} = \sigma_l \cos \vartheta, \qquad (3)$$

which was used as the equilibrium condition, yields only the difference between $\sigma_s$ and $\gamma_{sl}$, but cannot be used to find these two quantities separately ($\sigma_s - \gamma_{sl}$ is the work of wetting or the work of immersion). Owing to the lack of success of these investigations and the fact that the reproducibility of contact angles is often poor, interest in the wetting equilibrium subsequently declined.

### 2. The Critical Surface Tension for Wetting

The importance of the wetting equilibrium was recognized by *Zisman et al.* [30–32], who showed the existence of a relationship between the surface tension of a liquid $\sigma_l$ and the contact angle $\vartheta$ between the liquid and a solid surface having a low energy, *i.e.* having a specific surface free energy smaller than that of the liquid in question. In a homologous series of liquids, the contact angle with a given solid decreases almost linearly with decreasing surface tension of the liquid [33] (Fig. 1).

In his earlier publications, *Zisman* stated that, for a given solid, every homologous series of liquids gives a different straight line of $\cos \vartheta$ *versus* $\sigma_l$. These lines were all reported to intersect at a common point with $\cos \vartheta = 1$. The abscissa of this point depends on the solid, and was designated as the critical surface tension of wetting, $\gamma_c$, of the solid. In more recent


[16] *A. F. Joffe* and *M. A. Lewitskaja*, Zh. techn. Fiz. *13*, 12 (1924).

[17] *J. J. Gilman*, J. appl. Physics *31*, 2208 (1960).

[18] *A. J. Bailey* in: Haftsysteme und Haftfestigkeit. Dechema-Monographie No. 51. Verlag Chemie, Weinheim/Bergstr. 1964, p. 21.

[19] *M. Born* and *M. Göppert-Mayer* in: Handbuch der Physik. Springer, Berlin 1933, Vol. 24, p. 2.

[20] *J. Biemüller*, Dissertation, Universität Göttingen 1926.

[21] *E. J. Verwey*, Recueil Trav. chim. Pays-Bas *65*, 521 (1946).

[22] *B. M. Dent*, Philos. Mag Ser. 7, *8*, 530 (1929).

[23] *J. E. Lennard-Jones* and *B. M. Dent*, Proc. Roy. Soc. (London) *A 121*, 247 (1928).

[24] *F. van Zeggeren* and *G. C. Benson*, Canad. Physics *34*, 985 (1956).

[25] *G. C. Benson*, *H. P. Schreiber*, and *D. Patterson*, Canad. Physics *34*, 1553 (1956).

[26] *F. van Zeggeren* and *G. C. Benson*, J. chem. Physics *26*, 1077 (1957).

[27] *St. Berent*, Z. Kristallogr. *26*, 529 (1896).

[28] *A. Pockels*, Naturwiss. Rdsch. *30*, 383 (1899).

[29] *G. N. Antonoff*, Philos. Mag. Ser. 7, *1*, 1258 (1926); 7, *4*, 792 (1927).

[30] *W. A. Zisman* in *P. Weiss*: Adhesion and Cohesion. Elsevier, New York 1962, p. 176.

[31] *W. A. Zisman* in: Advances in Chemistry Series *43*. Contact Angle, Wettability and Adhesion. Washington 1964, p. 1.

[32] *A. W. Zisman*, Ind. Engng. Chem. *55*, 19 (1963).

[33] *H. W. Fox* and *W. A. Zisman*, J. Colloid Sci. *5*, 514 (1950).

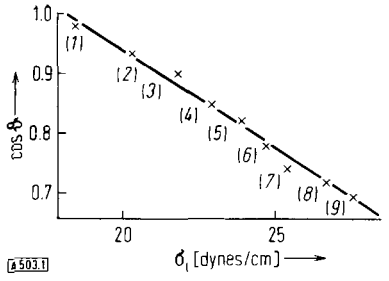



Fig. 1. Relationship between cos $\vartheta$ and $\sigma_l$ against polytetrafluoroethylene (DuPont) at 20 °C. Liquids: *(1)* hexane, *(2)* heptane, *(3)* octane, *(4)* nonane, *(5)* decane, *(6)* undecane, *(7)* dodecane, *(8)* tetradecane, *(9)* hexadecane.

papers (*e.g.*[31]), however, the values for non-homologous liquids were found to lie within a certain band, so that the value of $\gamma_c$ is not sharply defined. The values for liquids with reltatively high surface tensions do not lie on the lines obtained for those with relatively low surface tensions, but are displaced towards higher values of cos $\vartheta$; *Zisman* ascribes this to the effect of hydrogen bonds in liquids with high surface tensions (*e.g.* water). In recent years the critical surface tension for wetting, $\gamma_c$, has proved an important aid to the study of wetting, adhesion, and related phenomena, particularly in view of *Zisman*'s extensive work on the relationship between $\gamma_c$ and the chemical constitution of the solid (see also Section IV, 1 and Fig. 2).

### 3. Attempts to Identify the Critical Surface Tension of Wetting with the Surface Tension of the Solid

The fact that $\gamma_c$ is the first surface energy relating to solids alone, together with *Zisman*'s supposition that the critical surface tension for wetting is probably not very different from the surface tension of the solid, $\sigma_s$, suggests that $\gamma_c$ could be identical with $\sigma_s$.

The equality

$$\gamma_c = \sigma_s \tag{4}$$

was proposed almost simultaneously by *Gray*[34,35] and *Wolfram*[36]. *Wolfram*'s point of departure was *Antonow*'s rule:

$$\gamma_{sl} = \sigma_l - \sigma_s \tag{5}$$

He claimed this rule to hold at least when the liquid is just beginning to spread, *i.e.* when $\vartheta = 0$ and $\cos\vartheta = 1$, so that it follows from Equation (3) that

$$\gamma_{sl} = \sigma_s - \sigma_l \tag{6}$$

Comparison of Equations (5) and (6) then shows that

$$\gamma_{sl} = 0 \tag{7a}$$

and

$$\sigma_s = \sigma_l \tag{7b}$$

The proposed expression (4) then follows directly from the definition of $\gamma_c$ and Equation (7b).

The objection to this argument is that the vital Equation (7a) is derived indirectly *via* Equation (5), which probably cannot be proved (cf. Section IV, 1)[37]. In other words, since Equation (5) is supposed to be valid only when $\vartheta = 0$ and hence when $\gamma_{sl}$ becomes zero, it is identical with the proposed Equation (4) because of the definition of $\gamma_c$, and is equally lacking in proof.

*Gray*, on the other hand, started with the analytical equation of the straight line in Fig. 1.

$$\cos\vartheta = 1 + k(\gamma_c - \sigma_l) \tag{8}$$

where k is the slope of the line. He reasoned that if the liquid is replaced by the solid in question (assuming that some means is available for overcoming the cohesive forces of the solid), the liquefied solid spreads upon itself, so that Equations (7) are valid, and comparison of Equation (8) with Equation (3) gives the proposed Equation (4). Despite its plausibility, this reasoning, like the attempts to deduce the surface tension of the solid from that of the melt, is open to the objection that the surface tensions of the solid and of the melt should be different, their ratio being equal to the ratio of the heat of sublimation to the heat of fusion. Moreover, it is well known from crystal-growing practice that, when a crystal is being drawn from the melt, the latter often forms a finite contact angle with the growing crystal.

### 4. The Surface Tension of Solids, Contact Angles, and Intermolecular Forces

By analogy with an equation proposed by *Berthelot*[38], *Good et al.*[39–41] defined an interaction parameter[*]

$$\Phi = (\sigma_s + \sigma_l - \gamma_{sl})/2\sqrt{\sigma_s\sigma_l} \tag{9}$$

which represents the ratio of the work of adhesion and the mean work of cohesion of the two phases. These authors use this function in two ways to obtain information about the surface tension of solids:

1. *Girifalco* and *Good* calculated the interaction parameters[39] for many pairs of liquids from their surface and interfacial tensions. Within a group of chemically similar liquids, the values of $\Phi$ against water lie in a narrow range; *e.g.* between 0.51 and 0.60 for aliphatic hydrocarbons. On the assumption that the interaction parameters between *solid* aliphatic hydrocarbons and water also lie in this range, the surface tension of the solid, $\sigma_s$, can be estimated by measurement of the contact angle, since the interfacial tension, $\gamma_{sl}$, can be eliminated from Equations (9) and (3):

$$\sigma_s = \sigma_l(1 + \cos\vartheta)^2/4\,\Phi^2 \tag{10}$$

2. If the free energies in Equation (9) are replaced by the total specific surface energies $\Sigma_s$, $\Sigma_l$ and $\Gamma_{sl}$, combination of the resulting equation with that defining the heat of immersion or heat of wetting B:

$$B = \Gamma_{sl} - \Sigma_s \tag{11}$$

gives

$$\Sigma_s = (\Sigma_l - B)^2/4\,\Phi^2\Sigma_l \tag{12}$$

[34] *V. R. Gray*, Forest Prod. J. *12*, 452 (1962).

[35] *V. R. Gray*, Lecture to the 4th International Congress on Surface Active Substances, Brussels 1964.

[36] *E. Wolfram*, Kolloid-Z. u. Z. Polymere *182*, 75 (1962).

[37] *O. Driedger*, *A. W. Neumann*, and *P.-J. Sell*, Kolloid-Z. u. Z. Polymere *201*, 52 (1965).

[38] *D. Berthelot*, C. R. hebd. Séances Acad. Sci. *126*, 1703, 1857 (1898).

[*] The term interaction parameter was introduced by *J. C. Melrose*; as far as we know, *R. J. Good* did not give the function $\Phi$ any special name.

[39] *L. A. Girifalco* and *R. J. Good*, J. physic. Chem. *61*, 904 (1957).

[40] *R. J. Good*, *L. A. Girifalco*, and *G. Kraus*, J. physic. Chem. *62*, 418 (1958).

[41] *R. J. Good* and *L. A. Girifalco*, J. physic. Chem. *64*, 561 (1960).

Thus if $\Phi$ and $\Sigma_l$ are known, the specific total surface energy $\Sigma_s$ of the solid can be found from the measured heats of immersion [40].

On the assumption that the contributions of intermolecular forces to surface tension are additive, *Fowkes* [42–44] expressed the surface tension of water as

$$\sigma_{l_1} = \sigma_{l_1}^h + \sigma_{l_1}^d \tag{13}$$

where $\sigma_{l_1}^h$ is the contribution due to the hydrogen bonds and $\sigma_{l_1}^d$ that due to dispersion forces. The surface tension $\sigma_{l_2}$ of saturated hydrocarbons, on the other hand, consists only of the contribution due to dispersion forces

$$\sigma_{l_2} = \sigma_{l_2}^d \tag{14}$$

The interactions at the interface between saturated hydrocarbons and water are almost entirely dispersion forces, so that on the tacit assumption that $\Phi = 1$, Equ. (9) can be written

$$\gamma_{l_1 l_2} = \sigma_{l_1}^d + \sigma_{l_2} - 2\sqrt{\sigma_{l_1}^d \sigma_{l_2}} \tag{15}$$

The calculation of $\sigma_{l_1}^d$ from $\sigma_{l_2}$ and $\gamma_{l_1 l_2}$ for several saturated hydrocarbons gives $\sigma_{l_2}^d = 21.8 \pm 0.7$ dyne/cm for the dispersion component of the surface tension of water.

This method can be used to find the dispersion component of the surface tensions of liquids in general. The application of these considerations to solids simply requires the combination of Young's Equation (3) with Equation (15) ($l_1 = s$, $l_2 = l$).

$$\sigma_l^d (\cos\vartheta + 1) = 2\sqrt{\sigma_l^d \cdot \sigma_s^d} \tag{16}$$

Thus the dispersion component $\sigma_s^d$ of the surface tension of a solid can be calculated from contact-angle data and calculated values of the dispersion component of the surface tension of the liquid. *Fowkes* has applied the above considerations to heats of immersion and of adsorption [44].

*Girifalco* and *Good* [39] derived the most general expression for the interaction parameter, on the basis of work by *Fowler* and *Guggenheim* [45]:

$$\Phi = \frac{4(V_1 V_2)^{1/3}}{(V_1^{1/3} + V_2^{1/3})^2} \cdot \frac{A_{12}}{(A_{11} A_{22})^{1/2}} \tag{17}$$

where $V_1$ and $V_2$ are the molar volumes and the A values are the attraction constants in a Lennard-Jones potential. Taking into account the usual intermolecular forces, *i.e.* dispersion and dipole forces, one obtains [46]:

$$\Phi = \frac{4\,(V_1 V_2)^{1/3}}{(V_1^{1/3} + V_2^{1/3})^2} \cdot \frac{{}^3/_4\,\alpha_1\alpha_2[2I_1I_2/(I_1 + I_2)] + \alpha_1\mu_2^2 + \alpha_2\mu_1^2 + {}^2/_3[(\mu_1\mu_2)^2/kT]}{[({}^3/_4\,\alpha_1^2 I_1 + 2\,\alpha_1\mu_1^2 + {}^2/_3(\mu_1^4/kT))\,({}^3/_4\alpha_2^2 I_2 + 2\,\alpha_2\mu_2^2 + {}^2/_3(\mu_2^4/kT))]} \tag{18}$$

where the $\alpha_i$ denote polarizabilities, the $\mu_i$ dipole moments, and the $I_i$ ionization energies.

The surface tensions $\sigma_s$ of a number of solids, were calculated by *Good* with the aid of Equation (10) using the surface tensions of liquids whose contact angles with the solid in question had been determined by *Zisman et al.* The interaction parameters were calculated by means of Equation (18). For polytetrafluoroethylene, the values of $\sigma_s$ varied from 15 to 35 dynes/cm, the mean value being 24 dynes/cm; the dipole moment of the polymer surface was taken to be 1.2 Debye. A dipole moment of zero, which *Good* regards as less likely on physical grounds, would give $\sigma_s = 21$ dynes/cm.

*Good*'s calculations, like those of *Fowkes* and like *Zisman*'s work, are based on the assumption (which is supported by many arguments) that, if $\sigma_l > \sigma_s$, the liquid is not adsorbed on the surface of the solid. The validity of this assumption has recently been questioned by *Melrose* [47], who estimates that the change in surface tension of the solid as a result of adsorption of vapor is of the order of 10 dynes/cm, and thus obtains values for $\sigma_s$ that are distinctly higher than those obtained by *Good*, *Fowkes*, and *Zisman*. According to *Melrose*, for example, the surface tension of polytetrafluoroethylene is 34 dyne/cm.

## IV. The Equation of State for Surface Energies and the Surface Tension of Solids

### 1. Principle

The fundamental object of molecular treatments such as that carried out by *Good* is to obtain information about the various interfacial-energy properties, for example the surface tensions of solids, $\sigma_s$, from the known intermolecular interactions. The capillarity theory, on the other hand, answers [in the form of Young's equation (3)] the question of the nature of the equilibrium between a solid phase having the surface tension $\sigma_s$ and a liquid phase having the surface tension $\sigma_l$ for a given interfacial tension $\gamma_{sl}$. Thus neither of these approaches can provide any other relationship between the three fundamental interfacial energies $\sigma_s$, $\sigma_l$, and $\gamma_{sl}$.

The interfacial tensions between a solid and chemically different liquids of the same surface tension (as is approximately true of lower alcohols and alkanes) were thought to be different because of different intermolecular forces. However the relationship (19) [48] for two immiscible liquids, $l_1$ and $l_2$ has been postulated.

$$\gamma_{l_1 l_2} = |\sigma_{l_1} - \sigma_{l_2}| \tag{19}$$

Comparison with experiment shows that Eq. (19) is not generally valid, even if partial miscibility is taken into account.

Moreover $\sigma_s$, and hence also $\gamma_{sl}$, generally is known to only a crude approximation, so that a functional relationship, if there is one, between the fundamental interfacial energies of a solid and a liquid cannot be established directly.

[42] *F. M. Fowkes*, J. physic. Chem. *66*, 382 (1962).

[43] *F. M. Fowkes*, in [31], p. 99.

[44] *F. M. Fowkes*, Lecture to the 4th International Congress on Surface Active Substances, Brussels 1964.

[45] *R. H. Fowler* and *E. A. Guggenheim*: Statistical Thermodynamics. Cambridge University Press, Cambridge 1939.

[46] *R. J. Good* in [31], p. 74.

[47] *J. C. Melrose*, in [31], p. 158.

Nevertheless it is possible to answer this question by examination of the wetting equilibrium [49,50] between a given solid and various liquids. If we assume, in agreement with *Zisman*, that the surface tension of the solid is not affeced by contact with liquids and their vapors when $\sigma_l > \sigma_s$ [*], the contact angle between the solid and any liquid is a unique function of the interfacial tension $\gamma_{sl}$ because of Equation (3). If there is a functional relationship among the three fundamental interfacial energies $\sigma_s$, $\sigma_l$, and $\gamma_{sl}$, this means that when $\sigma_s$ is kept constant and $\sigma_l$ is continuously varied, the interfacial tension $\gamma_{sl}$, and hence cos $\vartheta$, also change continuously, *i.e.* a plot of the surface tension $\sigma_l$ of any liquid against cos $\vartheta$ for a given solid (or more accurately for a given value of $\sigma_s$) will give a continuous curve. Fig. 2 shows that, contrary to the expectations based on the specificity of intermolecular forces, this is in fact the case, particularly if all the uncertainties associated with contact angles are taken into

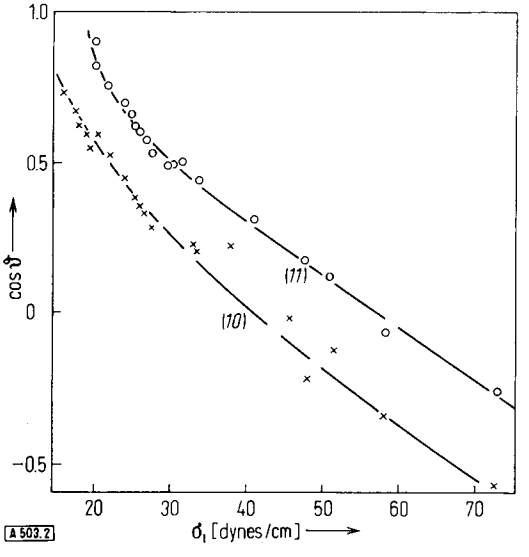



Fig. 2. Isotensosolids at 20 °C against *(10)*: pentadecafluorooctyl methacrylate, $C_7F_{15}-CH_2-OOC-C(CH_3)=CH_2$, and *(11)*: pentafluorononadecanoic acid [$CF_3-CF_2-(CH_2)_{16}-COOH$]. Liquids (examples): For *(10)*: n-alkanes, silicones, perhalogenated hydrocarbons, hydrocarbons. For *(11)*: n-alkanes ($C_7$, $C_8$, $C_{10}$, $C_{11}$, $C_{12}$, $C_{13}$, $C_{14}$, $C_{16}$), water, formamide, diiodomethane, glycol, tricresyl phosphate, bicyclohexyl.

account. Thus Fig. 2 proves that $\sigma_s$, $\sigma_l$, and $\gamma_{sl}$ are related by an equation of state:

$$F(\sigma_s, \sigma_l, \gamma_{sl}) = 0 \qquad (20)$$

(cf. also Fig. 1 and Section III, 2).

A quantitative treatment of such curves of constant solid surface tension ("isotensosolids") is precluded, *inter alia*, by the large scatter of the experimental data; however, if the work of wetting

$$\beta_{sl} \equiv \sigma_s - \gamma_{sl} = \sigma_l \cos\vartheta \qquad (21)$$

is plotted on the abscissa instead of $\sigma_l$, the scatter is greatly reduced (Fig. 3).

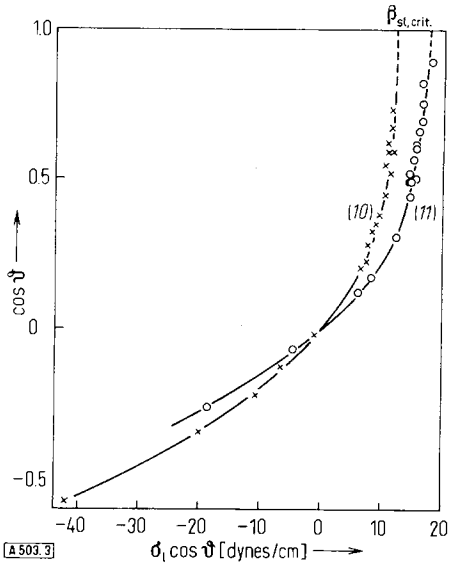



Fig. 3. Relationship between cos $\vartheta$ and $\sigma_l \cos\vartheta$. $\beta_{sl} = \sigma_s - \gamma_{sl}$. Conditions and substances as in Fig. 2.

In order to compare different solids, it is necessary to refer to equivalent points on the isotensosolids. For this purpose we use the maximum value of $\sigma_l$ obtained by extrapolation to cos $\vartheta = 1$, denoted as the critical wetting tension, $\beta_{sl,crit}$. A plot of these solid-specific values $\beta_{sl,crit}$. for various solids against cos $\vartheta$ for a given liquid according to Equation (20) also gives continuous curves (Fig. 4) ("isotensoliquids" [51]).

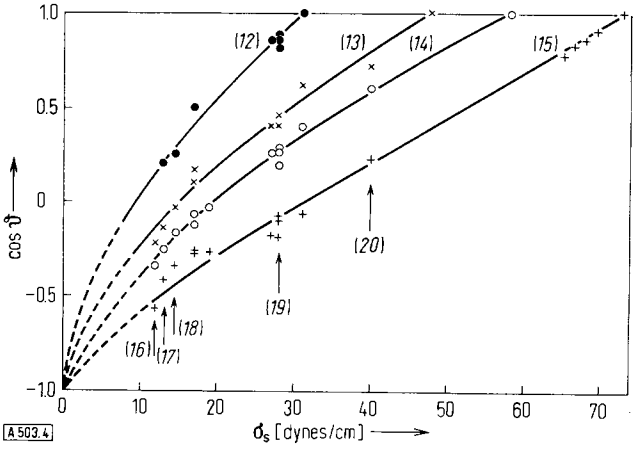



Fig. 4. Relationship between cos $\vartheta$ and $\sigma_s$ (= $\beta_{sl,crit}$), measured at room temperature for several solids against four liquids of different surface tensions (isotensoliquids).

*(12)*: bis-2-ethylhexyl sebacate ($\sigma_l$ = 31.0 dynes/cm), *(13)*: glycol (47.7), *(14)*: formamide (58.2), *(15)*: water (72.8).

$\beta_{sl,crit.}$ (= $\sigma_s$) = critical wetting tension. Some solids are indicated by vertical arrows: *(16)* perfluorolauric acid, *(17)* pentadecafluorotetracosanoic acid, *(18)* undecafluorodocosanoic acid, *(19)* polyethylene (BASF), *(20)* Ultramid (BASF). (See also Table 2).

It can be seen from Fig. 4 that, for a given solid, the contact angle decreases, *i.e.* cos $\vartheta$ increases, with decreasing surface tension of the liquid; Fig. 3 shows that the wetting tension $\beta_{sl}$ also increases with increasing cos $\vartheta$, so

[48] *G. Antonow*, J. Chim. physique *5*, 372 (1907).

[49] *A. W. Neumann* and *P.-J. Sell*, Z. physik. Chem. *227*, 187 (1964).

[50] *P.-J. Sell*, Z. physik. Chem. NF *39*, 322 (1963).

[*] When $\sigma_s > \sigma_l$, adsorption of the liquid is accompanied by an increase in the free energy of the surface of the solid.

[51] *A. W. Neumann* and *P.-J. Sell*, Z. physik. Chem. NF *41*, 183 (1964).

that, according to Equation (3), the interfacial tension decreases with decreasing surface tension of the liquid.

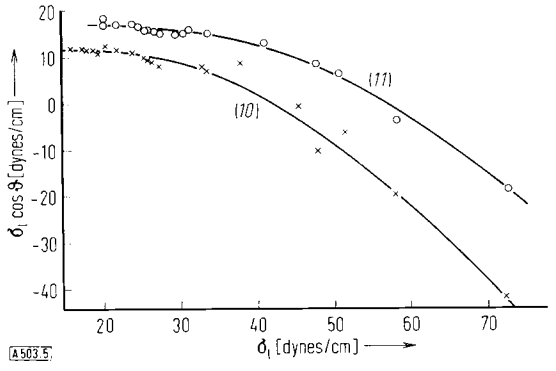



Fig. 5. Isotensosolids at 20 °C against several liquids (for examples see Fig. 2).

The curves of $\sigma_l \cos\vartheta$ *vs.* $\sigma_l$ [52] (Fig. 5) apparently pass through the points $\sigma_l = \beta_{sl,crit}$ parallel to the $\sigma_l$ axis. Since

$$d(\sigma_s - \gamma_{sl})/d\sigma_l = -d\gamma_{sl}/d\sigma_l \qquad (22)$$

it follows from Equation (3) that

$$(d\gamma_{sl}/d\sigma_l) = 0 \text{ for } \sigma_l \longrightarrow \beta_{sl,crit} \qquad (23)$$

*i.e.* $\gamma_{sl}$ assumes a minimum value when $\sigma_l \rightarrow \beta_{sl,crit}$. Since there is no reason why the interfacial tension between a solid and a liquid cannot be zero, whereas it assumes a minimum value for $\sigma_l = \beta_{sl,crit}$, it is reasonable, by analogy with the reasoning leading to Nernst's theorem, to postulate

$$(\gamma_{sl})_{\sigma_l \longrightarrow \beta_{sl,crit}} = 0 \qquad (24)$$

It then follows from Equation (21) that

$$\beta_{sl,crit} = \sigma_s \qquad (25)$$

In order to be able to formulate the interfacial-energy equation of state (20) explicitly [37], it is necessary to find a physically meaningful function of the three fundamental interfacial energies, the form of which is such that all possible values of the function are uniquely assigned to one of the three fundamental energies. Since $\sigma_s$ and $\sigma_l$ are naturally to be regarded as the independent variables, owing to the fact that the solid and the liquid are specified in advance, the dependent quantity that is to be assigned to the values of the function must be the interfacial tension $\gamma_{sl}$.

We examined *Girifalco* and *Good*'s interaction parameter [Equation (9)] to see whether it was suitable for use as a function of state. To test the supposition that $\Phi$ is only a function of $\gamma_{sl}$, the isotensosolids of the solids studied in [50] and [53] were plotted in the ($\sigma_l$; $\gamma_{sl}$) diagram, and $\Phi$ was calculated for various values of $\gamma_{sl}$. Within the scatter of the measurements in the energy range accessible ($10 \leqslant \sigma_s \leqslant 45$ dynes/cm and $20 \leqslant \sigma_l \leqslant 73$ dynes/cm), the $\Phi$ values assigned to one and the same $\gamma_{sl}$ value are constant.

A plot of the average $\Phi$ values against the corresponding $\gamma_{sl}$ values gives approximately a straight line, the equation of which is:

$$\Phi = -0.0075\,\gamma_{sl} + 1 \qquad (26)$$

If we eliminate $\Phi$ from Equations (9) and (26), we obtain the following approximation for the equation of state for the interfacial energies in the interfacial-tension range of 0 to about 40 dynes/cm:

$$\gamma_{sl} = (\sqrt{\sigma_s} - \sqrt{\sigma_l})^2 / (1 - 0.015\sqrt{\sigma_l \sigma_s}) \qquad (27)$$

With the aid of Equations (27) and (3) it is possible, in principle, to calculate the surface tension of the solid and the interfacial tension for any solid/liquid combination (in the energy range given above) from the surface tension of the liquid and the contact angle [54].

## 2. Results

Table 1 shows values obtained in this way for the surface tension of solid perfluorolauric acid, together with the surface tensions and contact angles [55] of some other liquids. There is no dependence of $\sigma_s$ on $\sigma_l$ within the limits of error; the same is found for the $\sigma_s$ values of the solids listed in Table 2. This may be regarded not only as confirmation of the above theoretical considerations, but also as evidence for the correctness of the constants in Equations (26) and (27). Column 3 of Table 2 contains some values of $\sigma_s$ calculated by *Good* from intermolecular force data with the aid of Equations (10) and (18). In view of the large number and uncertainty of the data used by *Good*, the agreement with the values in column 2 of Table 2 is remarkable.

Since the surface tension of a solid can in principle be determined from the surface tension of a single liquid

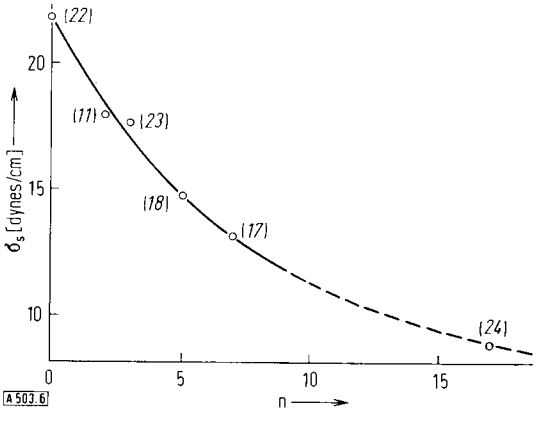



Fig. 6. Surface tensions of a number of solid fluorinated fatty acids as a function of the length of the perfluorinated hydrocarbon chain (for compounds, see Table 2).

[52] *P.-J. Sell* and *A. W. Neumann*, Z. physik. Chem. NF *41*, 191 (1964).

[53] *K. L. Wolf*, *O. Driedger*, *A. W. Neumann*, and *P.-J. Sell* in [18], p. 31.

[54] For details of the solution of the cubic equation obtained by combination of Equations (3) and (27) see *O. Driedger*, *A. W. Neumann*, and *P.-J. Sell*, Kolloid-Z. u. Z. Polymere *204*, 101 (1965).

[55] *E. F. Hare*, *E. G. Shafrin*, and *W. A. Zisman*, J. physic. Chem. *58*, 236 (1954).

and the corresponding contact angle, it is possible to study the relationships between the surface tension of a solid and its chemical constitution. For example, Fig. 6 is a plot of the surface tensions of solid stearic acid *(22)* and of a number of fluorinated acids against the length of the fluorinated chain. Compounds *(11)*, *(23)*, *(18)*, and *(17)* are stearic acids in which a hydrogen atom on C-18 has been replaced by a perfluoroalkyl group. As expected, it is found that the fluorination of a few C atoms causes a marked decrease in the surface tension,

Table 1. The surface tension, $\sigma_S$, of solid perfluorolauric acid at 20 °C, calculated from that of the liquid, $\sigma_l$, and contact angles, $\vartheta$, from Eqs. (3) and (27) [55].

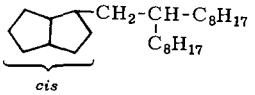
| Liquids | $\sigma_l$ [dynes/cm] | $\vartheta$ [deg] | $\sigma_S$ [dynes/cm] |
|---|---|---|---|
| $CH_3[Si(CH_3)_2O]_4Si(CH_3)_3$ | 18.1 | 60 | 10.4 |
| Perfluoroalkane (FCD-330) | 20.2 | 48 | 14.2 |
| Octane | 21.8 | 65 | 12.8 |
| $CF_2Cl-CCl_2-CF_2Cl$ | 22.8 | 49 | 15.8 |
| $H(CF_2)_6CH_2OH$ | 23.8 | 62 | 13.3 |
| Decane | 23.9 | 70 | 11.3 |
| $H(CF_2)_4CH_2OH$ | 24.5 | 65 | 12.9 |
| Di-n-amyl ether | 24.9 | 68 | 12.3 |
| Dodecane | 25.4 | 74 | 11.0 |
| Carbon tetrachloride | 26.7 | 69 | 13.0 |
| Tetradecane | 26.7 | 76 | 10.9 |
| *p*-Difluorobenzene | 27.0 | 66 | 14.0 |
| $H(CF_2)_2CH_2OH$ | 27.6 | 68 | 13.7 |
| 1-Octanol | 27.6 | 70 | 13.6 |
| Hexadecane | 27.6 | 78 | 10.9 |
| $CFCl_2-CF_2-CCl_3$ | 27.8 | 66 | 14.4 |
| Polyethylene V-120 | 27.8 | 78 | 11.0 |
| Di-n-decyl ether | 28.4 | 79 | 11.0 |
| Benzene | 28.9 | 75 | 12.3 |
| Octanoic acid | 29.2 | 69 | 14.3 |
| Hexamethylenebis-(2-ethyl hexanoate) | 30.2 | 77 | 12.3 |
| Pentaerythritol tetrahexanoate | 30.4 | 80 | 11.5 |
| Polyethylene SS 903 | 30.4 | 81 | 11.2 |
| 8-*p*-Tolylnonadecane | 30.7 | 83 | 10.8 |
| Bis-(2-ethylhexyl) sebacate | 31.1 | 79 | 12.1 |
| Bis(2-ethylhexyl) phthalate | 31.2 | 78 | 12.5 |
| n-Decylbenzene | 31.2 | 83 | 11.0 |
| 9-(*cis*-Bicyclo[3.3.0]oct-2-yl-methyl)heptadecane | 31.2 | 84 | 10.7 |
|  *cis* | | | |
| 4-Cyclohexyleicosane | 31.6 | 83 | 11.1 |
| 1-Cyclohexyl-2-(cyclohexyl-methyl)pentadecane | 32.7 | 84 | 11.3 |
| 1-Perhydronaphth-1-ylundecane | 32.7 | 84 | 11.3 |
| t-Butylnaphthalene | 33.7 | 86 | 11.0 |
| 9-n-Dodecylperhydro-phenanthrene | 34.2 | 86 | 11.2 |
| 1,1′:3′,1″-Tercyclopentane | 34.6 | 85 | 11.7 |
| 1,7-Dicyclopentyl-4-(3-cyclo-pentylpropyl)heptane | 34.6 | 86 | 11.4 |
| 1,1-Di(perhydronaphth-1-yl)-undecane | 35.1 | 88 | 10.9 |
| Perchlorobutadiene $CCl_2=CCl-CCl=CCl_2$ | 36.0 | 81 | 13.7 |
| Benzyl phenyl undecanedioate $C_6H_5-CH_2-OCO-(CH_2)_9-COO-C_6H_5$ | 37.7 | 92 | 10.6 |
| Perchloropropene | 38.1 | 81 | 14.6 |
| Tricresyl phosphate | 40.9 | 83 | 15.1 |
| Tetrachlorobiphenyl (Aroclor 1248) | 44.2 | 96 | 11.5 |
| 1-Bromonaphthalene | 44.6 | 92 | 13.1 |
| Trichlorobiphenyl (Aroclor 1242) | 45.3 | 94 | 12.6 |
| Diiodomethane | 50.8 | 103 | 11.0 |
| Glycerol | 63.4 | 102 | 16.3 |
| Water | 72.8 | 105 (?) | (19.8) |
| | | Average | 12.3 ± 0.2 |

Table 2. Surface tensions, $\sigma_S$, of a number of solids.

| Solid | $\sigma_S$ found [dynes/cm] [54] | $\sigma_S$ calc. [dynes/cm] [56] | Number of measurements |
|---|---|---|---|
| Polychlorotrifluoroethylene [57] | 30.0 ± 0.8 | 38 | 9 |
| Polytetrafluoroethylene (DuPont) *(21)* [58, 59] | 18.8 ± 0.3 | 24 (21) | 24 |
| Perfluorolauric acid *(16)* $C_{11}H_{23}COOH$ [55] | 12.3 ± 0.2 | 13 | 45 |
| Stearic acid *(22)* $C_{17}F_{35}COOH$ [60] | 21.8 ± 0.4 | — | 17 |
| Pentafluorononadecanoic acid *(11)* $CF_3-CF_2-(CH_2)_{16}-COOH$ [61] | 17.9 ± 0.3 | — | 18 |
| Heptafluoroeicosanoic acid *(23)* $CF_3-(CF_2)_2-(CH_2)_{16}-COOH$ [61] | 17.6 ± 0.3 | — | 16 |
| Undecafluorodocosanoic acid *(18)* $CF_3-(CF_2)_4-(CH_2)_{16}-COOH$ [61] | 14.7 ± 0.3 | — | 16 |
| Pentadecafluorotetracosanoic acid *(17)* $CF_3-(CF_2)_6-(CH_2)_{16}-COOH$ [61] | 13.1 ± 0.3 | — | 27 |
| Perfluorostearic acid *(24)* $C_{17}F_{35}COOH$ [60] | 8.8 ± 0.3 | — | 9 |

and that $\sigma_S$ converges towards a limiting value for very long perfluorinated chains.

The discussion of the wetting equilibrium has so far related to solids with low energies, in which the contact angle with liquids is a function of the chemical constitution of the solid, which is expressed in the surface tension $\sigma_S$. High-energy solids, *i.e.* those whose surface tensions are greater than that of water, generally are covered with an adsorbed film of atmospheric moisture, since the adsorption is accompanied by a gain in energy. To extend the present examination to cases of this kind, contact angle measurements were carried out on the cubic faces of potassium bromide, sodium chloride, and lithium fluoride against liquid mercury under a pressure of $10^{-4}$ mm Hg[*]. To remove the adsorbed aqueous film, the crystals were heated to about 500 °C at the working pressure before the measurements were carried out. After cooling, all three crystals gave the same contact angle as before (about 132–135 °). It can be concluded, therefore, that the crystal faces, which were undoubtedly cleaned at 500 °C[62], readsorbed some residual gas on cooling.

An attempt to measure contact angles at higher temperatures met with some success. It was found that the contact angles of the three crystals against mercury were not very strongly dependent on temperature between 150 and 200 °C, and showed a rapid increase only below 150 °C. Following *Johnson* and *Dettre*[63], special attention was paid to the receding angles $\vartheta_R$, which in the case of partial coverage of the surface by adsorbed substances characterize mainly the sites of higher surface tension of the solid. The measured values of the contact angle $\vartheta_R$ are listed in Table 3; however, the evaluation cannot be carried out mathematically from the equation of state, since the validity of the latter has only been

[56] *R. J. Good* in [31], p. 74.

[57] *H. W. Fox* and *W. A. Zisman*, J. Colloid Sci. *7*, 109 (152).

[58] *A. H. Elltson* and *W. A. Zisman*, J. physic. Chem. *58*, 260 (1954).

[59] *L. M. Schwarz*, *C. A. Rader*, and *E. Huey*, in [31], p. 250.

[60] *E. G. Shafrin* and *W. A. Zisman*, J. physic. Chem. *61*, 1064 (1957).

[61] *E. G. Shafin* and *W. A. Zisman*, J. physic. Chem. *66*, 740 (1962).

[*] The apparatus will shortly be described by *O. Driedger*.

[62] *H. Bethge*, Physica Status solidi *2*, 3 (1962).

[63] *R. E. Johnson* and *R. H. Dettre*, J. physic. Chem. *68*, 1744 (1964).

established for a relatively narrow energy range. The evaluation is therefore most easily carried out with the aid of the isotensoliquid of mercury.

Table 3. Contact angles of mercury against the {100} faces of alkali halides, and the corresponding solid surface tensions, $\sigma_S$ (measured at 150–180 °C, calculated values refer to room temperature).

| | $\vartheta_R$ [deg] | $\sigma_{SHg}$ exp. [dynes/cm] | $\sigma_S$ calc. [dynes/cm] [3] |
|---|---|---|---|
| KBr | 120 | 120 | 135 |
| NaCl | 115 | 138 | 170 |
| LiF | 104 | 181 | 354 |

As can be seen from Fig. 4, the isotensoliquids become almost linear with increasing surface tension, and exhibit an appreciable curvature only at low solid surface tensions, if at all. To determine any curvature present, the contact angles of mercury against Teflon, polystyrene, and a polyamide (Ultramid) were measured and plotted (Fig. 7) against the known surface tension of these solids. Since the points almost lie on the straight line joining the points (0; −1) and (480; +1), the isotensoliquid of mercury is fixed. It is possible, with the

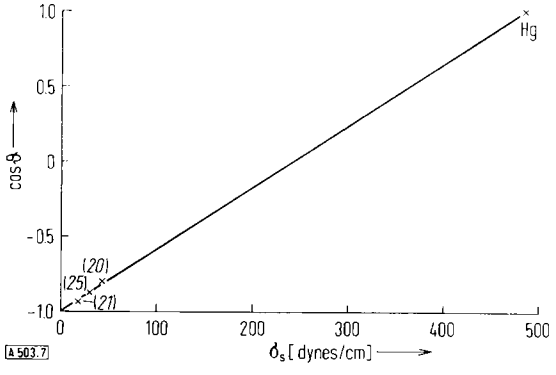



Fig. 7. Isotensoliquid of mercury at room temperature against *(21)* (see Table 2), *(25)*: polystyrene (BASF), *(20)*: see caption to Fig. 4.

aid of this line, to convert the contact angles listed in Table 3 into the desired surface tensions of the solids. The measured values for KBr and NaCl are somewhat lower than those calculated; the difference is slightly less if the temperature at which the measurements are carried out (150–180 °C) is taken into account, since the calculated values refer to room temperature. The discrepancy between the measured and the calculated value for LiF cannot be explained at present; it could be due to strong adsorption of residual gas on cooling.



The above concepts permit the determination of important interfacial energies, and provide an answer to the question of how far the various interfacial phenomena are determined by interfacial energies and to what extent directly by specific actions of intermolecular forces.

Parallels between coefficient of friction and adhesive strength appear to be due to the fact that both phenomena depend on interfacial energy relationships. The adhesive strength increases with decreasing interfacial tension between the adhesive and the adherend [53], just as the coefficient of friction increases with increasing surface tension of the solid [64]. Ordinary liquids and their vapors are surface active on solid surfaces; investigation of the wetting equilibrium permits a quantitative treatment of the phenomena observed [65]. Sedimentation and related phenomena in connection with powdered solids of low energy are dependent primarily on interfacial energies, as shown by the dependence of the sedimentation volume on the surface tension of the liquid in which the sedimentation takes place [66]. The surface tension of solid paints and varnishes evidently plays an important part in the processes of soiling, cleaning, and above all corrosion [67].

Equation (20) relates to the wetting equilibrium between a pure liquid and a solid. It can also be applied to solid/liquid/liquid systems, but it apparently does not characterize these completely [68]. Investigation of the temperature-dependence of contact angles (and of the surface tension of liquids) gives the temperature dependence of the surface tension of solids and solid/liquid interfacial tensions, *i.e.* the corresponding entropies [69, 70]; this makes possible a thermodynamic study of interfacial phenomena.

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Translated by Express Translation Service, London

[64] *P.-J. Sell*, Lecture to the 4th International Congress on Surface Active Substances, Brussels 1964.

[65] *O. Driedger* and *A. W. Neumann*, Tenside *1*, 3 (1964).

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[67] *Th. Steudel*, Farbe u. Lack *71*, 366 (1965).

[68] *O. Driedger* and *A. W. Neumann*, Tenside *2*, 325 (1965).

[69] *A. W. Neumann*, Lecture to the 4th International Congress on Surface Active Substances, Brussels 1964.

[70] *A. W. Neumann*, Kolloid-Z. and Z. Polymere *202*, 56 (1965); Lecture to the 3rd International Symposium on Surface Active Substances, Berlin, March 1966.

## Reaction of Alkylidenephosphoranes with Halogenoacetic Esters

By Prof. Dr. H. J. Bestmann, Dr. K. Rostock, and cand. chem. H. Dornauer

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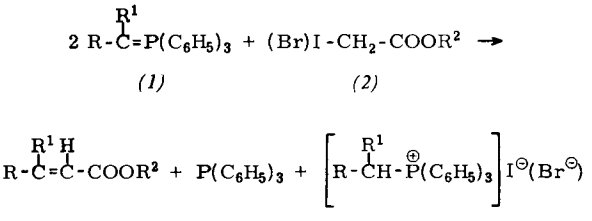
The halogen atom is decisive for the mode of reaction of alkylidenephosphoranes *(1)* with halogenoacetic esters.

1. On treating compounds *(1)* (salt-free solutions in boiling tetrahydrofuran or benzene[1]) with iodo- or bromo-acetic esters *(2)*, one obtains α,β-unsaturated carboxylic esters *(3)*, triphenylphosphine *(4)*, and a phosphonium salt *(5)*.

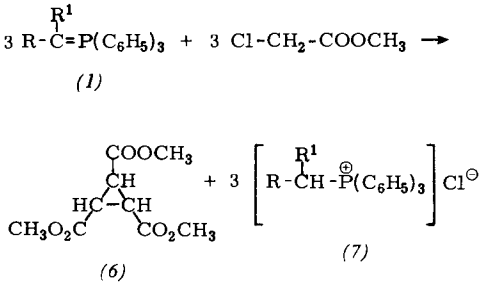


*(1)* *(2)* *(3)* *(4)* *(5)*

| R | $R^1$ | Halogen in *(2)* | Acid in *(3)* | B.p. of *(3)* [°C/mm Hg] | Yield of *(3)* [%] |
|---|---|---|---|---|---|
| $C_6H_5$ | H | Br | Cinnamic | 95/0.3 | 74 |
| *p*-$ClC_6H_4$ | H | Br | 4-Chlorocinnamic | 115/0.3 | 80 |
| n-$C_3H_7$ | H | Br | 2-Hexenoic | 32/0.2 | 50 |
| $C_6H_5CH_2CH_2$ | H | I | 5-Phenyl-2-pentenoic | 150/0.4 | 71 |
| cyclo-$C_6H_{11}$ | H | I | 3-Cyclohexylacrylic | 75/0.3 | 60 |
| $C_6H_5$ | $CH_3$ | Br | β-Methylcinnamic | 127/10 | 59 |

Other α-halogenocarboxylic esters can be used in place of bromo- or iodo-acetic esters. Thus *(1)*, R = $C_6H_5$, $R^1$ = H, and ethyl α-bromopropionate afford the α-methylcinnamic ester in 59 % yield.

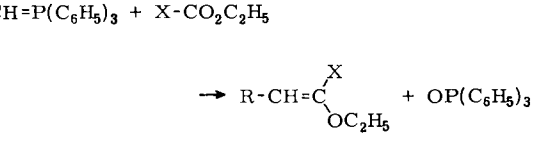
2. Trimethyl *trans*-cyclopropanetricarboxylate *(6)* and the corresponding phosphonium chloride are obtained in 55 % yield from alkylidenephosphoranes *(1)* and methyl chloroacetate in n-pentane at room temperature.



*(6)* *(7)*

The reaction does not involve a carbene intermediate. Presence of cyclohexene does not lead to formation of a norcaranecarboxylic ester. If the reaction mixture is treated with dimethyl fumarate fully deuterated at the double bond, deuterium is found in the product *(6)*.

3. Ethyl fluoroacetate and alkylidenephosphoranes (salt-free in boiling benzene[1]) undergo a Wittig reaction at the carbonyl group[2]. Enol ethers *(8)* of fluoroketones are obtained. Enol ethers *(9)* of trifluoroketones result analogously from ethyl trifluoroacetate and alkylidenephosphoranes.



*(8)*, X = $CH_2F$
*(9)*, X = $CF_3$

| R | X | B.p. of *(8)* or *(9)* [°C/mm Hg] | Yield [%] of *(8)* or *(9)* |
|---|---|---|---|
| $C_6H_5$– | $CH_2F$ | 78/0.4 | 65 |
| $C_6H_5$–$(CH_2)_2$– | $CH_2F$ | 88/0.4 | 45 |
| $CH_3$–$(CH_2)_2$– | $CH_2F$ | 50/13 | 50 |
| $C_6H_5$– | $CF_3$ | 84/13 | 82 |
| $C_6H_5$–$(CH_2)_2$– | $CF_3$ | 111/13 | 71 |
| $CH_3$–$(CH_2)_2$– | $CF_3$ | 36/13 | 59 |
| cyclo-$C_6H_{11}$ | $CF_3$ | 72/13 | 76 |

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[1] *H. J. Bestmann*, Angew. Chem. *77*, 609 (1965); Angew. Chem. internat. Edit. *4*, 583 (1965).

[2] At the IUPAC Symposium on Organophosphorus Compounds in Heidelberg in 1964, *H. Machleidt* and *W. Grell* reported ester-alkenylation of diethyl oxalate with ethoxycarbonylidenetriphenylphosphoranes and ester-alkenylation with derivatives of ethyl diethoxyphosphinylacetate. *H. Machleidt* and *W. Grell*, Liebigs Ann. Chem. *609*, 79 (1965).

## One-Step Syntheses of Fused Pyrimidinethiones[1]

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Previously available methods for the preparation of fused pyrimidinethiones involve either laborious and inefficient multistage syntheses, or drastic conditions. We have now found that fused pyrimidinethiones may be prepared from *o*-aminonitriles, ethyl orthoformate, and NaHS in a one-step reaction which proceeds in high yield and under mild conditions. 3.0 g of an *o*-aminonitrile is refluxed either with a mixture of 30 ml of ethyl orthoformate and 30 ml of acetic anhydride, or with 30 ml of ethyl orthoformate alone[2], for 1–3 hours. Evaporation of the reaction mixture under reduced pressure gives the intermediate, crude ethoxymethyleneamino derivative which, without further purification, is treated with 100 ml of a 1.5 N solution of sodium hydrosulfide in anhydrous ethanol. The reaction mixture is refluxed for 10–12 hours, evaporated to dryness and the residual solid taken up in hot water, treated with charcoal, filtered and acidified with glacial acetic acid. The fused pyrimidinethione precipitates in an extremely high state of purity and in yields often in excess of 90 % (see Table).

The effectiveness of this method may be illustrated by the synthesis of 4(5*H*)-pyrazolo[3,4-*d*]pyrimidinethione. This compound has previously been prepared[3] from 3-amino-4-cyanopyrazole by a 4-step sequence involving initial hydrolysis of the nitrile with concentrated sulfuric acid to the amide, cyclization with formamide to 4(5*H*)-pyrazolo[3,4-*d*]pyrimidinone, then to the 4-chloro derivative with phosphorus oxychloride, and finally conversion to the thione with thiourea. Direct conversion of the pyrimidinone to the thione with phosphorus pentasulfide proved even less satisfactory[3]. By

| o-Aminonitrile | Pyrimidinethione | Time [hrs.] | Yield [%] | m.p. [°C] |
|---|---|---|---|---|
| 4-Amino-1-benzyl-3-cyanopiperidine | 2-Benzyl-1,2,3,4-tetrahydro-8(7*H*)-pyridino[4,3-*d*]pyrimidinethione | 1 | 81 | 220–225 (decomp.) |
| 3-Amino-4-cyanopyrazole | 4(5*H*)-Pyrazolo[3,4-*d*]-pyrimidinethione | 3 | 97 | 354–356 (decomp.) |
| 5-Amino-4-cyano-1-methylpyrazole | 1-Methyl-4(5*H*)-pyrazolo[3,4-*d*]-pyrimidinethione | 2 | 91 | 309–311 (decomp.) |
| 5-Amino-4-cyano-1-phenylpyrazole | 1-Phenyl-4(5*H*)-pyrazolo[3,4-*d*]-pyrimidinethione | 2 | 94 | 280–282 (decomp.) |
| 4-Amino-5-cyanopyrimidine | 4(3*H*)-Pyrimido-[4,5-*d*]pyrimidinethione | 2 | 69 | > 360 |
| 2-Aminobenzonitrile | 4(3*H*)-Quinazolinethione | 2 | 73 | 326–330 (decomp.) |
| 1-Amino-2-cyanocyclopent-1-ene | 7(6*H*)-Cyclopenteno-[*d*]pyrimidinethione | 1 | 70 | 275–277 (decomp.) |
| 1-Amino-2-cyanocyclohex-1-ene | 8(7*H*)-Cyclohexeno-[*d*]pyrimidinethione | 0.75 | 68 | 268–274 (decomp.) |

contrast, 4(5*H*)-pyrazolo[3,4-*d*]pyrimidinethione may be prepared from 3-amino-4-cyanopyrazole by our procedure in a single step in 97 % yield; the product is analytically pure as isolated directly from the reaction mixture.

A second one-step synthesis of fused pyrimidinethiones, although less advantageous and involving more strenuous conditions, consists of the reaction of *o*-aminonitriles with phenyl isothiocyanate in acidic medium. Heating 1.2 g of 2-aminobenzonitrile and 1.4 g of phenylisothiocyanate in 15 ml of dimethylformamide (saturated at 0 °C with dry HCl) at 85 °C for 15 hrs. results in gradual dissolution followed by separation of a yellow solid. Evaporation under reduced pressure, trituration of the residue with water, filtration and recrystallization from methanol gives 1.3 g (79 %) of 4(3*H*)-quinazolinethione, m.p. 326–330 °C (decomp.). Similarly, 5-amino-4-cyano-1-methylpyrazole is converted into 1-methyl-4(5*H*)-pyrazolo[3,4-*d*]pyrimidinethione in 67 % yield, and 5-amino-4-cyano-1-phenylpyrazole to 1-phenyl-4(5*H*)-pyrazolo[3,4-*d*]pyrimidinethione in 48 % yield.

With the use of $^{14}C$-labelled dimethylformamide it was shown that the C-2 atom of 4(3*H*)-quinazolinethione originated from the dimethylformamide and not from the phenyl isothiocyanate. The reaction sequence probably involves nucleophilic attack of phenyl isothiocyanate upon the protonated *o*-aminonitrile to give thioanthranilamide, which then undergoes formylation by the dimethylformamide/hydrogen chloride mixture and subsequent cyclization. Strong support for this interpretation was found in the reaction of 4-amino-5-cyanopyrimidine with phenyl isothiocyanate and dimethylformamide/hydrogen chloride to give a 57 % yield of 4-aminopyrimidine-5-thiocarboxamide, which did not undergo subsequent formylation and cyclization, apparently because of decreased nucleophilicity of the 4-amino group.

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German version: Angew. Chem. *78*, 332 (1966)

[1] This work was supported by grants from the Smith Kline and French Laboratories and the National Cancer Institute, National Institutes of Health, Public Health Service (Grant CA-02551).

[2] A mixture of equal volumes of ethyl orthoformate and acetic anhydride is the reagent of choice for the formation of ethoxymethyleneamino derivatives. However, in some cases (3-amino-4-cyanopyrazole, 2-aminobenzonitrile, 1-amino-2-cyanocyclopent-1-ene) acetylation of the amino group may take precedence over formation of the latter derivative and resort must be made to the use of ethyl orthoformate alone.

[3] *C. C. Cheng* and *R. K. Robins*, J. org. Chemistry *21*, 1240 (1956).

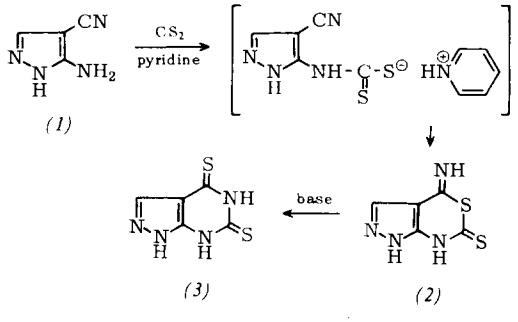
# A One-Step Synthesis of Fused Pyrimidinedithiones[1]

By Prof. Dr. E. C. Taylor, Dr. R. N. Warrener, and Dr. A. McKillop

Department of Chemistry, Princeton University, Princeton, New Jersey (U.S.A.)

The reaction of aromatic and heterocyclic *o*-aminonitriles with $CS_2$ in pyridine gives fused pyrimidinedithiones (dimercaptopyrimidines). 3.0 g of 2-aminobenzonitrile, 10 ml of $CS_2$, and 10 ml of pyridine were heated for 2 hrs. under reflux. On dilution of the reaction mixture with methanol, 4.82 g (97 %) of quinazoline-2,4(1*H*,3*H*)-dithione separated out. The other compounds listed in the Table were prepared in analogous fashion.

In order to investigate the course of this conversion, 5.00 g of 3-amino-4-cyanopyrazole *(1)*, 50 ml of $CS_2$, and 50 ml of pyridine were heated under reflux for 1 hr., whereupon 10.25 g of a yellow, crystalline pyridinium salt separated. Treatment of this salt with cold, dilute HCl gave 4(5*H*)-imino-6(7*H*)-pyrazolo[4,3-*d*]-thiazinethione *(2)*. The structure of this intermediate was established by microanalysis, by the absence of —CN absorption and the presence of a strong imine N—H band at 3510 $cm^{-1}$ in its infrared spectrum, by its ultraviolet spectrum [$\lambda_{max}^{EtOH}$ = 237, 262, 311, and 382 mμ (ε = 11,160, 12,270, 11,340, and 2,950)] and by its rearrangement in quantitative yield by 1 N sodium hydroxide to 4,6(5*H*,7*H*)-pyrazolo[3,4-*d*]pyrimidinedithione *(3)*.




*(1)* *(3)* *(2)*

| o-Aminonitrile | Pyrimidinedithione | Time [hrs.] | Yield [%] | M.p. [°C] |
|---|---|---|---|---|
| 2-Aminobenzonitrile | Quinazoline-2,4-(1*H*, 3*H*)-dithione | 2 | 97 | 335–338 (decomp.) |
| 2-Amino-5-methoxybenzonitrile | 6-Methoxyquinazoline-2,4(1*H*, 3*H*)-dithione | 1 | 99 | 350–352 (decomp.) |
| 2-Amino-5-piperidinobenzonitrile | 6-Piperidinoquinazoline-2,4(1*H*, 3*H*)-dithione | 1 | 95 | 282–285 (decomp.) |
| 2-Amino-5-bromobenzonitrile | 6-Bromoquinazoline-2,4-(1*H*, 3*H*)-dithione | 68 | 92 | > 360 |
| 4-Amino-5-cyanopyrimidine | 2,4(1*H*, 3*H*)-Pyrimido-[4,5-*d*]pyrimidinedithione | 10 | 68 | > 360 |
| 5-Amino-4-cyano-1-methylpyrazole | 1-Methyl-4,6(5*H*, 7*H*)-pyrazolo[3,4-*d*]-pyrimidinedithione | 52 | 87 | 321–323 (decomp.) |
| 5-Amino-4-cyano-1-phenylpyrazole | 1-Phenyl-4,6(5*H*, 7*H*)-pyrazolo[3,4-*d*]-pyrimidinedithione | 115 | 97 | 248–260 (decomp.) |
| 3-Amino-4-cyanopyrazole | 4,6(5*H*, 7*H*)-Pyrazolo[3,4-*d*]-pyrimidinedithione | 1 | 81 | > 360 |

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German version: Angew. Chem. *78*, 333 (1966)

[1] This work was supported by grants from the Smith Kline and French Laboratories and the National Cancer Institute, National Institutes of Health, Public Health Service (Grant CA-02551).

## Syntheses of Peptides by Means of Activated Units Bound to Resins [*]

By Prof Dr. Th. Wieland and Dipl.-Chem. Ch. Birr

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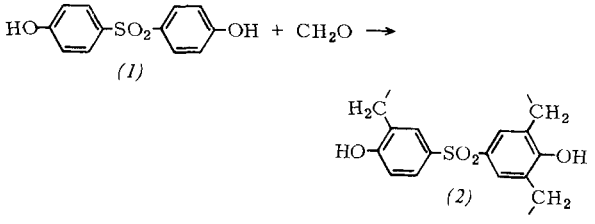
Frankfurt/Main (Germany)

Amino acids can be bound, in ester form, to polymers containing strongly acidic (*e.g.*, phenolic) hydroxyl groups and can then be used as "activated" amino acids for peptide syntheses. We have used a gel *(2)* prepared [2] by cross-linking *p,p'*-dihydroxydiphenyl sulfone *(1)* [1].



*(1)*

*(2)*

The capacity of this new phenoplast for acyl residues is 4.2 mmole/g (calc. 6.7 mmole/g) when loaded by reaction of its lithium salt with benzoyl chloride in tetrahydrofuran (THF). For *N*-benzyloxycarbonylamino acids the capacity is 0.8–1 mmole/g when loaded with dicyclohexylcarbodiimide [3] in THF or dimethylformamide (DMF), or 1.2 mmole/g when activated by the mixed anhydride method [4] in THF, or 0.9–1.1 mmole/g after activation of the resin with thionyl chloride. For the last-mentioned type of activation the $Li^+$ form of the resin, swollen in THF, is allowed to react as two equivalents of thionyl chloride in THF percolate through it, the excess of chloride being then washed out and the acid to be activated then allowed to react in the presence of an excess of triethylamine in THF at 20 °C for about 2 h. The resin can also be activated by reaction with phosgene.

An ester of a carboxylic acid and the phenoplast affords the carboxyamide when percolated in the column by a solution of the amine component in DMF at 20 °C. Thus with L-phenylalanine methyl ester as amine component, the benzyloxycarbonylglycyl resin, the t-butoxycarbonyl-L-alanyl resin, or the t-butoxycarbonylleucyl resin afford, respectively, benzyloxycarbonylglycyl-L-phenylalanine methyl ester (m.p. 97 °C, 56 % yield), t-butoxycarbonyl-L-alanyl-L-phenylalanine methyl ester (oil, 65 %), or t-butoxycarbonyl-L-leucyl-L-phenylalanine methyl ester (m.p. 146 °C, 63 %). Reaction of the benzyloxyglycyl resin with L-valyl-L-phenylalanine methyl ester afforded the tripeptide ester, which on hydrolysis of the ester group gave benzyloxycarbonylglycylvalylphenylalanine in 71 % yield, calculated on the amount of dipeptide ester used. The peptide syntheses could also be effected with the Na salts of the amino acids in formamide.

*Katchalski et al.* [5] recently reported the cyclization of peptides by a method also involving use of carboxyl groups activated on a resin (nitrated poly-*p*-hydroxystyrene).

Received: December 2nd, 1965 [Z 132/963 IE]
German version: Angew. Chem. *78*, 303 (1966)

[*] Part 34 of Peptide Syntheses. – Part 33: *Th. Wieland* and *W. Kahle*, Liebigs Ann. Chem., in press.

[1] *E. Überbacher*, German Patent 728276 (Dec. 3rd, 1940/Nov. 24th, 1942).

[2] Analogously to the procedure of *T. R. E. Kressmann* and *J. A. Kitchener*, J. chem. Soc. (London) *1949*, 1190.

[3] *J. C. Sheehan* and *G. P. Hess*, J. Amer. chem. Soc. *77*, 1067 (1955).

[4] *Th. Wieland* and *H. Bernhard*, Liebigs Ann. Chem. *572*, 190 (1951).

[5] *M. Fridkin*, *A. Patchornik*, and *E. Katchalski*, J. Amer. chem. Soc. *87*, 4646 (1965).

## Volume Change as Indicator for Reactions in Solution

By Prof. Dr. K. F. Jahr, Dipl.-Chem. E. Gegner [1], Dr. G. Wiese, and Dr. J. Fuchs

Institut für Anorganische Chemie der Freien Universität
Berlin (Germany)

Reactions in solution generally are accompanied by volume changes caused by a change in the nature of the solute particles. Previously it has not been possible to measure these changes continuously during a titration. With the aid of a new apparatus we have succeeded in using the volume change as endpoint indicator of reactions in solution.

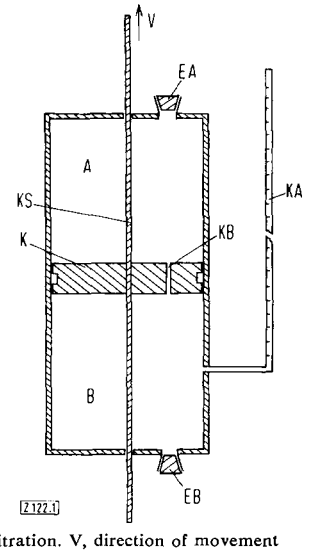



Fig. 1. Apparatus for dilatometric titration. V, direction of movement of piston K; KS, push rod; EA, EB, filling apertures; KA, KB, capillaries.

Figure 1 shows the principle of the apparatus. The initial solution (in compartment B) and the titrant (in compartment A) are gradually mixed in a syringe buret [2] by raising the piston K which contains a capillary hole KB. The volume of titrant solution entering B is proportional to the displacement of the piston K, which is measured mechanically; the proportionality factor is determined by calibration. The volume changes caused by the resulting reaction are indicated by a change in the height of the meniscus in the calibrated measuring capillary KA.

We have used this dilatometric indication for determination of the endpoint in neutralization, precipitation, redox, complex formation, and aggregation reactions. Accuracy, time required, and expenditure for apparatus are comparable to those of the usual physicochemical indicator procedures. An example of a dilatometric titration, the precipitation of sulfate ions by barium ions, is given in Figure 2.

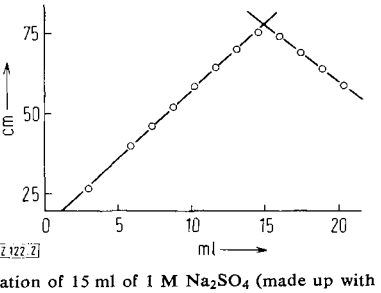



Fig. 2. Dilatometric titration of 15 ml of 1 M $Na_2SO_4$ (made up with water to the initial volume of compartment B) with 1 M $BaCl_2$ (in compartment A).
Abscissa: Consumption (ml) of $BaCl_2$ solution.
Ordinate: Position of meniscus in capillary KA (cm).

Received: December 16th, 1965 [Z 122/969 IE]
German version: Angew. Chem. *78*, 304 (1966)

[1] *E. Gegner*, Dissertation, Freie Universität Berlin, 1965.

[2] *G. Wiese*, German Patent Appl. W 40 274 III/12e.

## Excited-State Reactions of 1,2,4,5-Tetramethyl-3,5-cyclohexadiene-cis-1,2-dicarboxylic Anhydride

By Dr. R. N. Warrener and J. B. Bremner

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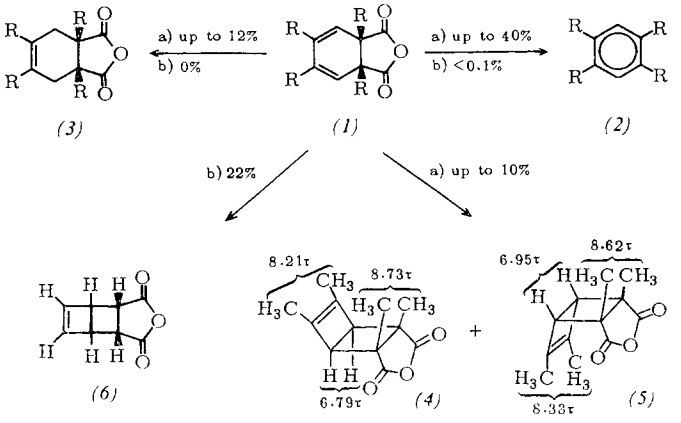
Ultraviolet irradiation[1] of the title diene *(1a)*[2] in ether gave the products *(2a)*–*(5a)* together with two unidentified compounds.




a) R = $CH_3$
b) R = H

We consider that the novel fragmentation of *(1a)* into durene *(2a)*, CO, and $CO_2$ is due to a multicenter valence-electron redistribution[3] of the excited-state diene, rather than a consequence of the anhydride group itself. This accounts for the photolytic stability of the reduction product *(3a)*. The source of the hydrogen atoms in *(3a)* is not certain, although solvent participation seems unlikely since *(3a)* is also formed with carbon tetrachloride as solvent.

Disrotatory electrocyclic ring closure, a favored photoreaction in the diene system of *(1a)*[4], accounts for the formation of both valence isomers *(4a)* (m.p. 150–151 °C) and *(5a)* (m.p. 100–101 °C). These structures are supported by thermal reconversion into the initial diene *(1a)*. The stereochemical assignments were based on the NMR spectra of *(4a)* and *(5a)*.

These results are in contrast with the photolysis pattern of the parent dienedicarboxylic anhydride *(1b)*[5]. In this case, photoaromatization is a minor reaction (< 0.1 %), no reduction product *(3b)* is observed and only a single valence isomer *(6)* is formed of unknown stereochemistry.

Vapour phase pyrolysis (800 ± 15 °C at 0.1 mm) of the diene *(1a)* also yielded durene (40 %), CO, and $CO_2$. This reaction may, however, be due to simple thermal anhydride fragmentation[5a]. A preliminary investigation[6] of the mass spectrum of *(1a)* showed that a unimolecular fragmentation of the parent ion (mass 206) to the durene molecular ion with loss of 72 mass units (CO + $CO_2$) is a major decomposition pathway.

Received: December 20th, 1965 [Z 137/967 IE]
German version: Angew. Chem. *78*, 305 (1966)

[1] At 15–20 °C in dilute solution (1–2%) under argon; Hanovia 450 watt high-pressure Hg lamp, water cooled quartz cylinder with a Vycor filter.

[2] Prepared after the method of *K. Ziegler*, German Patent 875573 (1953).

[3] For further details see *R. N. Warrener* and *J. B. Bremner*, Rev. pure appl. Chem., in the press.

[4] *R. B. Woodward* and *R. Hoffmann*, J. Amer. chem. Soc. *87*, 395 (1965).

[5] *E. E. van Tamelen* and *S. P. Pappas*, J. Amer. chem. Soc. *85*, 3297 (1963).

[5a] *F. O. Rice* and *M.T. Murphy*, J. Amer. chem. Soc. *64*, 896 (1942).

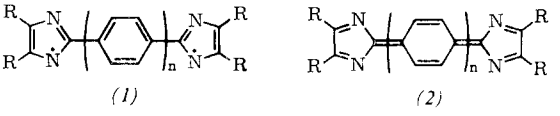
[6] We thank Dr. *C. S. Barnes*, C.S.R. Research Laboratories, Roseville, N.S.W. (Australia), for the mass spectra.

## Biradicals, Quinones, and Semiquinones of the Imidazole Series

By Dipl.-Chem. U. Mayer, Dr. H. Baumgärtel, and Prof. Dr. H. Zimmermann

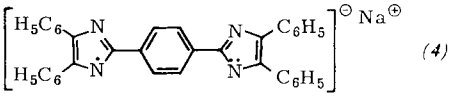
Institut für Organische Chemie der Universität München (Germany)

Biradicals of the imidazolyl series can occur as paramagnetic biradicals *(1)* or as diamagnetic quinonoid molecules *(2)*.

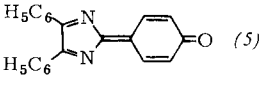



The homologous series of compounds *(2)* can be considered as derived from tetraazafulvalene. The first representative of this class of compound has now been prepared. When the disodium salt *(3)* of 1,4-bis-(4,5-diphenyl-2-imidazolyl)-benzene[1] is treated with bromine in methylene chloride, sodium bromide separates and 3,6-bis(4,5-diphenyl-2-imidazolylidene)-1,4-cyclohexadiene *(2)* (n = 1, R = phenyl), blue crystals, long wavelength absorption in $CHCl_3$ at $\lambda$ = 602 mμ, log ε = 4.95) is formed. This product contains some of the paramagnetic form but consists mainly of the diamagnetic quinonoid form.

Treatment of *(2)* with the disodium salt *(3)* in acetone affords the red, unstable semiquinone *(4)*, whose paramagnetism was detected by ESR spectroscopy in a stop-flow apparatus.

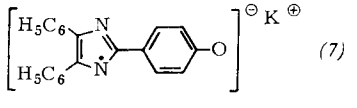



We have also prepared 4-(4,5-diphenyl-2-imidazolylidene)-2,5-cyclohexadienone *(5)* by dehydrogenation of *p*-(4,5-diphenyl-2-imidazolyl)phenol *(6)*[2] with lead dioxide in anhydrous ether. This compound forms red crystals, decomp.




at 155 °C, having long-wavelength absorption in $CHCl_3$ at $\lambda$ = 440 mμ, log ε = 4.64.

Treatment of *(5)* with the dipotassium salt of the phenol *(6)* in dioxane also gives a short-lived, green semiquinone *(7)*, which was detected by ESR spectroscopy.




The quinonoid molecules *(2)* and *(5)* were titrated with hydroquinone, which regenerated the starting materials *(3)* and *(5)*.

Received: December 20th, 1965 [Z 131/962 IE]
German version: Angew. Chem. *78*, 303 (1966)

[1] *T. Drefahl* and *W. Schmermer*, J. prakt. Chem. [4] *23*, 225 (1964).

[2] *Sh. Kori* and *Sh. Narisawa*, Asahi Garasu Kenkyu Hokoku *12*, 55 (1962); Chem. Abstr. *59*, 1622a (1963).

## Isosteres of Hexamethyldisiloxane and Tris(trimethylsilyl)amine

By Priv.-Doz. Dr. H. Schmidbaur and cand. chem. W. Wolfsberger

Institut für Anorganische Chemie der Universität Würzburg (Germany)

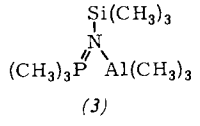
For the preparation of an isostere *(3)* of tris(trimethylsilyl)-amine *(2)* we required *P*-trimethyl-*N*-trimethylsilyliminophosphorane *(1)*. The latter is readily accessible from trimethylsilyl azide and trimethylphosphine[1,2]:

$$(CH_3)_3Si{-}N_3 + (CH_3)_3P \rightarrow N_2 + (CH_3)_3Si{-}N{=}P(CH_3)_3 \quad (1)$$

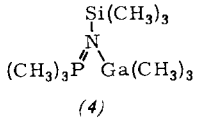
| A B | M.p. [°C] | B.p. [°C/mm] | NMR δ(CH₃)A [cps] | NMR δ(CH₃)B [cps] |
|---|---|---|---|---|
| $(CH_3)_3SiOSi(CH_3)_3$ | −56 | 100.5/760 | 3.5 | −3.5 |
| $(CH_3)_3SiNP(CH_3)_3$ *(1)* | 3–4 | 169/760 | +6.4 [c] | −80.8 [b] |
| $(CH_3)_3AlOP(CH_3)_3$ | +89 | 117/1 | [a] | [a] |

[a] Not measurable in $CCl_4$. [b] $J(^1H{-}C{-}^{31}P) = 12.4$. [c] $J(^1H{-}C{-}^{29}Si) = 6.4$.

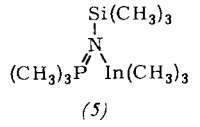
Compound *(1)* is a third[3] isostere of hexamethyldisiloxane. When warmed for a short time with trimethylaluminum etherate it affords *(3)*, in which, for the first time, the three neighbours Al, Si, and P in the Periodic Table are bound to the same nitrogen atom. Compound *(3)* is remarkably stable and does not dissociate even on vacuum distillation. The crystals are sensitive to oxidation and hydrolysis, are readily soluble in organic solvents that do not contain active protons, and give the simple molecular weight in benzene. Three signals of equal area appear in the $^1H$-NMR spectrum, one being a doublet due to $^1H$-C-$^{31}P$ coupling.



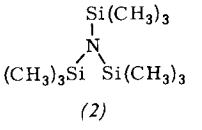
*(3)*



*(4)*



*(5)*



*(2)*

On reaction with trimethyl-gallium or -indium etherate in place of the aluminum compound, *(1)* affords *(4)* and *(5)*, respectively, in quantitative yield. The continuous decrease in chemical shifts and coupling constants along the series *(1)*, *(3)*, *(4)*, *(5)* shows that the bond order of P–N is higher than that of Si–N and that the acceptor strength of organometallic compounds decreases in the order $(CH_3)_3Al > (CH_3)_3Ga > (CH_3)_3In$.

| | *(3)* | *(4)* | *(5)* |
|---|---|---|---|
| M.p. [°C] | 79–80 | 32–34 | 43–44 |
| B.p. [°C/mm Hg] | 120/1 | 56/0.1 (decomp.) | — |
| NMR [4]: δ($CH_3Si$) | − 13.2 | 9.0 | − 6.6 |
| δ($CH_3P$) | −104.0 | −98.2 | −95.6 |
| δ($CH_3M$) | + 61.0 | +36.5 | +32.5 |
| $J(^1H{-}C{-}^{31}P)$ | 12.8 | 12.7 | 12.6 |
| $J(^1H{-}C{-}^{29}Si)$ | 6.6 | 6.55 | 6.5 |

*P*-triethyl-*N*-trimethylsilyliminophosphorane[2] yields, analogously, the *P*-triethyl homologues of *(3)* and *(4)*: *(3)* $(CH_3)_3SiNP(C_2H_5)_3{\cdot}Al(CH_3)_3$, m.p. 169 °C, subl. at 135 °C/1 mm; *(4)* $(CH_3)_3SiNP(C_2H_5)_3{\cdot}Ga(CH_3)_3$, m.p. 114 °C.

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German version: Angew. Chem. *78*, 306 (1966)

[1] *H. Staudinger* and *J. Meyer*, Helv. chim. Acta *2*, 635 (1919); *H. Staudinger* and *E. Hauser*, *ibid.* *4*, 861 (1921); *E. Bergmann* and *H. A. Wolff*, Ber. dtsch. chem. Ges. *63*, 1176 (1930).

[2] *L. Birkofer*, *A. Ritter*, and *S. M. Kim*, Chem. Ber. *97*, 2100 (1964).

[3] *F. Schindler*, *H. Schmidbaur*, and *G. Jonas*, Angew. Chem. *77*, 170 (1965); Angew. Chem. internat. Edit. *4*, 152 (1965); Chem. Ber. *98*, 3345 (1965).

[4] 60 Mc/s, $CCl_4$ solution, 30 °C, tetramethylsilane as internal standard.

## Hydrogallinations

By Priv.-Doz. Dr. H. Schmidbaur and cand. chem. H. F. Klein

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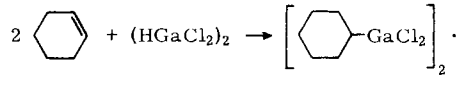
Addition of boron and aluminum hydrides to olefins is of great practical importance. Analogous addition of gallium hydrides has not previously been observed.

We have found that dichlorogallane $HGaCl_2$[1] reacts with olefins even under mild conditions, forming organogallium dihalides $RGaCl_2$[2]. A solution of $HGaCl_2$ (obtained from gallium trichloride and trimethylsilane) in chlorotrimethylsilane absorbs ethylene rapidly at 0 °C, with evolution of much heat. Ethylgallium dichloride[2] (75–78 %) can be obtained from the reaction mixture by distillation in a vacuum:

$$2\,CH_2{=}CH_2 + (HGaCl_2)_2 \rightarrow (C_2H_5GaCl_2)_2$$

Cyclohexene and a suspension of dichlorogallane in cyclohexane rapidly afford cyclohexylgallium dichloride (73 %), m.p. 67–69 °C, b.p. 142 °C/1 mm:



To determine the position of the entering component we have studied the addition of propene and 1-heptene to $HGaCl_2$. In both cases homogeneous products were formed, namely, n-propyl- and n-heptyl-gallium dichloride, respectively ($C_3H_7GaCl_2$: 88 %, m.p. 39–40 °C, b.p. 120–122 °C/1 mm; $C_7H_{15}GaCl_2$: 72 %, m.p. −30 °C, b.p. 155–160 °C/1 mm). NMR spectroscopy gave no indication of the formation of isopropylgallium dichloride; the structure of heptylgallium dichloride was established by degradation to heptyl iodide by means of iodine. This result proves the anti-Markovnikoff orientation in addition of > Ga-H to the > C=C < group, this being analogous to the results of hydroboration and hydroalanations.

Hydrolysis with HCl and oxidation with $H_2O_2$ convert compounds $RGaCl_2$ into hydrocarbons RH and alcohols ROH, respectively, but the yields are generally unsatisfactory.

Carbonyl compounds are reduced by $HGaCl_2$ to alkoxygallium dihalides. In this way isopropoxygallium dichloride (b.p. 95–97 °C/1 mm) is formed from acetone:

$$2\,CH_3{-}CO{-}CH_3 + (HGaCl_2)_2 \rightarrow [(CH_3)_2CH{-}O{-}GaCl_2]_2$$

Hydrolysis of these compounds leads to the alcohols without difficulty.

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German version: Angew. Chem. *78*, 306 (1966)

[1] *H. Schmidbaur* and *W. Findeiss*, Angew. Chem. *77*, 170 (1965); Angew. Chem. internat. Edt. *4*, 152 (1965).

[2] *H. Schmidbaur* and *W. Findeiss*, Angew. Chem. *76*, 752, 753 (1964); Angew. Chem. internat. Edit. *3*, 696, 696 (1964).

## Organogallogermoxanes, Compounds Containing the Structural Unit Ga-O-Ge

By Priv.-Doz. Dr. H. Schmidbaur and
cand. chem. Brunhilde Armer

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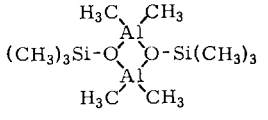
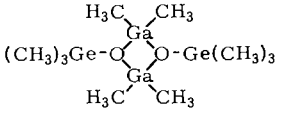
For preparation of the basic member ($R = CH_3$) of the homologous series of gallogermoxanes $R_3Ge-O-GaR_2$ we converted trimethylgallium etherate with ethereal HCl into dimethylgallium chloride: $(CH_3)_2GaCl$, m.p. 48–50 °C, b.p.164 to 165 °C, $^1$H-NMR: $\delta(CH)_3 = -16.0$ cps[1]. Treatment of $(CH_3)_2GaCl$ with lithium trimethylgemanolate in diethyl ether, removal of the separated LiCl, and sublimation afforded high yields of pentamethylgallogermoxane *(1)*:

$$[(CH_3)_2GaCl]_2 + 2\ LiOGe(CH_3)_3 \rightarrow 2\ LiCl + [(CH_3)_2Ga-O-Ge(CH_3)_3]_2 \qquad (1)$$

Compound *(1)* has m.p. 42–44 °C, b.p. 84–85 °C/1 mm, and, according to molecular-weight determinations in benzene, is dimeric. Its $^1$H-NMR spectrum contains the expected singlet signals of $\delta(CH_3Ga) = +25.0$ and $\delta(CH_3Ge) = -20.2$ cps (ratio of areas 2:3). Infrared-spectroscopic analogies to pentamethylalumosiloxane *(2)* permit structure *(3)* containing a four-membered ring to be assumed, and this was confirmed by X-ray analysis[2]; compound *(2)* is accordingly isomorphous with compound *(3)* and there are only slight differences in the dimensions of the unit cells. From this it is concluded that compounds *(2)* and *(3)* are isostructural, having a planar inorganic skeleton[3].



*(2)* Monoclinic, $P2_1/n$
$a = 7.008$ Å, $b = 12.220$ Å
$c \sin\beta = 10.655$ Å



*(3)* Monoclinic, $P2_1/n$
$a = 7.010$ Å, $b = 13.299$ Å
$c \sin\beta = 10.697$ Å

We have found another synthesis of compounds of the type $R_2Ga-O-GeR_3$ in the reaction of compounds $R_3GeOH$ with $GaR_3$:

$$2\ (C_6H_5)_3Ge-OH + 2\ Ga(CH_3)_3 \rightarrow 2\ CH_4 + [(C_6H_5)_3GeOGa(CH_3)_2]_2 \qquad (4)$$

*Ge*-Triphenyl-*Ga*-dimethylgallogermoxane *(4)*, like compound *(2)*, forms colorless crystals, m.p. 175–177 °C, sensitive to moisture. It is dimeric in benzene (by cryoscopy). $[(C_6H_5)_3GeOGa(C_6H_5)_2]_2$: m.p. 219–293 °C.

Received: December 22nd, 1965 [Z 127/959 IE]
German version: Angew. Chem. 78, 305 (1966)

[1] We were unable to confirm the different data of *G. E. Coates et al.* [J. chem. Soc. (London) *1963*, 243)]. All NMR data in this paper are for $CCl_4$ solutions at 30 °C and 60 Mc/s with tetramethylsilane as internal standard.

[2] We thank Dr. *P. J. Wheatley* for these investigations.

[3] *H. Schmidbaur*, J. organomet. Chemistry *1*, 28 (1963).

## Detection of the Forbidden Transition in Dimeric Carbocyanines at Low Temperatures

By Prof. Dr. G. Scheibe and Dipl.-Chem. O. Wörz

Arbeitsgemeinschaft für Strukturchemie und Physikalisch-Chemisches Institut der Technischen Hochschule
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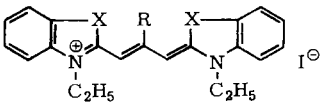
The absorption of a dimeric dye cation of carbocyanine type is shifted towards short wavelengths relative to that of the monomer[1–3]. According to a model proposed by *Förster*, the dimerization is accompanied by approximately symmetrical splitting of the principal absorption maximum, although the longer-wavelength transition is forbidden[4]. Prerequisite is that the dimer has symmetry $C_i$ (or $C_2$).



*(1a)*: R = $CH_3$; X = S; *(1c)*: R = $CH_3$; X = Se;
*(1b)*: R = $C_2H_5$; X = S; *(1d)*: R = $C_2H_5$; X = Se.

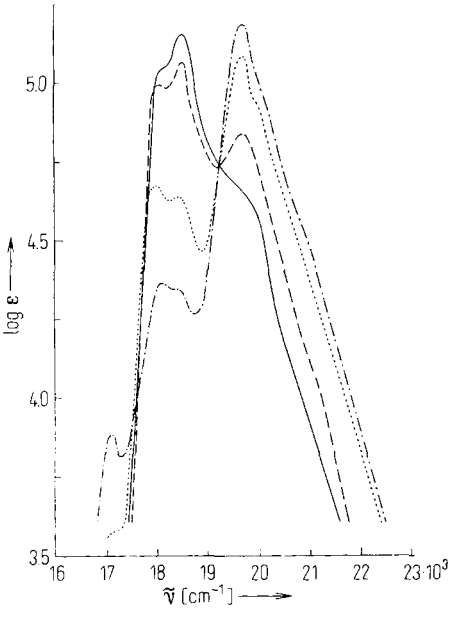



Fig. 1. Absorption spectra of *meso*-methylthiacarbocyanine iodide *(1a)* in ethanol at −180 °C. Concentrations (mole/l): $3.25\times10^{-6}$ (———); $1.33\times10^{-5}$ (– – –); $8.17\times10^{-5}$ (·····); $5.53\times10^{-4}$ (— · — · —).

If an alkyl group is introduced at the *meso*-position of certain thia- or selena-carbocyanines *(1)*, dimerization occurs in solution in 95 % aqueous ethanol at about −100 °C. The figure shows the spectra for various concentrations of *meso*-methylthiacarbocyanine iodide *(1a)* at −180 °C. With increasing concentration the monomer band decreases in intensity, and the short-wavelength, shifted, dimer band increases, but an additional, very weak, long-wavelength band also appears. The concentration dependence of the last-mentioned band, its small extinction coefficient, and its occurence at about the same distance from the monomer band as the short-wavelength dimer band (see table), lead to the conclusion that we have here the forbidden, long-wavelength dimer transition of the *Förster* model. That it can be observed is probably due to the low temperature and the fact that the *meso*-alkyl group somewhat distorts the $C_i$ (or $C_2$) symmetry of the dimer by steric hindrance and thus partly allows the transition.

Earlier attempts, by *Förster*[5] and *Levinson*[6,7], to find this band were apparently unsuccessful.

Wave numbers ($cm^{-1}$) of the absorption maxima of monomeric and dimeric thia- and selena-carbocyanines.

| Dye | Forbidden dimer transition | Monomer all-*trans*-form | Permitted dimer transition |
|---|---|---|---|
| *(1a)* | 17100 | 18500 | 19700 |
| *(1b)* | 16900 | 18300 | 19450 |
| *(1c)* | 16800 | 18150 | 19200 |
| *(1d)* | 16800 | 18000 | 19100 |

Splitting of the monomer bands was also observed; it is attributed to *cis-trans*-isomerism; the band of shorter wavelength is assigned to the all-*trans*-form, that of longer wavelength to a mono-*cis*-isomer that arises by rotation around the C-2/C-8 bond

Received: December 22nd, 1965 [Z 134/964 IE]
German version: Angew. Chem. *78*, 304 (1966)

[1] *G. Scheibe*, Z. Elektrochem. angew. physik. Chem. *47*, 73 (1941).

[2] *H. O. Dickinson*, J. photogr. Sci. *2*, 50 (1954).

[3] *G. Scheibe*, Angew. Chem. *52*, 631 (1939).

[4] *Th. Förster*, Naturwissenschaften *33*, 166 (1946).

[5] *Th. Förster* and *E. König*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 344 (1957).

[6] *G. S. Levinson, W. T. Simpson*, and *W. Curtis*, J. Amer. chem. Soc. *79*, 4314 (1957).

[7] *W. West* and *S. Pearce*, J. physic. Chem. *69*, 1894 (1965).

## Preparation of Fluoromethane in Molten Fluorides

By Dipl.-Chem. W. Verbeek and Dr. W. Sundermeyer

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Fluoromethane is usually prepared from methyl derivatives such as esters or alcohols that are cleaved by anhydrous HF or KF. Treatment of methane with fluorine leads to a difficultly separable mixture of fluorocarbons, containing mainly more highly fluorinated products. A fluorocarbon mixture is also obtained on electrofluorination of methane. Direct halogen exchange has hitherto been obtained only in the reaction of $CH_3I$ with $HgF_2$ or AgF.

We have led chloromethane, with vigorous strirring, into a LiF-NaF-KF melt at 500 °C, using an apparatus described previously[1] but with a nickel reaction vessel, inlet tube, stirrer, and thermoelement supports. $CH_3F$ resulted in 85 % yield with 42 % conversion, and was easily freed from traces of $CO_2$ and unchanged $CH_3Cl$. A yield of 96 % and conversion of 32 % can be attained if $CH_3Cl$ is led into a KF-HF melt at 350 °C. The $CH_3F$, which has thus become easily accessible, can be brominated to afford bromofluoromethanes, and these can be pyrolysed by a known method to yield hexafluorobenzene.

Reaction of $CH_2Cl_2$ with the KF-HF melt leads to $CH_2F_2$ with 82 % yield and 34 % conversion, whereas $CHCl_3$ gives, in the main, a mixture of partially substituted products.

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German version: Angew. Chem. *78*, 307 (1966)

[1] *W. Sundermeyer*, Z. anorg. allg. Chem. *313*, 290 (1962).

## Desulfuration with Hydroximoyl Chlorides

By the late Prof. Dr. A. Dornow and Dipl.-Chem. H. U. Voigt

Institut für Organische Chemie der Technischen Hochschule Hannover (Germany)

An exchange of sulfur for oxygen in good yield was observed on treatment of hydroximoyl chlorides with compounds containing a thiocarbamoyl group. The preferred hydroximoyl chloride was chlorohydroxyiminoacetic ester because of its stability and accessibility[1]. The reaction was carried out in anhydrous benzene or toluene; 1-methylpyrrolidone proved an excellent solvent for reactions of thioxo compounds, but experiments with dimethylformamide, dioxane, and nitromethane failed.

Equimolar amounts of the components were allowed to react for 5 to 12 hours at 80 to 100 °C, the solutions were concentrated, and the products were precipitated by light petroleum or water. Some examples are given in the Table.

| S-compound | Solvent [a] | Temp. (°C) | Reaction time (h) | Yield (%) of O-compound |
|---|---|---|---|---|
| *N*-2-Naphthylthiobenzamide | Benzene | 80 | 5 | 100 |
| Benzyl *N*-phenyldithiocarbamate | Benzene | 80 | 8 | 85 [b] |
| Methyl benzylidenedithiocarbazinate | Toluene | 110.8 | 10 | 80 [c] |
| Benzimidazole-2-thiol | Benzene | 80 | 10 | 95 |
| 4,5-Diphenylimidazole-2-thiol | NMP | 100 | 12 | 90 |
| 5-Methyl-1,2,4-triazoline-2-thione | NMP | 100 | 12 | 80 |
| 5-Phenyl-1,3,4-oxadiazoline-2-thione | Toluene | 110.8 | 10 | 85 |
| 6-Phenyl-3[4*H*]-thioxo-1,2,4-triazin-5[2*H*]-one | NMP | 100 | 12 | 80 |
| 4-Benzylideneamino-6-methyl-3[4*H*]thioxo-1,2,4-triazin-5[2*H*]-one | NMP | 100 | 12 | 78 |
| 3-Phenyl-2[4*H*]-thioxo-quinazolin-4[2*H*]-one | NMP | 100 | 12 | 90 |

[a] NMP = 1-methylpyrrolidone. — [b] Product: *S*-benzyl thiocarbanilate. [c] Product: *S*-methyl benzylidenethiocarbazinate.

The potential mercapto form of the thiocarbamoyl group is a prerequisite for the reaction; this group may comprise part of a ring (the sulfur being exocyclic), or it may be part of an open chain. The hydroximoyl chloride reacts with the thiol group that is in tautomeric equilibrium with the thioxo group, HCl being evolved, and the oxime group adds intramolecularly to the C=S double bond. The 1,4,2-oxathiazoles formed as intermediates in this way decompose to isothiocyanate and the O-analogue of the starting material[2]. Ready decomposition of 1,4,2-oxathiazoles was observed previously by *R. Huisgen* when he added nitrile oxides to *N,N*-disubstituted thioamides and obtained the O-products directly[3].

We have used this desulfuration repeatedly as a criterion for exocyclic sulfur, *e.g.*, with isomer pairs of 5-methyltriazole-2-thione, 5-methylthiadiazole-2-amine, and the like.

Received: January 3rd, 1966 [Z 135/965 IE]
German version: Angew. Chem. *78*, 308 (1966)

[1] *G. S. Skinner*, J. Amer. chem. Soc. *46*, 731 (1924).

[2] *A. Dornow* and *K. Fischer*, Chem. Ber., in press.

[3] *R. Huisgen*, Chem. Ber. *73*, 656 (1961).

## Acyl- and Sulfonyl-carbamoyl Azides

By Doz. Dr. R. Neidlein

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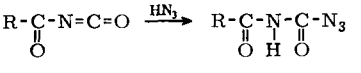
Acylcarbamoyl azides *(2)* (as far as we know not previously reported) were obtained by addition of equimolar amounts of hydrazoic acid to acyl isocyanates *(1)*[1] with stirring in cooled benzene solution.

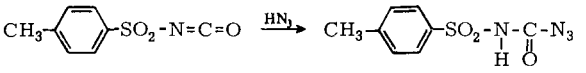


*(1)* *(2)*

| R | M.p. [°C] (decomp.) | Yield [%] |
|---|---|---|
| *(2a)* $C_6H_5-$ | 111—112 | 94 |
| *(2b)* *p*-Cl—$C_6H_4-$ | 141—142 | 88 |
| *(2c)* *p*-$CH_3$—$C_6H_4-$ | 112—113 | 89 |
| *(2d)* *o*-$CH_3O$—$C_6H_4-$ | 115—116 | 93 |
| *(2e)* *m*-$CH_3O$—$C_6H_4$ | 109—110 | 94 |

*p*-Toluenesulfonylcarbamoyl azide *(4)* is formed analogously from *p*-toluenesulfonyl isocyanate *(3)*[2] and hydrazoic acid.

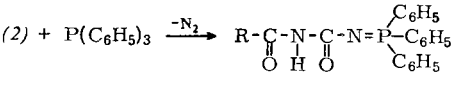
The structures of the compounds are proved by their spectra. Acylcarbamoyl azides have absorption bands characteristic of the $N_3$ group at 2155–2165 $cm^{-1}$, and sulfonylcarbamoyl azides at 2193 $cm^{-1}$. In the $^1H$-NMR spectrum of compound



*(3)* *(4)*

*(2a)* the signal of the NH-proton is at 9.34 ppm and there is a multiplet due to aromatic protons centered at 7.6 ppm (measurements in deuteriochloroform). The compounds are stable at room temperature. Satisfactory elemental analyses were obtained.

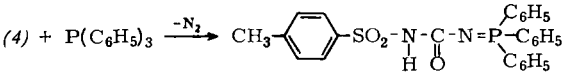
Acylcarbamoyl azides *(2)* react with equimolar amounts of triphenylphosphine in anhydrous tetrahydrofuran with loss of 1 mole of nitrogen and formation of (acylcarbamoylimino)-triphenylphosphoranes *(5)*:



*(5)*

| R | M.p. [°C] | Yield [%] |
|---|---|---|
| *(5a)* $C_6H_5$– | 153–154 | 89 |
| *(5b)* *p*-Cl–$C_6H_4$– | 175–176 | 82 |
| *(5c)* *p*-$CH_3$–$C_6H_4$– | 180–181 | 92 |
| *(5d)* *o*-$CH_3O$–$C_6H_4$– | 59– 60 | 87 |
| *(5e)* *m*-$CH_3O$–$C_6H_4$– | 170–171 | 94 |

(*p*-Toluenesulfonylcarbamoylimino)triphenylphosphorane *(6)*, m.p. 146–146.5 °C (yield 83 %), is obtained analogously from compound *(4)* and triphenylphosphine:



*(6)*

The structures of these products are also verified by their spectra.

Received: January 3rd, 1966 [Z 143/976 IE]
German version: Angew. Chem. 78, 333 (1966)

[1] *R. Neidlein*, Chem. Ber. *97*, 3476 (1964).
[2] *R. Graf*, Chem. Ber. *89*, 107 (1956).

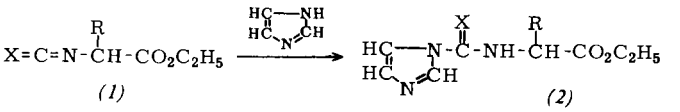
## Peptide Syntheses via N-(1-Imidazolylcarbonyl)- and N-(1-Imidazolylthiocarbonyl)-amino Esters

By Dr. J. Gante

Institut für Organische Chemie der Freien Universität Berlin (Germany)

The previously unknown *N*-(1-imidazolylcarbonyl)amino esters *(2a)–(2d)* are obtained on mixing the ethyl esters *(1a)–(1d)*[1] of α-isocyanato-fatty acids with equimolar amounts of imidazole. Ethyl isothiocyanatoacetate[2] and imidazole give *N*-(1-imidazolylthiocarbonyl)glycine ethyl ester *(2e)* analogously.

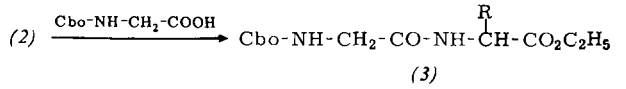
Compounds *(2a)–(2e)* are colorless and crystallize well from anhydrous ethyl acetate or ethyl acetate/light petroleum. The reactivity of the imidazolylcarbonyl group attached to an amino group is similar to that in "carboxyl-activated" *N*-benzyloxycarbonyl(Cbo)-amino acids[3], so that compounds *(2a)–(2e)* can be used in peptide syntheses, though only for



*(1)* *(2)*

| | R | X | Yield [%] | M.p. [°C] | Opt. rotation |
|---|---|---|---|---|---|
| *(2a)* | –H | O | 84 | 107–108 | |
| *(2b)* | $-CH_3$ | O | 92 | 73– 74 | |
| DL-Form | | | | | |
| *(2c)* | $-CH_2-C_6H_5$ | O | 89 | 130–132 | |
| DL-Form | | | | | |
| *(2d)* | $-CH_2-S-CH_2-C_6H_5$ | O | 79 | 59– 62 | $[\alpha]_D^{22} = -81.4°$ (c = 1, ethyl ace |
| L-Form | | | | | |
| *(2e)* | –H | S | 53 | 94– 96 | |

chain extension at the *amino* end. Thus, when heated with equimolar amounts of Cbo-glycine at 75–85 °C for 5–8 h they lose imidazole and $CO_2$ or COS, affording the dipeptides *(3a)–(3e)*. These products are purified by precipitation from ethanol/water or ethyl acetate/light petroleum.



*(3)*

| | R | Yield [%] | M.p. [°C] | Opt. rotation |
|---|---|---|---|---|
| *(3a)* | –H | 80 | 81–82 | |
| *(3b)* | $-CH_3$ | 63 | 54–56 | |
| DL-Form | | | | |
| *(3c)* | $-CH_2-C_6H_5$ | 70 | 88–89 | |
| DL-Form | | | | |
| *(3d)* | $-CH_2-S-CH_2-C_6H_5$ | 61 | 76–79 | $[\alpha]^{22} = -36.5°$ (c = 1, methanol) |
| L-Form | | | | |
| *(3e)* | –H | 49 | 80–82 | |

In contrast to the isocyanates from which they are obtained, compounds *(2a)–(2e)* are odorless and, being crystalline, easy to handle. Moreover, they react with Cbo-glycine under milder conditions (isocyanates react at 110 °C).

Received: January 10th, 1966 [Z 140/970 IE]
German version; Angew. Chem. 78, 334 (1966)

[1] *St. Goldschmidt* and *M. Wick*, Liebigs Ann. Chem. *575*, 217 (1952); *W. Siefken, ibid. 562*, 105 (1949).
[2] *T. B. Johnson* and *A. G. Renfrew*, J. Amer. chem. Soc. *47*, 242 (1925).
[3] *R. Paul* and *G. W. Anderson*, J. Amer. chem. Soc. *82*, 4596 (1960).

## Solid Perrhenic Acid

By Prof. Dr. G. Brauer and Dipl.-Chem. G. Sleater

Chemisches Laboratorium der Universität Freiburg (Germany)

Perrhenic acid has hitherto been known only in aqueous solution. We have prepared it in solid form by the reaction of $Re_2O_7$ with a small amount of water at room temperature. The hygroscopic oxide was treated dropwise with water or was allowed to take up water from the air; any excess of water was removed in a desiccator over $P_2O_5$ or $Mg(ClO_4)_2$. The solid acid is pale greenish-yellow, well crystalline, and exceedingly hygroscopic. As a result it gave on chemical analysis 1.2 mole of $H_2O$ per mole of $Re_2O_7$, *i.e.* somewhat more than corresponds to the composition $HReO_4$. The X-ray diagram of the acid contains many lines; it is totally different from that of rhenium heptoxide[1]. When warmed in a vacuum the acid begins to dissociate above about 65 °C into anhydride and water and to volatilize.

Received: January 12th, 1966; revised: February 7th, 1966 [Z 149/982 IE]
German version: Angew. Chem. 78, 336 (1966)

## Exchange of Ring Members in Cyclopolyphosphines [1]

By Prof. Ulrich Schmidt, cand. chem. R. Schröer, and Dr. H. Achenbach

Chemisches Laboratorium der Universität, Freiburg (Germany)

When heated with diethyl sulfide, pentaphenylcyclopentaphosphine (the so-called tetraphenylcyclotetraphosphine was recently found to be the pentamer) yields diethyl phenyldithiophosphonite, $C_6H_5-P(SC_2H_5)_2$. This reaction was interpreted as involving insertion of a phenylphosphinidene ($C_6H_5-P$:) into the disulfide linkage [1].

Thermal decomposition of cyclopolyphosphines into phosphinidenes should lead to "disproportionation" of two different symmetrical cyclopolyphosphines. We have now demonstrated such an exchange of ring members between pentamethylcyclopentaphosphine *(1)* and pentaethylcyclopentaphosphine *(2)* [2]:

$$\underset{(1)}{(MeP)_5} + \underset{(2)}{(EtP)_5} \downarrow$$

$$(1) + \underset{(3)}{Me_4EtP_5} + \underset{(4)}{Me_3Et_2P_5} + \underset{(5)}{Me_2Et_3P_5} + \underset{(6)}{MeEt_4P_5} + (2)$$

On simultaneous introduction of compounds *(1)* and *(2)* into a mass spectrometer [3] superposition of the mass spectra of these two compounds is observed. If, however, the mass spectrum is registered under the same conditions for a mixture that has been previously distilled (150 °C bath temperature, 0.1 mm), then ions of mass 244, 258, 272, and 286 are observed, in addition to the molecule ions and fragments of compounds *(1)* and *(2)*. These masses correspond to the molecule-ion weights of the mixed cyclopentaphosphines *(3)* to *(6)*.

Received: January 14th, 1966 [Z 136/968 IE]
German version: Angew. Chem. *78*, 307 (1966)

[1] Part 2 of Phosphinidenes. – Part 1: *U. Schmidt* and *Ch. Osterroht*, Angew. Chem. *77*, 455 (1965); Angew. Chem. internat. Edit. *4*, 437 (1965).

[2] Preparation: *W. A. Henderson, M. Epstein*, and *F. S. Seichter*, J. Amer. chem. Soc. *85*, 2462 (1963). According to these authors the product is identical with a cyclophosphine obtained by *K. Isleib* and *B. Mitscherling* [Z. Naturforsch. *15b*, 267 (1960)] for which the tetrameric structure was deduced from cryoscopic measurements. According to mass-spectrometric results the product is pentameric; the most important signals in the spectrum of *(2)* are at m/e = 300 ($Et_5P_5^+$; 70 %) and 271 ($Et_4P_5^+$; 100 %).

[3] Atlas-CH-4 mass spectrometer. The substances were introduced by the HTE system at 110 °C.

## Synthesis of Free Dithiocarbamic Acid, $SC(SH)(NH_2)$ [1]

By Prof. Dr. G. Gattow and Dipl.-Chem. V. Hahnkamm

Anorganisch-Chemisches Institut der Universität Göttingen (Germany)

Although there have been numerous papers concerning esters of dithiocarbamic acid, $SC(SH)(NH_2)$ *(1)*, and their *N*-substituted derivatives, as well as the ammonium salt, only the probable existence of the free acid *(1)* has been shown by *Mulder*'s investigations [2]. We have now prepared the acid *(1)* by a method analogous to that used for synthesis of trithiocarbonic acid, $SC(SH)_2$ [3]:

Concentrated HCl (1.4 ml, 0 °C) was dropped, with stirring, into a solution of 2 g of $NH_4[(SC(S)(NH_2)]$ in 16.5 ml of $H_2O$, previously cooled to 0 °C. The colorless acid *(1)* that crystallized was washed with ice-water, ligroin was poured over it twice, and the product was dried in a desiccator over $P_2O_5$. The yield was about 45 %.

The compound *(1)* [m.p. 35.7 ± 0.4 °C; $d_4^{20} = 1.479_6 \pm 0.001$ g/cm³] is almost insoluble in nonpolar solvents; the solubility increases with the polarity of the solvent. Chemical, kinetic, infrared-spectroscopic, and X-ray investigations showed that thermal decomposition of the acid *(1)* between 20 and 100 °C proceeds in two steps:

$$2\,SC(SH)(NH_2) \rightarrow NH_4[SC(S)(NH_2)] + CS_2$$
$$NH_4[SC(S)(NH_2)] \rightarrow NH_4SCN + H_2S$$

Infrared spectrum of *(1)*: 2170(m), 1551(w), 1519(st), 845(m) $cm^{-1}$ [4].

The equivalent conductivity [5] determined for aqueous solutions between 5 and 25 °C is described by the temperature functions

$$\Lambda_0 = 5.87\ T - 1348 \text{ for } (1)$$
$$\Lambda_0 = 0.918\ T - 222.8 \text{ for } [SC(S)(NH_2)]^-$$

[$\Lambda_0$ in $cm^2(g\text{-equiv})^{-1}$ $ohm^{-1}$; T in °K). The thermodynamic dissociation constant [5] of *(1)* is $K_a = (1.13 \pm 0.03) \times 10^{-3}$ at 20 °C.

Decomposition of the acid *(1)* in aqueous solution follows first-order kinetics, with a half-life of 85.5 ± 1.5 min. at 20 °C and an activation energy of 21.1 ± 0.5 kcal/mole at 20 °C.

Received: January 21st, 1966 [Z 141/971 IE]
German version: Angew. Chem. *78*, 334 (1966)

[1] Communication XXV on Chalkogenocarbonates. – Communication XXIV: *A. Müller, G. Gattow*, and *H. Seidel*, Z. anorg. allg. Chem., in the press.

[2] *E. Mulder*, J. prakt. Chem. *103*, 178 (1868); Liebigs Ann. Chem. *168*, 228 (1873).

[3] *G. Gattow* and *B. Krebs*, Z. anorg. allg. Chem. *321*, 143 (1963).

[4] st = strong, m = medium, w = weak.

[5] Cf. *A. Hantzsch* and *W. Bucerius*, Ber. dtsch. chem. Ges. *59*, 793 (1926).

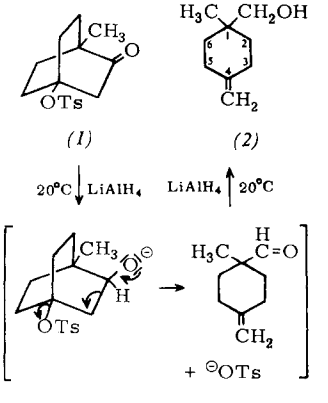
## Reductive Fragmentation of 1-Methyl-4-tosyloxybicyclo[2.2.2]octan-2-one [1]

By Dr. W. Kraus

Chemisches Institut der Universität Tübingen (Germany)

Sulfonic esters of β-hydroxy ketones are fragmented on hydrolysis with KOH [2,3] or treatment with a Grignard reagent [3]. Reductive cleavage of such compounds has not previously been described.

4-Hydroxy-1-methylbicyclo[2.2.2]octan-2-one [5,6], which is readily accessible from 4-acetyl-4-methylpimelic acid [4] by way of 4-acetyl-4-methylcyclohexanone [5,6], was converted into its *p*-toluenesulfonate *(1)*; (Ts = $CH_3C_6H_4SO_2$), m.p. 93.5–94.5 °C. This was stirred with $LiAlH_4$ in ether for 2 h at room temperature, leading to the previously unknown (1-methyl-4-methylenecyclohexyl)methanol *(2)*, b.p. 89 °C/10 mm, in 83 % yield.



Structure *(2)* follows from the NMR spectrum[7], which shows a singlet for the methyl group at $\tau = 9.04$ (3 H) and two unsymmetrical triplets ($A_2B_2$ spectrum) for the methylene groups at $\tau = 8.70$, 8.63, and 8.51 (4 H, at C-2 and C-6), and at $\tau = 7.94$, 7.84, and 7.73 (4 H, allyl protons at C-3 and C-5). In $CCl_4$ solution the singlet signal for the hydroxymethyl group is at $\tau = 6.68$ (3 H), but in dimethyl sulfoxide there are two signals with relative areas 1:2 ($OH/CH_2$). The signal for the vinyl protons occurs at $\tau = 5.42$ (2 H). Infrared spectrum: 880, 1640, 1770, 3070 ($=CH_2$), 1035, 3360 (broad association band), 3630 (primary OH), and 1365 $cm^{-1}$ ($CH_3$). The infrared spectrum of the alcohol *(2)* is identical with that of a sample prepared by reducing 1-methyl-4-methylenecyclohexane-1-carboxylic acid[2] with $LiAlH_4$.

Received: February 1st, 1966 [Z 144/977 IE]
German version: Angew. Chem. *78*, 335 (1966)

[1] Part VII of Bicyclic Compounds.-Part VI: *W. Kraus* and *P. Schmutte*, Chem. Ber., in press.

[2] *S. Julia* and *C. Gueremy*, Bull. Soc. chim. France *1965*, 3002. – Cf. *C. A. Grob* and *W. Baumann*, Helv. chim. Acta *38*, 594 (1955); *C. A. Grob*, Bull. Soc. chim. France *1960*, 1360.

[3] *A. Eschenmoser* and *A. Frey*, Helv. chim. Acta *35*, 1660 (1952).

[4] *H. A. Bruson* and *T. W. Riener*, J. Amer. chem. Soc. *64*, 2850 (1942).

[5] *J. Colonge* and *R. Vuillemet*, Bull. Soc. chim. France *1961*, 2235.

[6] *H. D. Holtz* and *L. M. Stock*, J. Amer. chem. Soc. *86*, 5183 (1964); *H. D. Holtz*, Ph.D. Thesis, University of Chicago 1963, p. 80.

[7] Varian HR-100 spectrometer; internal standard, tetramethylsilane. We thank Dr. *H. Suhr* for measurement and discussion of the spectrum.

## Explosion of Nitrogen Trifluoride on Active Charcoal. – Reaction of $NF_3$ with Carbon

By Dr. J. Massonne and Dr. R. Holst

Zentrallaboratorium der Kali-Chemie AG.,
Hannover (Germany)

A violent explosion occurred during an attempt to free $NF_3$ from small amounts (less than 2 vol-%) of $N_2F_2$ and $N_2O$ by adsorption on active charcoal at low temperatures.

Active charcoal grains (600 g, previously dried at 120 °C; manufactured by Messrs. Riedel, Seelze) were placed in a 2-liter steel pressure flask. The vessel was cooled to −100 °C and evacuated for a considerable time. About 25 g of $NF_3$ was introduced during about 10 min and then the gas flow was interrupted at a pressure of 1.5 kg/cm² in the adsorption vessel. A short time thereafter an explosion fractured the metal vessel and ejected glowing active charcoal.

According to *Ruff*[1], carbon does not react with $NF_3$ even at red heat. *Gould* and *Smith*[2,3] found that $NF_3$ reacts with petroleum coke in a fluidized bed at 400–500 °C to give $N_2F_4$, $CF_4$, and $C_2F_6$.

The reaction

$$4\,NF_3 + 3\,C \rightarrow 3\,CF_4 + 2\,N_2 \qquad (a)$$

was observed only above 500 °C.

We have heated active charcoal grains in a nickel tube and treated them with $NF_3$ (93.2 vol-% $NF_3$; 2.22 % $N_2$; 0.42 % $O_2$, 1.9 % $N_2O$; 1.31 % $N_2F_2$) at atmospheric pressure. Up to 100 °C no reaction could be observed. At 150 °C the charcoal reacted with incandescence. $N_2$ and $CF_4$ were the sole products found. $N_2F_4$ could not be detected. The reaction (a) is thus energetically preferred to that leading to $N_2F_4$, $CF_4$, and $C_2F_6$, which is bypassed.

We assume that the reaction leading to explosion was initiated by the heat of adsorption, which could not be removed sufficiently rapidly. Experiments with 30 g of active charcoal grains, carried out without thermal insulation, resulted in temperature increases of 40 to 70 °C when gaseous $NF_3$ was led at atmospheric pressure into a vessel containing charcoal and previously evacuated to 1–2 mm.

When impure $NF_3$ is passed through active charcoal at −80 °C, $N_2F_2$ and $N_2O$ are completely retained, but at +20 °C only $N_2O$ is adsorbed.

*Warning: Special precautions are required if $NF_3$ is to be purified over active charcoal.*

Received: February 2nd, 1966 [Z 145/978 IE]
German version: Angew. Chem. *78*, 336 (1966)

[1] *O. Ruff*, Z. anorg. allg. Chem. *197*, 273 (1931).

[2] *I. R. Gould* and *R. A. Smith*, Abstracts of Papers, 138th Meeting ACS, New York, September 1960, p. 7M.

[3] Chem. Engng. News *38*, No. 38, p. 85 (1960).

## Radiation-Chemical Synthesis of Phosphonium and Arsonium Salts

By Dr. H. Drawe and Dipl.-Chem. G. Caspari

Hahn-Meitner Institut für Kernforschung,
Sektor Strahlenchemie, Berlin (Germany)

γ-Irradiation ($^{60}Co$-source) of mixtures of triphenylphosphine or triphenylarsine with aryl halides gives tetraarylphosphonium (see Table) or -arsonium salts. G-values are in the usual range for one-stage reactions. They are high enough for quantitities of 10 to 100 g to be prepared in one batch if a sufficiently intense source of radiation is used. Yields of arsonium salts are about one-tenth of those of phosphonium salts. The quantum yields are independent of the dosage and

| Starting materials | Mole-% | Phosphonium salt | G (molecules/100 eV) | Yield based on $(C_6H_5)_3P$; dose [a] | M.p. (°C) [b] |
|---|---|---|---|---|---|
| Chlorobenzene | 76 | $[P(C_6H_5)_4]Cl$ | 1.4 | 15 % | 274–278 |
| Triphenylphosphine | 24 | | | $25\times10^7$ r | white crystals |
| Bromobenzene | 73.5 | $[P(C_6H_5)_4]Br$ | 3.4 | 43 % | 286–294 |
| Triphenylphosphine | 26.5 | | | $25\times10^7$ r | white crystals |
| Iodobenzene | 91.7 | $[P(C_6H_5)_4]I$ | 6.5 | 78 % | 335–343 |
| Triphenylphosphine | 8.3 | | | $5.6\times10^7$ r | transparent needles |
| 1-Chloro-4-iodobenzene | 74.8 | $[(C_6H_5)_3P{-}C_6H_4{-}Cl]I$ | 4.4 | 55 % | 219–222 |
| Triphenylphospine | 25.2 | | | $3.5\times10^7$ r | yellow crystals |
| 1,4-Dibromobenzene | 79.7 | $[(C_6H_5)_3P{-}C_6H_4{-}Br]Br$ | 5.1 | 25 % | 134–150 |
| Triphenylphosphine | 20.3 | | | $2\times10^7$ r | white crystals |
| 1,4-Dichlorobenzene | 71.5 | $[(C_6H_5)_3P{-}C_6H_4{-}Cl]Cl$ | 3.9 | 90 % | 157–180 |
| Triphenylphosphine | 28.5 | | | $20\times10^7$ r | white crystals |
| *p*-Bromotoluene | 64 | $[(C_6H_5)_3P{-}C_6H_4{-}CH_3]Br$ | 2.1 | 41 % | 228–237 |
| Triphenylphosphine | 36 | | | $4\times10^7$ r | white crystals |

[a] Dosimetry according to *Fricke*.
[b] The large melting ranges are due to traces of water of hydration.

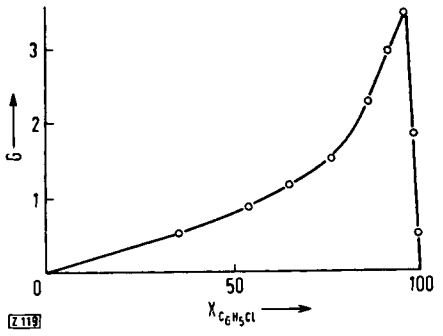



Fig. 1. Quantum yield G (molecules/100eV) of tetraphenylphosphonium chloride.

Abscissa: Mole-% of chlorobenzene in the mixture with triphenylphosphine.

are not influenced by the oxygen content of the mixture. The Figure shows that the yield of tetraphenylphosphonium chloride is a maximum with a molar ratio of chlorobenzene: triphenylphosphine of 96:4. This indicates a capture mechanism[1], *i.e.*, absorption of energy by the solvent chlorobenzene and capture of the decomposition products by triphenylphosphine:

$$C_6H_5Cl \rightsquigarrow C_6H_5\bullet + Cl\bullet$$
$$C_6H_5\bullet + (C_6H_5)_3P \rightarrow (C_6H_5)_4P\bullet$$
$$(C_6H_5)_4P\bullet + Cl\bullet \rightarrow [(C_6H_5)_4P]^+ + Cl^-$$

Received: November 26th, 1965 [Z 119/966 IE]
German version: Angew. Chem. *78*, 331 (1966)

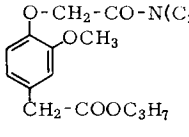
[1] *A. Henglein* in: Large Radiation Sources in Industry. International Atomic Energy Agency, Vienna 1960, Vol. 2, p. 139.

# CONFERENCE REPORTS

## Therapy Congress and Pharmaceutical Exhibition

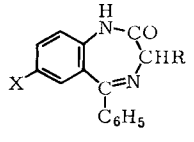
The 17th German Therapy Congress held in Karlsruhe (Germany) from August 29th to September 4th, 1965, was attended by about 6000 people from Germany and abroad. Of the new therapeutic agents only those are listed in the following report which contain new compounds or are marketed now for the first time in Germany.

Epontol®, a short-duration narcotic for intravenous application, has been introduced by Farbenfabriken Bayer. Its active principle is n-propyl 4-(*N,N*-diethylcarbamoylmethoxy)-3-methoxyphenylacetate *(1)* (generic name: propanidide), a colorless to yellow oil, insoluble in water. Epontol is characterized by rapid inception and particularly rapid cessation of the narcotic action. Patients can be released from clinical supervision 20 to 30 minutes after Epontol narcosis, which lasts for 3 to 4 minutes.




*(1)*

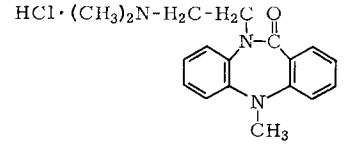
Mogadan®, introduced to the market by Hoffmann-La Roche, is a new soporific resembling the tranquilizers Librium and Valium in structure and properties, and suitable particularly when sleep is disturbed by irritability, overexertion, anxiety, *etc.* Its active agent is 2,3-dihydro-7-nitro-5-phenyl-1,4-benzodiazepin-2(1*H*)-one *(2)*.




*(2)*: R = H, X = $NO_2$
*(3)*: R = OH, X = Cl

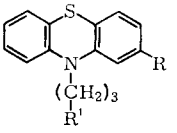
Praxiten®, a psychotherapeutic drug, also has a close structural relation to Librium and Valium. It was developed in the Wyeth Laboratories in USA and is marketed by Wyeth-Pharma GmbH., Münster (Germany). It consists of 7-chloro-2,3-dihydro-3-hydroxy-5-phenyl-1,4-benzodiazepin-2(1*H*)-one *(3)* (generic name: oxazepam), a white crystalline substance that is sparingly soluble in water. Praxiten, which is marketed in USA under the name "Serax", is suitable for relief of anxiety states, strain, agitation, irritability, and sleeplessness.

A new group of psychotropic drugs, the dibenzodiazepines, is represented by Noveril®, which is put forward by Dr. A. Wander GmbH., Frankfurt/M. It is described as an intensely active, broad-spectrum antidepressant, which is active mainly against endogenous depressions. Noveril contains 10-(2-*N,N*-dimethylaminoethyl)-5-methyl-1,4-dibenzodiazepin-11(10*H*)-one hydrochloride *(4)*, a compound readily soluble in water.




*(4)*

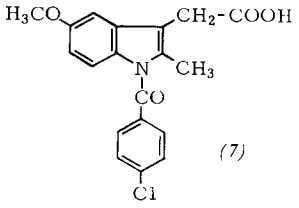
Two further new psychotherapeutic drugs have been introduced. The psychosedative Pasaden®, from Chemiewerk Homburg, contains 10-[γ-{hexahydro-4-(2-hydroxyethyl)-1,4-diazepin-1-yl}-propyl]-2-trifluoromethylphenothiazine dihydrochloride *(5)*, a white crystalline powder (m.p. 210 °C). It is suitable for treatment of disturbances of neurovegetative control, such as vegetative dystony, neurasthenia, nervousness, disquiet, *etc.* The neuroleptic Aolept® from Farbenfabriken Bayer consists of 2-cyano-10-[γ-(4-hydroxypiperidino)propyl]phenothiazine *(6)* (generic name: propericiazin) and is suitable particularly for prolonged therapy of all psychoses of schizophrenic type.




*(5)*: R = $CF_3$,
R' = -N⟨⟩N-$CH_2$-$CH_2$OH · 2 HCl

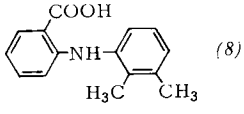
*(6)*: R = CN, R' = -N⟨⟩-OH

A new antirheumatic, introduced some months ago in USA under the name "Indocin", has been placed on the market under the name Amuno® by Sharp & Dohme GmbH, a subsidiary of Merck & Co., Inc., Rahway, USA. It contains the antiphlogistic, analgetic, and antipyretic agent 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid *(7)* (generic name: indometacin), that does not belong to any of the previously known antiphlogistic groups. Indometacin is a pale yellow powder (m.p. 156–160 °C) that dissolves in alcohol, acetone, ethylene dichloride, or acetonitrile but not in water or hydrocarbons.



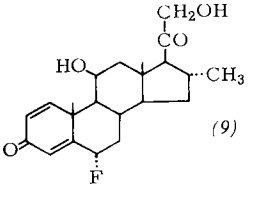
(7)

Parkemed®, from Parke Davis & Co., is an analgetic with antiphlogistic properties, that also belongs to a new group of analgetics, the *N*-phenylanthranilic acid derivatives. The active ingredient is *N*-(2,3-xylyl)anthranilic acid *(8)*, a white powder whose solubility in water is strongly pH-dependent. This preparation is marketed in the USA under the name "Ponstan".



(8)

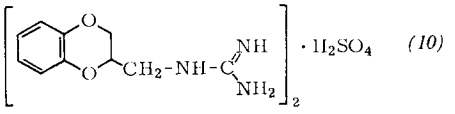
A new corticoid, 6α-fluoro-11β,21-dihydroxy-16α-methyl-1,4-pregnadiene-3,20-dione *(9)* (generic name: fluocortolon), is contained in Ultralan® cream, which is marketed by Schering AG., Berlin, and is suitable for treatment of inflammatory and allergic skin conditions. Whereas the anti-inflammatory steroids hitherto known belong to the hydrocortisone or 21-deoxyhydrocortisone class, fluocortolon is a derivative of corticosterone.



(9)

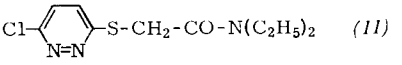
Remarkably, five firms have brought out or announced analgesic or antiphlogistic preparations containing dimethyl sulfoxide (Dolicur from Schering AG., Berlin; DMS-70 and DMS-90 from Sharp & Dohme GmbH., Munich; Hyadur from Chemie Grünenthal, Stolberg; Infiltrina from Chemische Fabrik von Heyden AG., Munich; Somipront from H. Mack Nachf., Illertissen.) The analgesic and anti-inflammatory action of dimethyl sulfoxide was first observed a few months ago and requires clinical evaluation for a further period. The utility of the above preparations can therefore not yet be finally estimated; they have in the meantime been recalled from the market.

Envacar®, developed in the Pfizer Research Laboratories as a new drug for depression of blood pressure, has been placed on the market by Pfizer GmbH., Karlsruhe (Germany). It contains 2-guanidinomethyl-1,4-benzodioxane (generic name: guanoxan), which is suitable for treatment of all cases (mild to severe) of essential and renal hypertony. Envacar contains guanoxan as its sulfate *(10)*, a white crystalline substance of m.p. 204–208 °C.



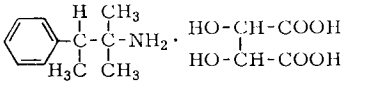
(10)

A new choleretic, α-(6-chloro-3-pyridazinylthio)-*N*,*N*-diethylacetamide *(11)* (m.p. 97–98 °C) is present, with various enzymes, in Oragallin®, a medium for regulation of digestion, from Byk-Golden-Lomberg GmbH., Konstanz (Germany). The active component increases the flow of gall in the manner of a true choleresis and in doses of 400 mg/kg has neither depressant nor stimulating effect on the central nervous system. The choleretic action is said to begin 10 min after application and to last for about an hour.



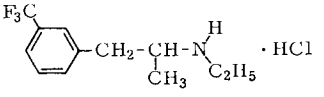
(11)

Modatrop®, an appetite-controller with lipolytic activity, has been brought out by Nordmark-Werke GmbH., Hamburg. Its active ingredient is α,α,β-trimethylphenethylamine hydrogen tartrate *(12)* (m.p. 159–162 °C), which depresses the appetite and the centers in the hypothalamus that control the feeling of hunger, at the same time as controlling the motility of the stomach. Modatrop also mobilises body fat and accelerates its removal.



(12)

Another appetite-controller has been introduced by Byk-Gulden-Lomberg GmbH., Konstanz, under the name Ganal®. This contains the new appetite-depressant *N*-ethyl-α-methyl-3-trifluoromethylphenethylamine hydrochloride *(13)*, a white

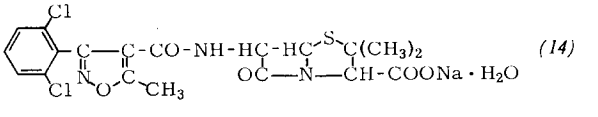


(13)

crystalline substance, soluble in water and ether (m.p. 166 to 168 °C). Ganal does not stimulate the central nervous system and is characterized by its powerful and prolonged action.

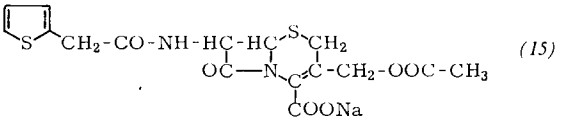
A few further preparations may be mentioned that contain new semisynthetic antibiotics.

A penicillin derivative that is stable to penicillinase and to acid, the sodium salt of [3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]penicillin *(14)* (generic name: dicloxacillin), has been placed on the market under the name Stampen® by the German Beecham GmbH., Biberach/Riss, and under the name Dichlorstapenor® by Farbenfabriken Bayer. Dicloxacillin is a colorless, microcrystalline powder that is readily soluble in water or methanol and decomposes at 222–225 °C. The preparations are suitable for treatment of all types of staphylococcal infections.



(14)

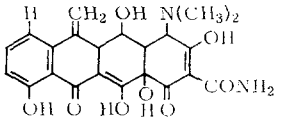
Cefalotin®, introduced by Eli Lilly GmbH., Giessen (Germany), is a semisynthetic antibiotic derived from cephalosporin C. It consists of the sodium salt of 7-[α-(2-thienyl)acetylamino]cephalosporic acid *(15)*, a cream-colored crystalline substance. Cefalotin must be administered parenterally. It is claimed to be particularly useful against severe infections that do not respond to penicillin or other antibiotics.



(15)

Rondomycin® is a new broad-spectrum antibiotic that has been developed from oxytetracyclin and belongs to the semisynthetic tetracyclin series. This substance is 5-hydroxy-6-methylenetetracyclin *(16)* (generic name: methacyclin). It is

absorbed rapidly from the stomach and intestinal tract, but is only slowly excreted through the kidneys. The antimicrobial



(16)

activity of Rondomycin is exerted against both Gram-positive and Gram-negative microorganisms. Its action against staphylococci, streptococci, haemophyllum species, and coli bacteria is particularly strong.

[VB 969/270 IE]

German version: Angew. Chem. *78*, 337 (1966)

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## Stereochemistry and Mechanism of Some Reactions of Ketenes

*H. Pracejus*, Halle (Germany)

Addition of symmetrical alcohols to asymmetrically disubstituted ketenes in the presence of catalytic amounts of optically active bases leads to optically active esters. The influence of the structure and configuration of the catalyst and of temperature on the steric course of the reaction has been studied for the synthesis of methyl 2-phenylpropionate. It was found that the spatial structure of the catalyst can be brought into better relation to the form of the temperature-stereospecificity function measured over a wide range of temperature than to the specificity at only one temperature. In favorable cases the enthalpy and entropy of activation of the two sterically competing reactions [formation of the (+) and of the (−) ester] can be calculated or estimated from the effect of temperature. It was found that $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ always have the same sign. This explains the finding that not only the degree, but also the direction of the stereospecificity depend on the temperature. Kinetic measurements indicate that the specificity-determining step in the reaction is a proton transfer from an ammonium ion (catalyst-$H^+$) to an ester carbanion formed in the rate-determining step. Consideration of the relative stabilities of the possible conformations of the two diastereoisomeric transition states leads to correct prediction of the sign of $\Delta\Delta H^{\neq}$; the simplest results are obtained when the catalyst molecule is a very rigid one (a bicyclic base with an asymmetric N or a base with an asymmetric carbon atom next to a bridgehead nitrogen). The stereospecificity ($\Delta\Delta H^{\neq}$) of acyclic catalysts with a freely rotating dimethylamino group attached to an asymmetric carbon atom can be evaluated on the Curtin-Hammett principle. This principle is, however, not applicable if the rotation about the C–N bond is hindered by bulky substituents (*e.g.* t-butyl).

The asymmetric synthesis of amides from ketenes and primary amines is suitable in principle also for asymmetric synthesis of dipeptide derivatives, as we have shown for the example t-butylphthalimidoketene (3,3-dimethyl-2-phthalimido-1-buten-1-one) + D-alanine isopropyl ester → *N*-(3,3-dimethyl-2-phthalimidobutyryl)-D-alanine isopropyl ester (D,D/L,D = 85:15 at −60 °C).

[Lecture at Freiburg (Germany), on November 5th, 1965]

[VB 965/273 IE]

German version: Angew. Chem. *78*, 340 (1966)

## Osmosis, Anomalous Osmosis, and Determination of Molecular Weight

*A. J. Staverman*, Leiden (Holland)

Measurement of osmotic pressure is often used for determination of the molecular weight of polymers. This requires the use of membranes that are strictly semipermeable, *i.e.*, permit no passage at all of the solute. Such membranes can be only approximated and then permit passage of the solvent only with difficulty, so that times required for measurement become very long. In practice, membranes are normally used that permit some passage of the solute, and the experimental osmotic pressure $\pi_{exp}$, *i.e.*, the opposing pressure at which passage through the membranes just ceases, is extrapolated to zero time, *i.e.*, to the time at which no solute has yet passed through.

The author has shown[1] that this procedure is unwarranted because a molecule capable of permeation contributes incompletely to the osmotic pressure, even before it has permeated. Diffusion of the solute can be allowed for in determination of molecular weights by carrying out, alongside the measurement of the osmotic pressure, a second experiment – ultrafiltration – in which a solution of the same concentration, c, is pressed through an identical membrane in another cell, the change in concentration being then measured. The solvent and solute do not flow through the membrane at the same rate. The selectivity of the membrane can be expressed by a reflection coefficient $\sigma$, which is determined from the change in concentration $c' = (1 - \sigma)c$ on ultrafiltration of the dissolved, only slowly diffusing component. According to the theory the measured osmotic pressure $\Pi_{exp}$ is equal to the product of $\sigma$ and the theoretical thermodynamic osmotic pressure $\Pi_{th}$, whence the molecular weight M can be calculated directly: $M = \sigma RTc/\Pi_{exp}$.

The theory has been tested for sucrose solutions on membranes of porous Vycor glass (Corning Glass Works, Corning, N.Y.)[2]. The ultrafiltration experiment gave $\sigma \approx 0.2$, the osmotic pressure was $\Pi_{th}/5$, and the molecular weight determined for sucrose in this way agreed with the correct value within experimental error; $\sigma$ was independent of concentration.

Aqueous solutions of polyethylene glycol showed quite different behavior towards glass membranes. The polymers were strongly adsorbed on the glass membranes and the $\sigma$ values depended greatly on the concentration; at high concentrations ($c \approx 2$ g/*l*) they approached unity (complete reflection), whereas at lower concentrations ($c \approx 1$ g/*l*) $\sigma$ was much lower and sometimes even assumed negative values. These results are in agreement with earlier measurements by *Elias*[3], who found negative osmotic pressures in this system, *i.e.*, the solvent diffused against the concentration gradient. This phenomenon is designated anomalous osmosis. Our method of determination of molecular weight could thus be used also in cases of anomalous osmosis. A theoretical explanation of the strong concentration-dependence of $\sigma$ has been given[4] on the basis of concentration-independent frictional coefficients and strong selective adsorption of the solute on the membrane (as observed experimentally).

[Lecture at Aachen (Germany), November 5th, 1965]

[VB 964/272 IE]

German version: Angew. Chem. *78*, 309 (1966)

[1] *A. J. Staverman*, Trans. Faraday Soc. *48*, 176 (1952).

[2] *J. L. Talen*, Dissertation, University of Leiden, 1963.

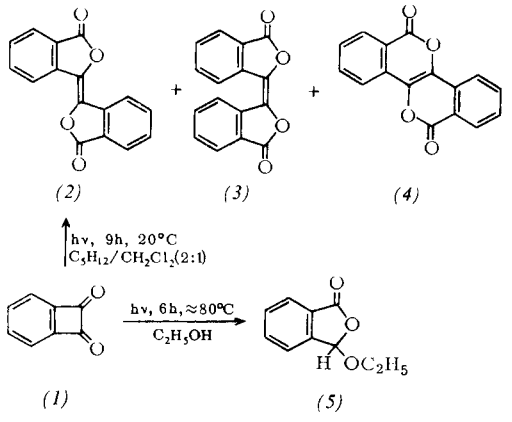
[3] *H. G. Elias*, Z. physik. Chem. N.F. *28*, 301 (1961).

[4] *A. J. Staverman, D. T. F. Pals*, and *C. A. Kruissink*, Trans. Faraday Soc., in press.

## Photochemical Reactions of Benzocyclobutene-1,2-dione

*H. A. Staab* and *J. Ipaktschi*, Heidelberg (Germany)

Benzocyclobutene-1,2-dione *(1)*[1], on irradiation in inert solvents with a high-pressure mercury lamp, gives the dimers *(2)*, *(3)*, and *(4)*, whereas in ethanol a 39 % yield of compound *(5)* is obtained together with 4 % of *(4)*.



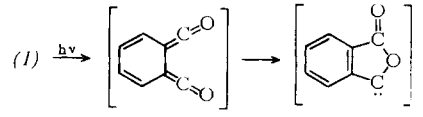
(2) (3) (4)

hν, 9h, 20°C
$C_5H_{12}/CH_2Cl_2$(2:1)

hν, 6h, ≈80°C
$C_2H_5OH$

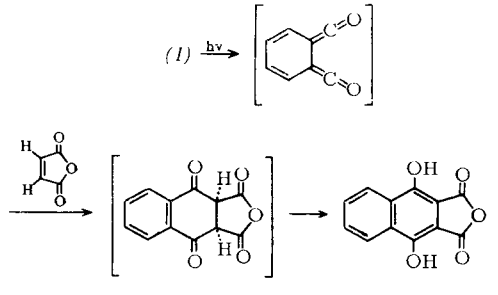
(1) (5)

These results led to the hypothesis that the primary photochemical reaction converts compound *(1)* into the bisketene *(6)*, from which the carbene *(7)* could be formed by aromatization as a second reactive intermediate. The existence of the two intermediates was demonstrated by specific trapping



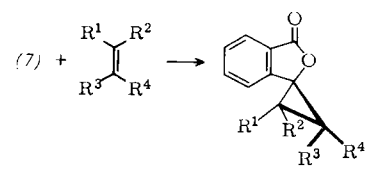
(6) (7)

experiments: On irradiation of the diketone *(1)* in the presence of maleic anhydride, 1,4-naphthalene-2,3-dicarboxylic anhydride was formed in 67 % yield by a Diels-Alder reaction involving the bisketene *(7)*; if 1,4-naphthoquinone is used, 6,11-dihydroxy-5,12-tetracenequinone is obtained.



(8)

If compound *(1)* is irradiated in the presence of an excess of an alkene, compounds are obtained which according to their compositions and molecular weights are 1:1 adducts of compound *(1)* and the alkene and for which the spirolactone structures *(9)* were proved spectroscopically and chemically. Examples: $R^1 = R^3 = H$, $R^2 = R^4 = CH_3$, m.p. 68–69 °C, 65 % yield; $R^1 = R^3 = H$, $R^2R^4 = (CH_2)_4$, m.p. 67–68 °C, 35 % yield; $R^1 = R^2 = R^3 = H$, $R^4 = CH{=}CH_2$, m.p. 101 to 102 °C, 54 % yield. The normal Schönberg reaction, namely, the photochemical reaction of 1,2-dicarbonyl compounds with alkenes to give 1,4-dioxins, was not observed with compound *(1)*; it would have led in this case to a benzocyclobutadiene derivative.



(9)

The results obtained so far confirm our hypothesis that the primary reaction on irradiation of compound *(1)* is conversion into the bisketene *(6)* which is favored by the ring strain in *(1)*; this bisketene rearranges in the absence of a dienophile into the carbene *(7)*, whose presence can be demonstrated by its reactions with alkenes.

[Lecture at Heidelberg (Germany), November 23rd, 1965]

[VB 966/274 IE]

German version: Angew. Chem. *78*, 308 (1966)

[1] *M. P. Cava, D. R. Napier*, and *R. J. Pohl*, J. Amer. chem. Soc. *85*, 2076 (1963).

## Studies on Formamidines

*M. Seefelder*, Ludwigshafen (Germany)

Many substituted formamidines can be synthesized by reaction of anhydrous hydrogen cyanide with amines. Whereas according to *Stewart* and *Fontana*[1] amines and hydrogen cyanide yield only salts, *Erickson*[2] isolated formamidines after prolonged reaction and subsequent hydrolysis. The assumption of the coupled equilibria

$$RR'NH + HCN \rightleftarrows RR'NH_2^{\oplus} + CN^{\ominus}$$

$$RR'NH + HCN \overset{\text{Slow}}{\rightleftarrows} RR'N{-}CH{=}NH$$

$$RR'N{-}CH{=}NH + HCN \rightleftarrows RR'N{-}CH{=}NH_2^{\oplus}\ CN^{\ominus}$$

*(1)*

affords a plausible explanation of all the products. The amidinium salt *(1)* present in the equilibrium mixture reacts with nucleophilic agents: water affords formamides[2], and $H_2S$ thioformamides[3]. This synthesis of thioformamides has been found to be very useful. Primary amines can replace ammonia in the salts *(1)*, yielding *N,N'*-disubstituted[4] and *N,N,N'*-trisubstituted formamidines *(2)* (R' = H or alkyl).

$$RR'N{-}CH{=}NH_2^{\oplus}\ CN^{\ominus} \xrightarrow{H_2NR''} RR'N{-}CH{=}N{-}R''$$

*(2)*

The trisubstituted formamidines can be obtained from both aliphatic and aromatic amines, sometimes in excellent yield. Analogous reactions with secondary amines afford the cyanides *(3)*, which spectra and molecular-weight determinations indicate as existing in solution in equilibrium with glyoxylonitrile aminals *(4)*, the position of equilibrium depending on the polarity of the solvent. Compounds *(4)*, and not *(3)*, occur in the solids.

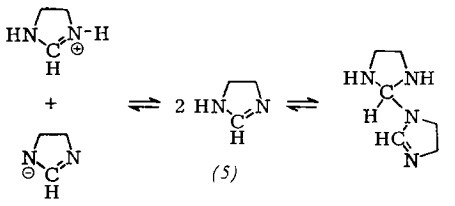
$$RR'N{-}\overset{\oplus}{C}H{=}NRR'\ CN^{\ominus} \rightleftarrows NC{-}CH(NRR')_2$$

*(3)* *(4)*

Compounds *(3)* are obtained in good yield on reaction of an excess of strongly nucleophilic secondary cycloalkylamines with hydrogen cyanide. They behave like amidinium salts *(1)* in their reaction with water, $H_2S$, and amines, forming formamides, thioformamides, and trisubstituted formamides.

Contrary to statements in the literature *N,N'*-disubstituted formamidines can be converted smoothly into sulfonyl derivatives in the presence of stoichiometric amounts of a base (*e.g.* NaOH). Reaction of aromatic amines to trisubstituted formamidines and subsequent quaternization and hydrolysis provide a synthesis of very pure aromatic secondary amines that is more selective than all previous methods.

*N,N'*-Disubstituted formamidines are strongly associated in solution. For tetrahydropyrimidine and imidazoline *(5)* molecular-weight determinations and spectroscopic findings suggest equilibria of the type:



(5)

[Lecture at Freiburg (Germany), November 26th, 1965]

[VB 971/278 IE]

German version: Angew. Chem. 78, 339 (1966)


[1] *T. D. Stewart* and *B. J. Fontana*, J. Amer. chem. Soc. *62*, 328 (1940).

[2] *J. G. Erickson*, J. org. Chemistry *20*, 1569 (1955).

[3] *P. L. Benneville, J. S. Strong*, and *V.T. Elkind*, J. org. Chemistry *21*, 772 (1956); *M. Seefelder*, unpublished work.

[4] *W. Jentzsch* and *M. Seefelder*, Chem. Ber. *98*, 1342 (1965).


## Synthesis of Azide Halides and Nitride Halides and some Related Structural Problems [1]

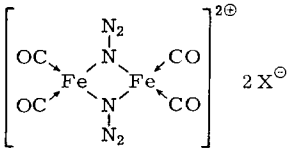

*K. Dehnicke*, Stuttgart (Germany)


Reaction of $WBr_5$ and $BrN_3$ afford the highly explosive compound $WBr_5N_3$ (symmetry class $C_{4v}$), soluble in $CCl_4$:

$$WBr_5 + BrN_3 \rightarrow WBr_5N_3 + {}^1/_2\,Br_2 \qquad (a)$$

An analogous reaction occurs with $UCl_5$ and $ClN_3$, affording an azide chloride, probably $UCl_5N_3$, which loses $N_2$ and $Cl_2$ in boiling $CCl_4$ and thus yields polymeric $UNCl_3$.

$ClN_3$ or $BrN_3$ react with the metal carbonyls $Fe(CO)_5$, $Mo(CO)_6$, and $W(CO)_6$ with formation of well-defined carbonyl azide halides $M(CO)_2N_3X$ (X = Cl or Br). Their infrared spectra and magnetic behavior indicate that a substantially planar four-membered ring occurs in these iron compounds, the halide being ionic:



These compounds show the paramagnetism of the unperturbed $Fe^{2+}$ ion ($\mu$ = 5.29 B.M., $\Theta$ = 0 °K) and are the first examples of paramagnetic iron-carbonyl compounds. The Fe–C linkage appears to be a pure $\sigma$-bond without back-donation. On thermal decomposition at 90 °C in a vacuum the CO-free azide halides $FeClN_3$ and $FeBrN_3$ ($\mu$ = 4.80 B.M., $\Theta$ = 12 °K) are formed. The carbonyl azides and the simple azide halides of $Fe^{II}$ are not explosive; this is attributed to locking of the lone electron pair on the $\alpha$-N atom. The carbonyl azide halides of Mo and W, $M(CO)_2ClN_3$, are polymeric (n = 6), both Cl and $N_3$ acting as bridges. Intense metal-metal interaction results, as shown by the magnetic behavior: $Mo(CO)_2ClN_3$: $\mu$ = 0.93 B.M., $\Theta$ = −20 °K; $W(CO)_2ClN_3$: $\chi_m = -74.9 \times 10^{-6}$ EMU/mole.

$ClN_3$ reacts with organometallic compounds such as $Cd(CH_3)_2$ and $[Al(C_2H_5)_3]_2$ with partial replacement of alkyl by azide:

$$Cd(CH_3)_2 + ClN_3 \rightarrow N_3CdCH_3 + CH_3Cl \qquad (b)$$

Azidomethylcadmium forms colorless crystals that do not melt and for which infrared spectra indicate an ionic structure: $[CdCH_3]^{\oplus}N_3^{\ominus}$. Azidodiethylaluminum is a colorless distillable liquid (b.p. 63 °C/$10^{-3}$ mm Hg), which dimerizes through the azide group; its infrared spectrum indicates a strictly planar four-membered Al–N ring.

[Lecture at Erlangen (Germany), December 2nd, 1965]

[VB 970/277 IE]

German version: Angew. Chem. 78, 339 (1966)

[1] With collaboration of *G. Lange, J. Müller, D. Seybold*, and *J. Strähle*.

## Synthesis of Graft and Block Copolymers


*G. Greber*, Freiburg (Germany)


Addition of dialkylaluminum hydrides to molecules with C=C double bonds in side chains or at chain ends, and treatment of the products with transition-metal halides (*e.g.* $TiCl_4$), afford macromolecular Ziegler catalysts that initiate graft and block polymerization of ethylene and $\alpha$-alkenes. Graft polymers with stereoregular poly-$\alpha$-alkene side chains become accessible in this way.

Macromolecules containing RC=NM linkages are formed on addition of organometallic compounds of lithium (LiR) or magnesium (MgRHal) to the N≡C triple bond in styrene-acrylonitrile copolymers, and they initiate anionic graft polymerization of acrylonitrile (AN), methyl methacrylate (MMA), 2-vinylpyridine (2-VP), and 4-vinylpyridine (4-VP).

Reaction with Na of macromolecules containing O=C, N≡C, or C=C linkages in side chains gives macromolecular radical anions (*e.g.* high-polymeric ketyls in the case of poly-*p*-vinylbenzophenone) or dianions, formed by electron-transfer from the metal to the multiple bond. Both the radical anions and the dianions initiate anionic graft polymerization of AN, MMA, 2-VP, 4-VP, butadiene, and styrene, and in this way pure graft copolymers are formed, free from "backbone molecules" and from homopolymers of the grafted monomer.

Pure graft copolymers are formed also on use of macromolecular organometallic initiators, such as those formed by metalation of poly-4-chlorostyrene or 4-chlorostyrene-styrene copolymers with stoichiometric amounts of naphthalene sodium.

Since the anionic end groups of the growing side chains remain "living" during these processes, second and third monomers can be added to afford graft copolymers whose side chains are block copolymers. If the growing chains are terminated, *e.g.* by chlorosilanes containing functional groups, then reactive end groups are introduced into the side chains.

Finally, graft and, in particular, block copolymers can be obtained when "finished" macromolecules containing very reactive silicon side or end groups (*e.g.* HSi–, ClSi–, HOSi–, $CH_2$=CH–$CH_2$–Si–) are joined together by chemical reactions. These methods open a route to block copolymers having stereoregular blocks. Macromolecules containing suitable functional groups attached to silicon atoms also provide a bridge to anionic processes. For instance, macromolecules containing *p*-vinylphenylsilicon end groups react surprisingly readily with sodium to yield radical anions which effect block copolymerization of vinyl monomers.

[Lecture at Krefeld (Germany), December 16th, 1965]

[VB 972/279 IE]

German version: Angew. Chem. 78, 309 (1966)

## Ammonolytic Processes in Liquid Ammonia


*O. Schmitz-DuMont*, Bonn (Germany)


The hexamminecobalt(III) ion behaves as a cationic ammono acid in liquid ammonia:

$$[Co(NH_3)_6]^{3+} + NH_3 \rightleftarrows [Co(NH_3)_5NH_2]^{2+} + NH_4^+ \qquad (1)$$

Addition of 1 equivalent of $KNH_2$ and then of potassium phenoxide at −20 °C precipitates amidopentamminecobalt(III) phenoxide. At +20 °C the amidopentamminecobalt(III) ion *(1)* undergoes condensation to a binuclear complex $[(NH_3)_4Co(NH_2)_2Co(NH_3)_4]^{4+}$ *(2)*, which reacts further with the ion *(1)* to afford the trinuclear complex *(3)*.

$[(NH_3)_4Co(NH_2)_2Co(NH_3)_3NH_2Co(NH_3)_5]^{6+}$ *(3)*

Products *(2)* and *(3)* are isolated as nitrates. It is thus shown for the first time that ammonolysis of ammine complexes in liquid ammonia proceeds analogously to the hydrolysis of aquo complexes in aquous media.

The ammonolysis of $Si(C_6H_5)_4$, $Sn(C_6H_5)_4$, $Pb(C_6H_5)_4$, $P(C_6H_5)_3$, $As(C_6H_5)_3$, and $Sb(C_6H_5)_3$ in liquid ammonia containing $KNH_2$ has been studied. $Si(C_6H_5)_4$ gives the dipotassium salt of hexaamidocyclotrisilazane *(4)*, which even at 0 °C undergoes polycondensation with loss of ammonia[1]. This product *(4)* is also obtained on ammonolysis of hexaphenylcyclotrisilazane. $Sn(C_6H_5)_4$ is also completely ammonolysed at 0 °C, with formation of $K_2[Sn(NH_2)_6]$[2]. Ammonolysis of $Pb(C_6H_5)_4$ leads partly to a black, very explosive nitride of quadrivalent lead and, with loss of nitrogen, to $K[Pb(NH_2)_3]$. $P(C_6H_5)_3$, when heated in an autoclave at 100 °C (not otherwise), is partly cleaved to yield triphenylcyclotriphosphazane $(C_6H_5PNH)_3$. $As(C_6H_5)_3$ and $Sb(C_6H_5)_3$ are completely ammonolysed to $K[As(NH)_2]$ and $K[Sb(NH)_2]$. Tetracyclohexyltin is completely resistant even at 100 °C, whereas tricyclohexylphenyltin suffers ammonolysis with loss of the phenyl group. Thus ammonolysis is the easier the more polar the M–C bond.

[Lecture at Aachen (Germany), December 17th, 1965]

[VB 975/282 IE]

German version: Angew. Chem. *78*, 340 (1966)

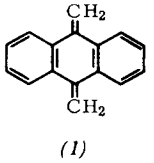

[1] *O. Schmitz-DuMont, W. Jansen,* and *W. Schaal,* Z. anorg. allg. Chem. *339*, 113 (1965).

[2] *O. Schmitz-DuMont, G. Müller,* and *W. Schaal,* Z. anorg. allg. Chem. *332*, 263 (1964).

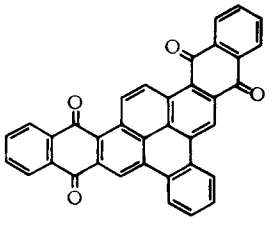

# SELECTED ABSTRACTS

**The homoserine dehydrogenase from Rhodospirillum rubrum** has been found by *P. Datta* and *H. Gest* to show interesting control phenomena. The enzyme, which the authors concentrated by a factor of 1800, catalyses the DPNH-dependent oxidation of homoserine to 2-amino-4-oxobutanoic acid. The enzyme exhibits end-product inhibition by L-threonine. However, this inhibition is eliminated in the presence of L-isoleucine or L-methionine. Both of these amino acids are end-products of another reaction path starting with homoserine. In the absence of threonine, isoleucine and methionine activate the oxidation of homoserine, but not the reduction of 2-amino-4-oxobutanoic acid. The regulating effects of the amino acids are completely reversible. The regulating effect of threonine and isoleucine can no longer be observed in the absence of $K^+$. / J. biol. Chemistry *240*, 3023 (1965) / −Hö. [Rd 405/614 IE]

**Diels-Alder reactions of 9,10-anthraquinodimethane** *(1)* have been studied by *I.T. Millar* and *K. E. Richards.* The compound *(1)* forms adducts with 2 moles of dienophile, whereas other *p*-quinodimethanes react with only 1 mole of dienophile. *Cis-* or *trans*-9,10-dimethyl-9,10-dihydroanthracene-9,10-diol is dehydrated in the presence of excess dienophile, and the compound *(1)* formed reacts with the dienophile to form the diadduct. Aromatization takes place in nitrobenzene. The dimethyl ester of acetylenedicarboxylic acid




*(1)*




*(2)*

reacts with *(1)* to form the tetramethyl ester of benzo[*e*]-pyrene-2,3,6,7-tetracarboxylic acid [m.p. 321 °C, yield 23 % (in boiling nitrobenzene)]. The reaction of *(1)* with maleic anhydride in boiling acetic anhydride leads to the formation of 1,2,3,6,7,8,8a,12b-octahydrobenzo[*e*]pyrene-2,3:6,7-dicarboxylic anhydride (m.p. 230 °C, yield 60 %). *(1)* reacts with 1,4-naphthoquinone in boiling nitrobenzene to form the diquinone *(2)* (m.p. 360 °C, yield 46 %). / Chem. Commun. (London) 1965, 369 / −Ma. [Rd 384/593 IE]

**The specificity of snake-venom protease** has been studied by *G. Pfleiderer* and *A. Krauss.* From the crude poison of *Crotalus atrox* three isoenzymic proteases were separated by chromatography. The substrates are peptides with known amino acid sequences: insulin, the oxidized A and B chains of insulin, and glucagon. Peptide linkages in which the amino group belongs to a leucine or phenylalanine unit are hydrolysed preferentially. High-molecular weight native proteins are not attacked; the digestion must be preceded by denaturation by heat or urea. The substrates must have a chain length of between 5 and 20 amino acid units. / Biochem. Z. *342*, 85 (1965) / −Hö. [Rd 410/619 IE]

**o-Carboranyl derivatives of boron compounds** have been synthesized by *J. L. Boone, R. J. Brotherton,* and *L. L. Patterson* by double decomposition of monolithio-*o*-carborane *(1)* with chlorobis(dimethylamino)borane *(2)* in ether:

$$\underset{(1)}{o\text{-}HCB_{10}H_{10}CLi} + \underset{(2)}{ClB[N(CH_3)_2]_2} \rightarrow \underset{(3)}{o\text{-}HCB_{10}H_{10}CB[N(CH_3)_2]_2} + LiCl$$

Bis(dimethylamino)-*o*-carboranylborane *(3)* is obtained from this reaction in 45 % yield; m.p. 46 °C. This compound undergoes alcoholysis with quantitative formation of dimethylamine according to

$$\underset{(3)}{o\text{-}HCB_{10}H_{10}CB[N(CH_3)_2]_2} + 3\ CH_3OH \rightarrow o\text{-}HCB_{10}H_{10}CH + B(OCH_3)_3 + 2\ (CH_3)_2NH$$

Hydrolysis of *(3)* in ether gives 70 % of the theoretical amount of dimethylamine, together with a viscous, insoluble precipitate. Infrared examination of the non-volatile material showed that the products of this reaction include a small quantity of *o*-carborane (but no dihydroxy-*o*-carboranylborane).

$$\underset{(4)}{o\text{-}(n_4\text{-}CH_9)CB_{10}H_{10}CLi} + \underset{(5)}{(ClBNCH_3)_3}\ KH \rightarrow \underset{(6)}{[o\text{-}(n\text{-}C_4H_9)CB_{10}H_{10}CBNCH_3]_3} + 3\ LiCl$$

*N,N',N''*-Trimethyl-*B,B',B''*-trichloroborazine *(5)* reacts with *C*-monolithio-*C'*-n-butyl-*o*-carborane *(4)* in an ether-heptane mixture to give a 64 % yield of *B,B',B''*-tris-(n-butyl-*o*-carboranyl)-*N,N',N''*-trimethylborazine *(6)*. This last compound is a light yellow, low-melting wax. / Inorg. Chem. *4*, 910 (1965) / −Sch. [Rd 428/637 IE]

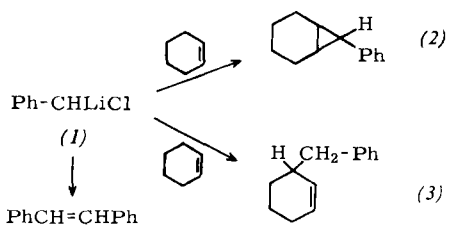
**The synthesis of tetracyanooxirane** *(1)* is described by *W. J. Linn, O. W. Webster*, and *R. E. Benson*. This compound is obtained in yields of from 65 to 70 % when a 30 % solution of $H_2O_2$ is added dropwise to a cooled solution of tetracyanoethylene in acetonitrile. Oxidation of the tetracyanoethylene radical anion with acidic $H_2O_2$ in water also leads to the formation of *(1)* (58 %). The compound (m.p. 177–178 °C) crystallizes in the form of needles, is stable in air, and is slowly decomposed by water.

$$(NC)_2C{=}C(CN)_2 + H_2O_2 \longrightarrow (NC)_2C\overset{O}{\diagup\!\diagdown}C(CN)_2 + H_2O$$
*(1)*

It is attacked at one of the nitrile groups by iodide and bromide ions with formation of cyanogen halide and the tricyanovinylalkoxide anion. Pyridine derivatives and dialkyl sulfides open the ring to form stable dicyanomethylides and carbonyl cyanide. When di-n-butyl sulfide is used, carbonyl cyanide is obtained in a yield of 86 to 91 %. / J. Amer. chem. Soc. *87*, 3651 (1965)] / –Ma. [Rd 381/590 IE]

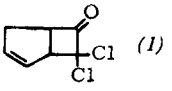
**Automatic equipment for the synthesis of polypeptides** is being operated in the Rockefeller Institute, New York. *R. B. Merrifield* and *J. M. Steward* have succeeded in automating the heterogeneous polypeptide synthesis. The C-terminal amino acid of the polypeptide to be synthesized is anchored to an insoluble particle (polystyrene with 2 % of divinylbenzene, diameter 10 to 80 mμ). The other amino acids are then attached to this first acid by essentially conventional methods. An important advantage of the process is the insolubility of all the intermediates, so that the only purification required at each stage is washing. The particles to which the polypeptide chains are anchored remain in the reaction vessel throughout the process. Thus the process consists simply in the changing of the reactant and wash solutions and in the programming of the amino-acid sequence, all of which are technically simple operations. With the aid of this apparatus, it is possible to lengthen a peptide by 6 amino acids in 24 hours. So far, the peptide hormones bradykinin (9 amino acids), methionylsilylbradykinin (11), and angiotensin II (8) have been synthesized with full biological activities and in yields of about 70 %. / Chem. Engng. News *43*, no. 25, p. 540 (1965) / –Hö. [Rd 400/609 IE]

**The reaction of ω-dichlorotoluene with lithium and cyclohexene** in tetrahydrofuran between 5 and 10 °C has been studied by *P. Mavrikos* and *A. Cheng*. Gas chromatography of the distillate shows that in addition to 26 % of dibenzyl, 11 % of stilbene, and 8 % of benzyl chloride, it also contains 20 % of 7-phenylnorcarane *(2)* (two isomers) and 6 % of 3-benzylcyclohexene *(3)*. It is thought that the carbenoid α-chloro-α-lithiotoluene *(1)* is first formed, and that this is converted into the products *(2)* and *(3)* either directly or *via* free phenylcarbene, by addition across the double bond or by insertion into an allyl C–H bond of the cyclohexene. *(1)* can also be assumed to be a precursor of stilbene. Further, *(1)* undergoes transmetalation to form benzyl chloride, which is probably responsible for the formation of dibenzyl. The




similarity of the product composition to that obtained in the reaction of benzyl chloride with butyl-lithium suggest a common intermediate. / J. org. Chemistry *30*, 1675 (1965) / –Eb. [Rd 424/633 IE]

**A new tropolone synthesis using dichloroketene** is described by *D. R. Brandt, K. R. Fountain, E. J. Gaughan, D. A. Reich*, and *H. C. Stevens*. Dichloroketene is prepared at a low temperature by the dehydrochlorination of dichloroacetyl chloride with triethylamine, and is treated *in situ* with cyclopentadiene to form the 1:1 adduct (yield 70 to 75 %), which probably has the bicyclic structure *(1)*. Hydrolysis of the adduct with aqueous potassium acetate in acetic acid yields tropolone, which can be isolated as the copper complex



*(1)*

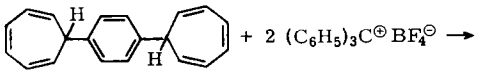
(m.p. 320 °C, yield 52 %). The free tropolone is obtained by treatment of the complex with $H_2S$ in $CHCl_3$. / 150th Meeting Amer. Chem. Soc. *1965*, 62S / –Ma. [Rd 383/592 IE]

**The determination of alcohols in water by the ATR technique** (attenuated total reflection) has been described by *C. P. Malone* and *P. A. Flournoy*. Infrared radiation is passed through a material with a high refractive index, *e.g* AgCl, KRS-5 (TlBr + TlI), or germanium, at an angle slightly greater than the critical angle for total reflection, onto the interface with the absorbing substance (alcohol/water mixture.) The radiation penetrates the material to a depth (fraction of λ) that depends on the angle of incidence, the refractive index of the substance, and the wavelength. Owing to partial absorption, reflection back into the optically denser medium is not total. The radiation, after reflection one or more times, is subjected to a spectrophotometric examination in which it is compared with the totally reflected radiation obtained with air in place of the absorbing sample. Until now it has been practically impossible to determine alcohols in water by infrared spectroscopy, owing to the solubility of the cell windows in water and owing to the difficulty of obtaining layer thicknesses of a few μ with high reproducibility. Alcohol-water mixtures obey the Beer-Lambert law at all alcohol concentrations from 0 to 100 %. / Spectrochim. Acta *21*, 1361 (1965) / –Hz. [Rd 396/605 IE]

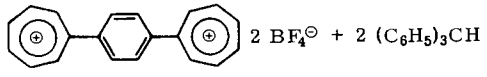
**The gas-chromatographic detection of monosaccharides in the septanose and open-chain forms** has been reported by *E. Bayer* and *R. Widder*. The sugars are converted into glucosides and then permethylated, in order to "freeze in" the forms that exist in the solution. The gas chromatography is then carried out on polyethylene glycol/kieselgur. The permethyl ethers can be separated preparatively. Depending on the methylation conditions, the above procedure yields furanosides, pyranosides, septanosides, and acyclic carbonyl forms (al forms). For example, by direct methylation of galactose with $BaO/CH_3I$, the authors obtained considerable quantities of the septanose form. The al form occurs in proportions of up to 3.4 % in the case of fructose, and up to 2.1 % in the case of galactose, but only up to 0.1 % in the case of glucose. / Liebigs Ann. Chem. *686*, 181, 197 (1965) / –Bu. [Rd 443/265 IE]

**Unsolvated "Grignard compounds"** do not crystallize as such as has been shown by *E. Weiss* for methylmagnesium and ethylmagnesium bromides. Alkylmagnesium halide crystals obtained from ether solutions lose ether of crystallization at 100 to 120 °C/$10^{-3}$ mm Hg; this is accompanied by the disappearance of all the X-ray reflections that suggest the existence of an unsolvated Grignard compound. These are replaced by the diffraction lines for (polymeric) dialkylmagnesium $(R_2Mg)_\infty$ (R = $CH_3$, $C_2H_5$) and for magnesium halide $MgX_2$ (X = Cl, Br). It is uncertain whether all Grignard compounds undergo disproportionation on desolvation, or whether Grignard compounds prepared in non-solvating solutions are disproportionated even in solution. The $MgX_2$ reflections are distinctly broadened, indicating the presence of lattice defects. / Chem. Ber. *98*, 2085 (1965) / –Eb. [Rd 425/634 IE]

**The synthesis of p-phenyleneditropylium difluoroborate** *(1)*, a stable salt of a dicarbonium ion, is described by *R. W. Murray* and *M. L. Kaplan*. The starting material *(2)* is obtained in a poor yield by the thermal or chemical decomposition of 1,4-bis(diazomethyl)benzene in benzene. When a solution of *(2)* in $CH_2Cl_2$ is treated with excess trityl fluoroborate (64 h), the



*(2)*



*(1)*

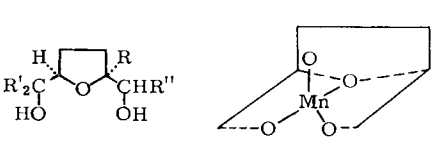
rust-red, crystalline difluoroborate *(1)* separates out in 97 % yield (m.p. < 350 °C). The unusual stability of the dicarbonium ion is due to the presence of the aromatic tropylium system. / Tetrahedron Letters 1965, 2903 / –Ma. [Rd 391/600 IE]

**The synthesis of sulfonates by cleavage of ethers with sulfonic acids** is reported by *D. Klamann* and *P. Weyerstahl*. Dialkyl and alkyl aryl ethers undergo cleavage when heated with anhydrous sulfonic acids such as *p*-toluenesulfonic acid *(1)* and methanesulfonic acid *(2)*; symmetrical aliphatic ethers consume two moles of sulfonic acid to form the ester of the sulfonic acid, while alkyl aryl esters react with one mole of sulfonic acied to form the alkyl sulfonate and the phenol.

$$R{-}O{-}R' + 2\,R''{-}SO_2OH \rightarrow 2\,R''{-}SO_2OR + H_2O$$

The reactions take from 5 to 15 hours at 150 to 180 °C. The reaction is stopped at a moderate yield by the water formed. In the case of high-boiling ethers, the water can be eliminated continuously, and the yield can be increased to about 70 %. Examples: R–O–R′: R = R′ = $C_2H_5$, cleavage with *(1)*, b.p. of ester 79–80 °C/0.05 mm Hg, yield 26 %; R = R′ = n-$C_4H_9$, *(1)*, b.p. 105–106 °C/0.1 mm, yield 55 %; R = $C_6H_5$, R′ = $CH_3$, *(1)*, b.p. 82–84 °C/0.07 mm, yield 74 %; R = $C_6H_5$ R′ = $CH_3$, *(2)*, b.p. 41–42 °C 1 mm, yield 38 %. / Chem. Ber. *98*, 2070 (1965) / –Ma. [Rd 386/595 IE]

**High yields of *cis*-2,5-bis-hydroxymethyltetrahydrofurans were obtained by the permaganate oxidation of 1,5-dienes** by *E. Klein* and *W. Rojahn*. Geranyl acetate gives only the *erythro* form of the tetrahydrofuran derivative (70 % yield),



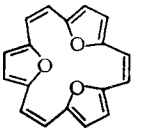
*(3)*

*(1)* R = R′ = $CH_3$
R″ = $CH_2OAc$, m.p. 107–108 °C

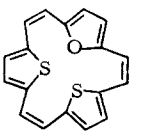
*(2)* R = R′ = R″ = H, $d_4^{20} = 0.944$, $n_D^{20} = 1.4446$

whereas neryl acetate gives only the *threo* form (68 % yield). *(2)* is obtained in 20 % yield from 1,5-hexadiene. The strict stereospecificity has been explained by the authors and by *G. Wilke*, but the explanation does not cover the simultaneous cyclization and oxidation. In the $MnO_4^-$ ion, manganese has the coordination number 4 and a formal valence of +7. A very large number of electrons are withdrawn from the manganese atom, so that its electron affinity should be very high. The complex *(3)* is suggested as an intermediate in the oxidation. / Tetrahedron *21*, 2353 (1965) / –Bu. [Rd 445/654 IE]

**Triepoxy[18]annulene and epoxydiepithio[18]annulene** have been synthesized by *G. M. Badger*, *J. A. Elix*, *G. E. Lewis*, *U. P. Singh*, and *T. M. Spotswood*. Furan-2,5-diacetic acid and methyl *cis*-α,β-bis-(5-formylfur-2-yl)acrylate were condensed in acetic anhydride and triethylamine and the product



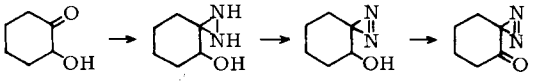
*(1)*



*(2)*

was esterified to form 1,4:7,10:13,16-triepoxy[18]annulene-5,11,18-tris(methyl carboxylate); hydrolysis and decarboxylation of this compound yields the trioxide *(1)* (decomp. 215 to 216 °C, red platelets). 1,4-Epoxy-7,10:13,16-diepithio[18]-annulene *(2)* (m.p. 103 to 103.5 °C, orange needles) was obtained in a similar manner. The NMR spectrum of *(1)* indicates an appreciable ring current, whereas there is no ring current in *(2)*. / Chem. Commun. (London) 1965, 269 / –Ma. [Rd 390/599 IE]

**A diazoketone with a diazirine ring** has been synthesized by *E. Schmitz*, *A. Stark*, and *C. Hörig*. 2-Hydroxycyclohexanone reacts with $NH_3$ and hydroxylamine-*O*-sulfonic acid to form the spirodiaziridine *(1)* (45 % yield), the dehydration of which with $Ag_2O$ yields *(2)* (b.p. 46–47 °C/0.8 mm Hg). Oxidation of *(2)* with t-butyl hypochlorite leads to the diazoketone 1,2-diazaspiro[2.5]octan-4-one (m.p. 6 °C, yield



*(1)* *(2)* *(3)*

36 %). Compounds *(2)* and *(3)* are sensitive to acids, the latter being extremely so. The decomposition of *(3)* yields 2-methylenecyclopentanone and cyclopentanecarboxylic acid. *(3)* reacts with hydrazines to form cyclopentanecarboxylic acid hydrazides, or rearrange to form substituted 1-amino-5,6,7,8-tetrahydrobenzo[*d*]-[1,2,3]triazoles. / Chem. Ber. *98*, 2509 (1965) / –Ma. [Rd 392/601 IE]

**The preparation of ε-caprolactam from cyclohexanecarboxylic acid in liquid $SO_2$** is reported by *N. Tokura*, *T. Kawahara*, and *T. Sato*. In place of the nitrosylsulfuric acid used in the SNIA method, these authors used fuming nitric and fuming sulfuric acids. They assume that nitrosylsulfuric acid is formed *in situ*. Anhydrous $SO_2$, fuming nitric acid, and fuming sulfuric acid were mixed by stirring at 20 °C. Cyclohexanecarboxylic acid was added, and the mixture was heated slowly to 68–70 °C and then poured after an hour into ice-water. ε-Caprolactam (m.p. 68 to 70 °C) was formed in 60 % yield. / Bull. chem. Soc. Japan *38*, 849 (1965) / –Bu. [Rd 444/653 IE]

**The von Auwers-Skita rule** is still a useful means of determining configurations, as is shown by measurements carried out by *H. Feltkamp* and *K. D. Thomas* on methylcyclohexylamines and their *N*-substituted derivatives. This rule states that for *cis-trans* isomers of hydroaromatic compounds, the *cis*-isomer has the higher density and the higher refractive index, but the lower molar refractivity [R]. The rule can also be used in the modified form proposed by *H. van Bekkum*[1] for 1,3-disubstituted cyclohexanes or for polysubstituted rings.

Examples:

| Substance | Form | $d_4^{20}$ | $n_D^{20}$ | [R] |
|---|---|---|---|---|
| 4-t-Butyl-cyclohexylamine | *trans* | 0.8660 | 1.4645 | 49.525 |
| | *cis* | 0.8716 | 1.4670 | 49.435 |
| *N*-Methyl-4-methyl-cyclohexylamine | *trans* | 0.8418 | 1.4511 | 40.704 |
| | *cis* | 0.8500 | 1.4531 | 40.466 |

Liebigs Ann. Chem. *685*, 148 (1965) / –Bu. [Rd 442/651 IE]

[1] *H. van Bekkum*, Recueil Trav. Chim. Pays-Bas *80*, 1310 (1961).

**Brennstoffelemente. Moderne Verfahren zur elektrochemischen Energiegewinnung** (Fuel Cells. Modern Processes for Electrochemical Production of Energy). Monograph No. 82 to "Angewandte Chemie" and "Chemie-Ingenieur-Technik". By *W. Vielstich*. Verlag Chemie, GmbH., Weinheim/Bergstr. 1965. 1st Edit. XV + 388 pp., 267 figs., 31 tables, plastic cover, DM 54.– (about $ 14.–).

In recent years the problems involved in fuel cells, where chemical energy is converted directly into electrical energy, have drawn the attention of an increasing number of technologists and scientists. *W. Vielstich* has chosen the right moment for a comprehensive review of the results and for delineation of unsolved problems.

The introductory chapter lists the cells according to the physical state of the reactant materials. Understanding is made easy for the novice by clear diagrammatic drawings.

In accord with their importance, much space is given to description of methods of electrochemical investigation, to electrode kinetics, and to transport phenomena. Special treatment is accorded to anodic oxidation of hydrogen, mono- and di-hydric alcohols, aldehydes, carboxylic acids, hydrocarbons, ammonia, hydrazine, and borohydrides, as well as to cathodic reduction of oxygen hydrogen peroxide, nitric acid, bromine, and chlorine. This section includes unpublished work by the author concerning, *e.g.*, the pH-dependence of the exchange current density of the $H_2$ reaction and potentiostatic potential diagrams of smooth noble-metal electrodes. The fundamental studies have contributed materially to a better understanding of the effects observed, but it remains for the future to show whether they provide a basis for new, promising technical developments.

The treatment of low-, medium-, and high-temperature cells, and of cells containing dissolved fuel, occupies more than 100 pages. This chapter, completed in 1964, makes it particularly apparent how vigorously development of cells and batteries is progressing. Special types, such as redox cells, and amalgam-oxygen and biochemical fuel cells, receive separate treatment.

Discussion of the conversion of heat and nuclear energy by electrochemical processes is a novel feature for a monograph on fuel cells. Electrochemical energy storage and electrochemical enrichment of deuterium and tritium are included in the border problems that are treated in about 30 pages. For the preparation of individual chapters *W. Vielstich* enlisted collaboration of *A. Küssner* (hydrogen foil electrodes), *R. P. Tischer* (fuel cells at medium and high temperatures), *H. Schmidt* (high-temperature cells with solid electrolytes), and *G. Grüneberg* (heat and nuclear energy converters).

The book is excellently produced and, because of the balanced treatment of the theory and technical status of fuel cells, will certainly receive a good reception by a wide audience. *F. von Sturm* [NB 446/299 IE]

**Trivialnamenkartei** (Card File of Organic Trivial Names). Issued by the Editorial Office of Chemisches Zentralblatt, Berlin. Verlag Chemie, GmbH., Weinheim/Bergstr. 1964. 8000 Cards (72 mm×104 mm) in 3 cartons, DM 280.– (about $ 70.–).

Trivial names are a necessity, but often also a source of annoyance: the latter always when the structure cannot be derived from the name no matter how great one's knowledge of nomenclature and the like. It is the aim of this set of cards, compiled in the Editorial Office of Chemisches Zentralblatt, to offer help in this situation. On each card there is in the center the structural formula, in the top left corner the German trivial name (or names), in the top right corner the English trivial designation, in the bottom left corner the molecular formula, and in the bottom right corner literature references (mostly to Beilstein and to abstracts in Chemisches Zentralblatt or Chemical Abstracts). The cards are numbered consecutively according to their alphabetical order, which facilitates replacement in the correct position. The German and the English forms of the trivial names have independent numbers, so that by simply sorting into rising numbers the cards can be arranged according to the alphabetical order of either the German or the English keywords.

Compounds having several trivial names have a corresponding number of cards. For example, ouabain appears also as acocanthenin and as g-strophanthin at appropriate places. This system is, however, not always followed strictly. Thus diphosphopyridine nucleotide is not to be found under that designation. But a corresponding card appears under DPN, and other trivial designations of this coenzyme are present as separate cards: yet there is no card for NAD, which has recently become the customary abbreviation in place of DPN. It is very welcome that abbreviations are treated here as trivial names. In most cases the cards contain also an explanation of how these abbreviations arose, *e.g.*, NAA = naphthylacetic acid, or DDD = dichlorodiphenyldichloroethane, but occasionally (CMU, PAN) such explanation is omitted.

In addition to references to Beilstein, Chemisches Zentralblatt, and Chemical Abstracts there are literature citations such as "Karrer 2203" or "Negwer 1971", but the inexperienced are not told what these mean (at least not in the set of cards supplied for review).

In some cases the user will fail in his search for a trivial name. This is not surprising for 8000 cards, but regular supplements are envisaged which are to complete the file and also to bring them up to date [*]. The Editorial Office of Chemisches Zentralblatt asks specifically to be informed of further trivial names that should be included and, in the reviewer's opinion, it is to be hoped that this request will find the strongest possible echo, because the cards are and will continue to be a great help to all who possess them; they furnish the information sought quickly, reliably, without long thumbing over, and without ballast. *H. Grünewald* [NB 447/300 IE]

**Struktur und Synthese von Vitaminen** (Structure and Synthesis of Vitamins). *G. Kempter*. WTB-Wissenschaftl. Taschenbücher – Chemie, Vol. 22, Akademie-Verlag, Berlin 1964. 1st Edit., 155 pp., numerous illustrations, DM 8.– (about $ 2.–).

This small volume presents a lucid survey of the structures and syntheses of nearly all the vitamins. The author writes fluently and competently. He describes the efforts of the organic chemists that led to the elucidation of the structures of most of the vitamins in the early 1930's making this one of the highlights of natural product chemistry; the book then shows how the time required for investigations of this nature is greatly reduced nowadays by the application of physical methods, although these methods can only be based on knowledge gained by classical methods

One or two technically important syntheses or syntheses that provide evidence of the structure are appended to the structural elucidation of each vitamin, in a style that betrays the authors detailed technical knowledge The properties of the vitamins and a number of antagonists are described. The chapters on the fat-soluble vitamins are particularly good; however, the stereochemistry of tachysterol is only touched upon. In the case of the water-soluble vitamins, the cofactor form and its synthesis is not generally considered, but this does not form part of the object of the book. In the discussion of vitamin $B_{12}$, the recent attempts to synthesize the corrin ring system are not mentioned.

[*] The first supplement comprising about 1100 cards will appear shortly.

The layout of the book is very clean, and the formulae are particularly clear. The few misprints and biochemical incongruities in the text are of no importance. The book closes with a glossary in German, English, and Russian. The literature survey is unfortunately confined to fairly recent reviews. Onthe whole, however, this is an excellent little book, and contains everything that the student is likely to absorb from very good special lectures. *L. Jaenicke* [NB 440/275 IE]

**Die Oxydation organischer Verbindungen mit Sauerstoff** (The Oxidation of Organic Compounds with Oxygen). By *R. Schöllner*. Wissenschaftliche Taschenbücher, Vol. 23. 1st Edit., Akademie-Verlag, Berlin 1964, 195 pp., 8 tables, 6 illustrations, cardboard DM 12.50 (about $ 3.10).

If one is not disturbed by sentences such as "The rapid development of the chemical industry in the Soviet Union and in the entire socialist camp will greatly favor the application of efficient processes for the oxidation of organic raw materials to form high-quality base chemicals", or by a number of inaccuracies and misprints, this book will provide a good picture of the many reactions of the oxygen molecule with organic substances. In addition to preparative aspects, on which the greatest stress is placed the kinetics of autoxidation also are discussed.

The question arises, however, of the type of reader for whom this book is intended. It contains too many specialized data for the student whereas the number of references to original publications is too small for the research worker (the 22 references given are mainly reviews); the book must therefore be intended primarily for industrial chemists. For this type of reader, in fact, the book may provide many suggestions in the course of a few hours' easy reading.

*R. Criegee* [NB 428/298 IE]

**Silicate Science.** Vol. II. Glasses, Enamels, Slags. By *W. Eitel*. Academic Press, New York-London 1965. 1st Edit., XII + 707 pp., numerous figures, $ 26.–.

This volume, the second of the planned series of five, deals with glasses, enamels, and slags. The chemical and physicochemical properties, such as the viscosities of glass melts, surface tension, electrical conductivity, and changes in density, are discussed in detail. Considerable space is devoted to the structures of glasses and to theories on the subject. Non-silicate glasses are also mentioned. A special chapter is given to the surface structure and surface reactions of glass. The second section deals more fully with industrial glasses, their homogeneity, color correction, reaction residues, gas inclusions, and the relationships between physico-chemical properties and chemical composition than with enamels. The chapter on slags reports recent findings relating to the constitution of slags, and includes sections on the viscosity and corrosiveness of molten slags and on equilibria between molten slags and molten metals.

The literature covered is mainly that published between 1952 and 1962. The section on glass contains 703 references from this period, while that on enamels and industrial glasses contains 458. The chapter on slags contains 186 references. The division into short, numbered chapters makes the book tidy and useful as a reference work. It is regrettable that, in keeping with the publishers' wishes, the contents of the book "Physical Chemistry of Silicates" (1954) are assumed to be known, and that the publications discussed in this earlier work are dismissed with a mere reference in the present volume. Apart from this, the author has been extremely successful in his use of the extensive literature. Misprints (*e.g.* page 511, where a phenylene complex is given instead of a catechol complex) are few.

As a reference book and handbook, this work is practically indispensable for all laboratories and institutes concerned with this field. *Armin Weiss* [NB 443/278 IE]

**Methods in Carbohydrate Chemistry.** Edited by *R. L. Whistler* in collaboration with *J. N. BeMiller* and *M. L. Wolfrom*. Vol. V: General Polysaccharides. Academic Press, New York-London 1965. 1st Edit., XXII + 463 pp., 26 figures, 11 tables. $ 16.50.

The present volume completes the provisional object of this series[1]. Like the previous volume, it contains a collection of reliable procedures. Volume V is devoted to methods in polysaccharide chemistry (cellulose and starch are excluded). 86 procedures are presented by 75 well-known specialists. The text is divided into seven main parts: methods of isolation (18 contributions), preparation of polysaccharides (25 contributions), chemical (4 contributions) and physical (5 contributions) analysis, molecular weight determinations (4 contributions), structural analysis (13 contributions), and the preparation of polysaccharide derivatives (7 contributions).

The first part describes the modern methods of extraction and purification of polysaccharides by chromatography, gel filtration, precipitation, dialysis, ultrafiltration, and zone electrophoresis. Dehydration and freeze-drying of preparations are explained. The second part contains particulars on the isolation of selected polysaccharides from plants, animals, and microorganisms, including mucopolysaccharides and lipopolysaccharides, glycogen, heparin, hyaluronic acid, cellulose, hemicelluloses, inulin, chitin, pectin, dextran, and plant gums. Part III contains only methods for the determination of lignin, acetyl and ester groups in pectin, and primary hydroxyl groups in polysaccharides The physical methods (Part IV) cover only the electrophoretic homogeneity, the optical rotation, the thixotropy and pseudoplasticity, the film properties, and the immunology of the polysaccharides. Part V then deals with molecular weight determinations by end-group analysis with $^{14}CN^{\ominus}$ and periodate, or by osmometry and isothermal distillation.

Methods of hydrolytic and oxidative degradation of polysaccharides and their methylated derivatives for the purpose of structural analysis account for the major part of Part VI. An exhaustive table (44 pp.) of methyl ethers of sugars should be very useful to the practical chemist. The oxidation and reduction of uronic acids, esterification and deacetylation desulfurization (of heparin), and etherification are some of the points dealt with in connection with the preparation of polysaccharide derivatives.

Since the book does not deal exhaustively with the subject "General Polysaccharides," references are made to methods published in earlier volumes of this or other series. The author index is large (18 pp.), since each contribution is followed by an average of 10 to 15 references. On the other hand, the subject index (a 20-page collective index for volumes III to V) is rather meagre, and contains only about 2000 keywords.

Volume V satisfactorily fulfils the purpose for which it is intended, *i.e.* to serve as a handbook for research and practical laboratory work. Both the experienced carbohydrate chemist and the newcomer to the field will quickly realize that "Methods of Carbohydrate Chemistry" is as valuable and as reliable as is "Organic Syntheses" in organic chemistry or "Biochemical Preparations" in biochemistry.

*J. M. Harkin* [NB 444/279 IE]

**The Proteins: Composition, Structure, and Function.** Edited by *H. Neurath*. Academic Press, New York-London. 2nd Edit., Vol. II, 1964, XIV + 840 pp., numerous illustrs. and tables, $ 26.00 (by subscription $ 24.00); Vol. III, 1965, XIV + 585 pp., numerous illustrs. and tables, $ 21.00 (by subscription $ 18.50).

Soon after its publication, the first edition of "The Proteins" (Chemistry, Biological Activity, and Methods), together with the standard monograph by *Cohn* and *Edsall*, became

[1] Review of Vol. IV: Angew. Chem. *77*, 226 (1965).

the standard handbook of every protein chemist. Now, ten years later, the first volumes of the second edition have been published. Owing to the illness and untimely death of the co-editor of the first edition, *K. Bailey*, the second edition is edited by *Neurath* alone.

The second edition, like the first, is to comprise four volumes. However, it is not a new edition in the true sense, but a completely new version oriented along different lines. This is evident from the subtitle: "Composition, Structure, and Function", and from the fact that only three of the contributors to the first edition have also contributed to the second. The principal theme of the work is no longer the question of the chemical structure of the proteins, but the problem of the relationship between the structure of a protein and its specific biological function. Comparison of the new edition with the old will make clear the progress that has been made in this field of biochemistry.

The first chapter of Volume II deals with the conformation of the polypeptide chains of proteins in solution (*J. A. Schellman* and *C. Schellman*), while the last chapter is concerned with the X-ray structure analysis of proteins (*Dickerson*); these two chapters are closely related, and even overlap in part. The general theoretical principles and the experimental methods used in the determination of the structures of proteins are described in detail, and the facts noted are discussed. *Dickerson* gives a list of the proteins that are under investigation by X-ray analysis.

The chapters by *Steinhardt* and *Beychok*, "Interaction of Proteins with Hydrogen Ions and Other Small Ions and Molecules," and by *Nichol, Bethune, Kegeles*, and *Hess*, "Interacting Protein Systems," are devoted to the interactions of proteins with proteins or components of low molecular weight. The first of these two chapters is mainly concerned with the acid-base equilibria of proteins, and so provides a basis for the discussion of the pH-dependence of various protein functions. The chapter on protein-protein interactions has a pronounced physico-chemical bias. This chapter is very informative on the subject of the quaternary structure of many proteins and on the problem of the antigen-antibody reaction. A particularly impressive chapter is "Polyamino Acids as Protein Models" by *Katchalski, Sela, Silman*, and *Berger*, which describes the synthesis and the chemical, physico-chemical, and biological properties of polypeptides, and deals with all the results published in this field. It becomes clear from this chapter how much the elucidation of the structure of proteins, of the genetic code, and of immunological problems owes to studies on synthetic polypeptides.

The first and last chapters of Volume III are of a general nature, while the other four chapters deal with the structures and functions of various proteins. *Sober, Hartley, Carroll*, and *Peterson* give a very instructive treatment of the "Fractionation of Proteins" (solubility, chromatography, electrophoresis, sedimentation, dialysis, ultrafiltration, and immunological methods), and also describe the methods used for the characterization of proteins and the determination of their purity. *Weber* and *Teale* ("Interaction of Proteins with Radiation") discuss the infrared and ultraviolet spectroscopy, fluorescence, light scattering, and optical rotatory dispersion of proteins *Fraenkel-Conrat* gives a brief outline of the structures and functions of virus proteins, and *Putnam* ("Structure and Function of the Plasma Proteins") and *Singer* ("Structure and Function of Antigen and Antibody Proteins") presents a lucid, impressive survey of the plasma proteins and the antigen-antibody proteins. Finally, *Davie* and *Ratnoff* give a clear description of the various factors that effect the coagulation of blood.

The various chapters are well written by competent authors, and special emphasis is laid throughout on the description of the experimental methods. The literature covered includes very recent publications, so that we are shown the latest situation in each field. These reports are indispensable to anyone who is concerned with proteins. There is only one objection to this work: one gains the impression that the arrangement of the chapters is arbitrary (*e.g.* chapters 7, 11 and 17 would be expected to appear together in that order). This gives the volumes a certain "Advances" character. Regrettable omissions include a somewhat more detailed treatment of denaturation and a chapter on the size and shape of protein molecules such as that contributed by *Edsall* in the 1st Edition (which will consequently still have to be consulted as before). Only a few misprints were found, and the print and layout, with the exception of the cover, are good.

*H. Sund* [NB 441/276 IE]

**Coincidence Tables for Atomic Spectroscopy.** By *J. Kuba, L. Kučera, F. Plzák, M. Dvořak*, and *J. Mráz*. Elsevier Publishing Comp., Amsterdam-London-New York 1965. 1st Edit., XXXI + 1136 pp., about $ 18.00

Anyone who is concerned with trace analysis by emission spectroscopy must constantly ask himself what foreign elements could interfere with a detection or even make it doubtful. *Kuba* and his co-workers have now used all the published data to produce a comprehensive book of tables (about 1150 pages) that supplies the answer to this question immediately.

The emission lines of 90 elements (only At, Bk, Cf, Es, Fm, Fr, Md, No, Pm, Po, and Tc are excluded) between 2000 and 10000 Å are presented in 17 tables. Table IV and V give lines that can be used for the analysis of the rare earths, Table VI for a number of actinides, and Tables VII and VIII for gases. Table IX gives the spark spectrum of air, and calibration lines for the secondary standard Fe are given to at least three decimal places in Tables X and XI. Tables XII and XIII contain the emission lines of inorganic molecules and fragments (*e.g.* AlO, BeO, $C_2$, CN, and CaF). Finally, Table XIV gives the ionization energies of the elements and of their ions.

The principal tables – Table XVI for 73 elements, with a total of 683 analytically important lines (*e.g.* resonance lines), and Table XVII for the rare earths – cover 1050 pages, the elements being arranged alphabetically and in order of increasing wavelength of the most important lines. All interfering emission lines there are always a few dozen!) due to foreign elements are also listed on the following basis: the entire coincidence region is assumed to be so wide that the resolution of two lines on a photographic plate must be possible; the coincident lines are then noted according to their relative intensities for three ranges $\pm \Delta\lambda$. To save unnecessary searching on the part of analysts with high-resolution equipment, the coincident lines are given in three types of print bold, normal, and italic (corresponding to linear dispersions of 0.5 to 5, 2 to 30, and $> 30$ Å/mm). A very disturbing fault is the fact that the tables contain practically no legends or explanations for the symbols used, so that the explanations must be sought in the text in the very early part of the book. Thus in Table I (p. XVII) reference should be made to Table XVI (p. 95), and the explanation of the table "Dislocation of Main Lines" (pp. 63–91) is given on p. XVIII. The values given in Tables X and XI for the standard Fe do not agree exactly; no indication of the source of Table X is given. According to the text on p. XVI, Table XI should contain calibration lines for the standards Cd, Kr, and Fe, whereas according to p. 52 these lines refer only to Fe.

On the whole, this is an excellent and important book in a very good and hard-wearing form – a book for the practical analyst.

*W. Jung* [NB 442/277 IE]

**Coordination Chemistry.** By *F. Basolo* and *R. C. Johnson*. W. A. Benjamin, Inc., New York-Amsterdam 1964. 1st Edit., XII + 180 pp., numerous illustrs. and several tables, linen, $ 4.35.

This book is intended as an introduction to coordination chemistry for American chemistry students. A very skilful treatment of molecular orbital methods and ligand field

theory are given in the explanation of the coordinate bond. In view of the purpose of the book and the class of reader for whom it is intended, the mathematical details are kept to a minimum. Nevertheless, the reviewer knows of no German book on coordination chemistry that would provide such a good theoretical background.

A short chapter on stereochemistry is followed by a section on the preparation and reactions of coordination compounds. Owing to the number of reactions and syntheses to be dealt with in a limited space, the material in this chapter is greatly simplified, and appears in fact to be too simple in many cases. Although original in itself, an exhaustive presentation of this kind can offer the beginner too little real information, while at the same time understating the preparative problems. The next chapter deals with the stability of complexes, and is again very well executed The last section, which is concerned with kinetics and mechanisms, deals mainly with substitutions and redox reactions

The book does excellently what it sets out to do, *i.e.* to provide an introduction to the chemistry of coordination compounds, and also in Germany it could serve as a basis for a one-semester lecture course on coordination chemistry. However, it will also be useful to more experienced chemists who wish a rapid grounding in coordination chemistry as an approach to more advanced literature. The illustrations are very clear, and misprints are rare. One unfortunate error in the Index is the mis-spelling "Zeigler" for "Ziegler", particularly noticeable because it is the last entry.

*Ernst Bayer* [NB 438/273 IE]

**The Chemistry of Alkenes.** Edited by *S. Patai*. The Chemistry of Functional Groups. A series of advanced treatises. Interscience Publishers, a Division of J. Wiley & Sons, London-New York-Sydney 1964. 1st Edit., IX + 1315 pp., numerous illustrations and tables, £ 15.15.0.

The olefinic double bond occupies a central position in organic chemistry by virtue of the unsurpassed variety of reactions in which it takes part. It is therefore gratifying to find that in this first volume of a series dealing with the chemistry of functional groups, the alkenes are accorded a treatment, by authorities, in keeping with their importance. The first of the fourteen chapters in the book presents a wave-mechanical discussion of the olefinic double bond (*C. A. Coulson* and *E. P. Steward*, 147 pp.). Three chapters are then devoted to the formation of olefins by eliminations in solution (*W. H. Saunders, jr.*, 53 pp.), in the gas phase (*A. Maccoll*, 38 pp.), and by condensation (*T. I. Cromwell*, 30 pp.). In the chapter on methods for detection and analysis of olefins (*E. J. Kuchar*, 63 pp.), in which physical methods are discussed in detail, mention might have been made of the papers published in 1962 on the quantitative analysis of simple olefins by far ultraviolet spectroscopy. The chapter on complexes with transition metals (*M. Cais*, 49 pp.) is followed by a section on rearrangements of olefins (*K. Mackenzie*, 81 pp ), which, together with the chapter on allyl compounds (*P. H DeWolfe* and *W. G. Young*, 58 pp.), provides a very comprehensive picture. The next three, rather extensive chapters describe the behavior of olefins towards nucleophiles (*S. Patai* and *Z. Rappoport*, 116 pp.) and free radicals and carbenes (*J. I. G. Cadogan* and *M. J. Perkins*, 96 pp.), as well as in cycloadditions (*R. Huisgen, R. Grashey*, and *J. Sauer*, 215 pp.). The peculiarities of olefins in combination with other double bonds are discussed in the articles on conjugated dienes (*M. Cais*, 71 pp.), cumulenes (*H. Fischer*, 135 pp.), and ketenes (*R. N. Lacey*, 67 pp.), the chapter on cumulenes giving a particularly comprehensive description of this class, which generally receives far too little attention. The book ends with a complete author index, the keying of which might advantageously be imitated in other books, and a subject index.

The up-to-date conception of the subject-matter of the individual chapters and the completeness and clarity of the whole make this book a model work, on which the editor and the authors are to be congratulated. An indication of the quantity of material presented in the book may be obtained from the fact that it contains more than 3500 references extending up to 1962/1963. As is pointed out in the preface, two chapters that were to be included, dealing with the important electrophilic reactions of olefins and the biochemical aspects of the carbon-carbon double bond, have been omitted because of late delivery by the authors; this is a regrettable loss in a book that is so much based on teamwork. Other topics that could have been included in the book are the chemistry of vinylmetal compounds and eliminations from olefins, reference to which is restricted to a few scattered examples. It must be admitted, however, that any additions to the text would have made it impossible to keep the book in the form of a single volume.

The book is well presented and, apart from a few printing errors, carefully produced. It is an important reference book that should have a place in every chemical library. Its broad distribution will be subject to the limits imposed by the price, which is unusually high even for a scientific book.

*G. Köbrich* [NB 425/295 IE]

**The Isoquinoline Alkaloids. A Course in Organic Chemistry.** By *K. W. Bentley*. Pergamon Press, Oxford-London- Edinburgh-New York-Paris-Frankfurt 1965. 1st Edit. VII + 264 pp., £ 1.5.0.

The isoquinoline alkaloids form a chemically and pharmacologically important group of natural products, with more than 400 members, including morphine and the tubocurare poisons. A monograph on this subject written by a leading expert in the field is therefore very welcome.

The book begins with a description of the methods of chemical degradation used in the determination of the structures of isoquinoline alkaloids. In the next twelve chapters, the various alkaloids are dealt with in turn, mainly from the point of view of the substances themselves, and a final chapter is devoted to their biosynthesis. This somewhat one-sided presentation may provide useful information for the initiated. Unfortunately, however, the author fails in his aim of producing a well-rounded monograph suitable for chemistry students. Thus the introduction to this book states that "in these days the structures of complex natural products may be elucidated with scarcely a reaction done at the bench, by the application of the modern tools of ultraviolet, infrared, nuclear magnetic resonance and mass spectrometry, and X-ray crystallography . . .", but no further information about these methods is given, despite the fact that they have been particularly useful in the study of the isoquinoline alkaloids.

The complete absence of references gives a false impression of the recent literature, and the reader will sometimes mistake the author's opinions for published findings (*e.g.* p. 65). On page 81, morphinan structures are given for crotonosine and its derivatives, and this is used as a basis for biogenetic conclusions; on page 154, on the other hand, we find that crotondsine is not a morphinan alkaloid. It is assumed that the numbering often used in the text of the sometimes complicated ring systems is known, and no explanation is given on any of the formulae. The amaryllidacea alkaloids with isoquinoline structures are not mentioned. Misprints which could easily cause confusion occur on pages 15, 18, 97, 243, and 247.

Nevertheless, as a valuable source of information, this book is worth a place in the specialist's reference library, and it might be possible to recommend a revised and enlarged second edition to a wider audience.

*B. Franck* [NB 439/274 IE]

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# The Scientific Work of Hans Meerwein

BY PROF. DR. R. CRIEGEE, KARLSRUHE (GERMANY) [*]

I have been honored with the difficult task of surveying the scientific work of *Hans Meerwein*. I shall base this outline on the 70 or so publications he produced in the course of 63 years (from 1903 to 1965), and on a manuscript prepared by him probably last year, which is to be published in "Chemische Berichte". I am not myself a student of *Meerwein*, but I worked in his institute as senior assistant for five years, from 1932 to 1937, and was therefore able to observe his work during this period from close quarters.

If, of the 70 publications mentioned, we disregard a few short communication, some reviews, and a number of papers on miscellaneous subjects, we are left with about 35 important and fundamental publications, each of which would justify a lecture by itself. Therefore I must confine my remarks to a very small selection.

The first step is to look for the sources of *Meerwein*'s creativeness. In the case of scientists, it is usually the teacher that gives the deciding impulses. However, *Meerwein* did not follow in the footsteps of *Schroeter*, his teacher. His development naturally was strongly influenced by the times in which he lived and by the people he met. Since he mentions nothing about this, even in his notes, we can only suppose that the people who had the greatest influence on him, through their personalities or through their work, were *Anschütz* in Bonn, *Claisen* in Godesberg, *Bredt* in Aachen, and *Werner* and *Pfeiffer*.

Many chemists, and not only the mediocre ones, allow themselves to be led by experiment. They make observations, they follow these up and try to explain them. Attempts to explain lead to new experiments, and these lead in turn to new observations. This was not *Meerwein*'s approach, who started off with deliberation, postulation, and hypothesis. These enabled him to make certain predictions, while experiment served to confirm these predictions – and his predictions nearly always were confirmed. How often, therefore, do we read in his publications that: "The result was as expected". Thus by far the major part of *Meerwein*'s discoveries were not accidental, but the logical outcome of his thinking. Only the discovery of the trialkyloxonium salts fell into his lap unexpectedly in the course of experiments; however, it seems certain that even without this "accident", he would have discovered these compounds later by planned experiments.

Let us now consider a few examples that illustrate *Meerwein*'s method of working, his arguments, and his results.

I shall begin with a field studied by *Meerwein* in his earlier years, namely that of Michael additions and ester condensations. This field is probably not so well known as the others, since the work was completed in 1922. The investigations led to a general method for the preparation of 1,5-dialdehydes and 1,5-ketoaldehydes, and culminated in a simple two-step synthesis of the bicyclo[3.3.1]nonane system from formaldehyde and malonic ester [1].

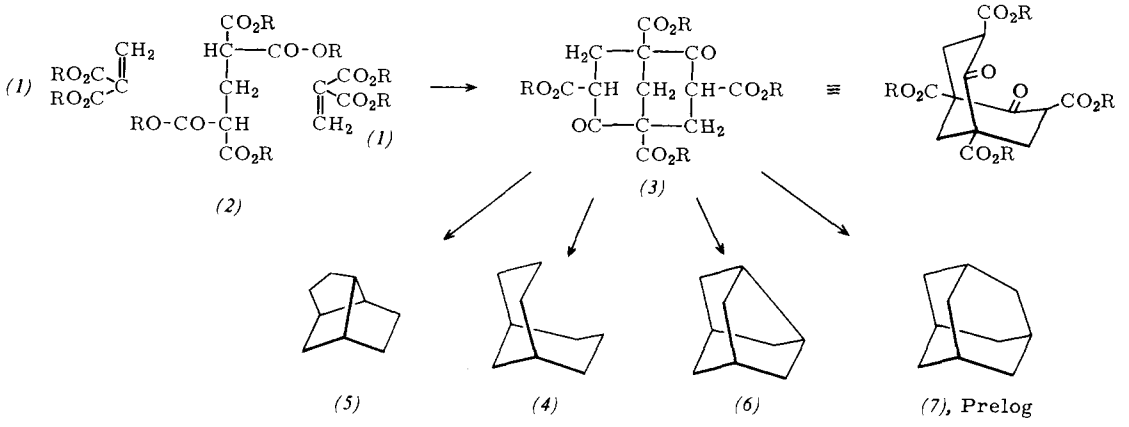
Two moles of a methylenemalonic ester *(1)* condense with one mole of a methylenebis(malonic ester) *(2)* under the influence of sodium ethoxide; a double Michael addition is followed by double elimination of carbonic ester to form the bicyclic diketotetracarboxylic ester *(3)*. This product could be converted not only into the unsubstituted hydrocarbon *(4)* but also into derivatives of two isomeric tricyclononanes *(5)* and *(6)*. Bicyclo[3.3.1]nonane *(4)* is a strainless hydrocarbon, which can be imagined to be cut out of the diamond

[*] Address given at a memorial service held at Marburg University (Germany) on January 15th, 1966.

[1] *H. Meerwein* and *W. Schürmann*, Liebigs Ann. Chem. *398*, 242 (1913); *H. Meerwein*, J. prakt. Chem. [2] *104*, 161 (1922).

The portrait of Prof. *Meerwein* is taken from the archives of Gesellschaft Deutscher Chemiker.
Photograph by *Tita Binz*, Mannheim.

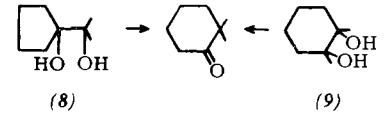
lattice, and in which both six-membered rings are in the chair form. Of the two tricyclic compounds, *(6)* also contains two cyclohexane rings in the chair form, whereas *(5)* contains two somewhat distorted cyclohexane boats. At a time when *Mohr* had just revived *Sachse*'s views on strainless rings, *Meerwein*'s experiments

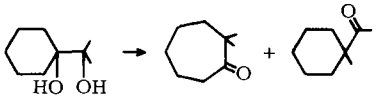



provided one of the earliest proofs. The freedom from strain of cycloheptane and the difference in reactivity of what are nowadays termed axial and equatorial OH groups were also first postulated and demonstrated experimentally by *Meerwein*. However, although he tried to synthesize adamantane *(7)* from his bicyclononane derivative *(3)*, it was not until 20 years later that this synthesis was achieved by *Prelog*.

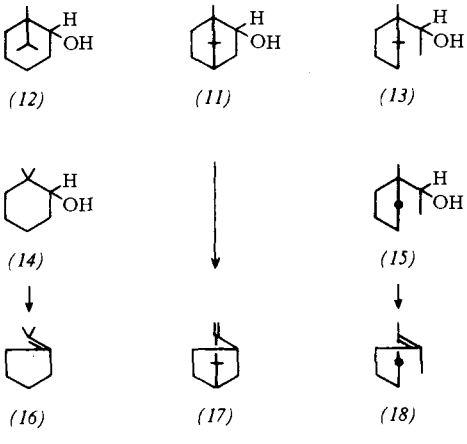
*Meerwein* was interested in the bicyclononane also because of its similarity to bicyclo[2.2.1]heptane (which, however, is strained). The latter system, which according to *Bredt* and others is the basis of camphor and its derivatives, fascinated *Meerwein* at an early stage, not as a structural unit of important natural products (the chemistry of which in the narrower sense remained foreign to him throughout his life), but because of the numerous rearrangements with far-reaching changes in the carbon skeleton that take place in this system. Though the structural relations among pinene, bornyl chloride, camphene, isoborneol, *etc.* were largely elucidated, the nature of the various rearrangements was still obscure.

*Meerwein* entered this field with model reactions on simple cyclic pinacols *(8)–(10)* [2]. He found that the




readily occuring pinacol rearrangement of these compounds is almost always accompanied by a change in the ring system, even though the starting compounds contain strainless rings. The same is true of the retro-pinacol rearrangement, an example of which, according to *Wagner*, is the conversion of borneol into camphene. If we imagine the bicyclic system of borneol *(11)* to be cut open in one of two places, we obtain two monocyclic "pinacolone alcohols" *(12)* and *(13)*. On acid-catalysed dehydration, the somewhat simpler lower homologues




*(14)* and *(15)* of these "model borneols" gave the olefins *(16)* and *(18)*, which differ from camphene *(17)* only in the position of the double bond. This showed that these rearrangements are by no means restricted to the bicyclic systems [3].

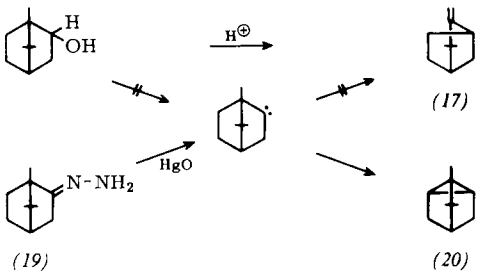
The possible occurrence of epoxides or cyclopropanes as intermediates in these rearrangements could be ruled out immediately, since the conversion of these into the end-products obtained proceeds (if at all) more slowly than that of the pinacols or pinacolone alcohols. The formation of "1,1-diradicals" (we would nowadays say "carbenes") by α-elimination, as suggested by *Tiefeneau*, was also ruled out by experiment. Thus camphor hydrazone *(19)* should give the 1 1-diradical on treatment with mercuric oxide. However, the product is not camphene *(17)*, but consists almost entirely of tricyclene *(20)* [4].

The solution of the problem was published in 1922 by *Meerwein* and *van Emster* (an old friend and colleague) in a paper entitled: The Equilibrium Isomerism Be-

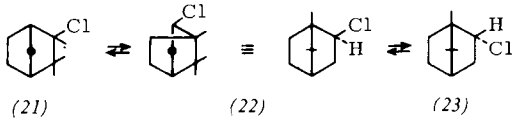
[2] *H. Meerwein*, Liebigs Ann.Chem.*376*,152(1910); *396*,200(1913).

[3] *H. Meerwein*, Liebigs Ann. Chem. *405*, 129 (1914); *417*, 255 (1918).

[4] *H. Meerwein* and *K. van Emster*, Ber. dtsch. chem. Ges. *53*, 1815 (1920).



(19) (17) (20)



(21) (22) (23)

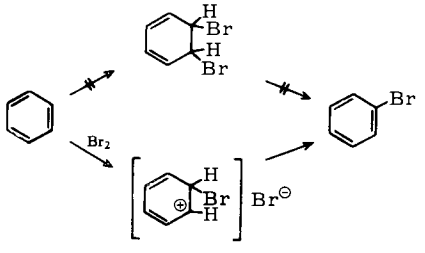
tween Bornyl Chloride, Isobornyl Chloride, and Camphene Hydrochloride [5]. First an analytical method was developed for the determination of the three chlorides *(21)–(23)* in the presence of one another, on the basis of the different reactivities of their chloro-substituents, and it was then possible to follow the rearrangements kinetically. They were all found to be first-order reactions, with rates depending very strongly on the solvent. The extremes were cresol on the one hand, and ether on the other. The effectiveness of the solvent was found to be determined by its "dissociating power", which *Walden* had determined by conductivity measurements on solutions of triphenylchloromethane. The rate of equilibration was affected to an equal or greater extent by complexing agents such as $ZnCl_2$, $FeCl_3$, $SnCl_4$, $SbCl_5$, *etc.* Somewhat later *Hamel*, *Serini*, and *Voster* showed that the rates of the corresponding rearrangements of esters of borneol, isoborneol, and camphene hydrate are also strongly affected by the strength of the esterifying acid.

This led to the now obvious, but then revolutionary conclusion that all these rearrangements are preceded by an ionization, and that the regrouping of carbon atoms takes place in the resulting carbonium ions. Solvents with high dielectric constants, complexing agents, and strong esterifying acids stabilize the ions and so facilitate the heterolysis leading to their formation. Since the ions can only be detected indirectly, *Meerwein* called them "cryptoions".

The idea of ionic reaction mechanisms in organic chemistry was not generally accepted at first, since ionic reactions were held to belong to the realm of inorganic chemistry. It must be remembered that *Lewis*' electronic theory had only just been developed and had not yet found a foothold in Germany, so that concepts such as lone pair of electrons, electron deficiency, sharing of electron pairs, nucleophilic, and electrophilic were still unknown. Nevertheless, *Meerwein* used just these concepts, though in his own terminology derived from complex chemistry.

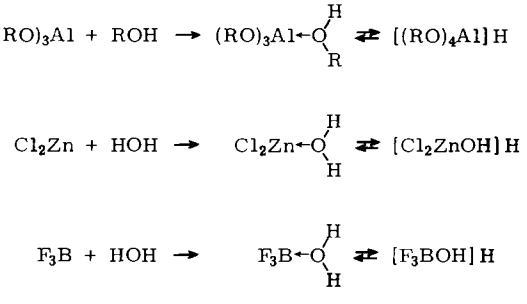
In the meantime, the number of known Wagner-Meerwein rearrangements, as rearrangements proceeding *via* a sextet of electrons on carbon are now generally called, has increased tremendously. To these have been added rearrangements involving sextets on nitrogen and on oxygen. The question now no longer is whether these rearrangements are ionic, but whether they involve classic or non-classic ions, or intimate or solvent-separated ion pairs. It is easy to forget that these are mere questions of detail in comparison with *Meerwein*'s fundamental discoveries.

*Meerwein* was quick to recognize the significance of his ideas, which extended far beyond the rearrangements in the camphor series. In a lecture to the 1925 meeting of the Verein Deutscher Chemiker in Nuremberg on the problem of orientation in substitutions on aromatic compounds [6] he modified the *Thiele-Wieland* theory of substitution *via* addition by assuming that only a single bromine cation was added to the benzene, while the bromide anion remained bound in the "outer coordination sphere". However, this is nothing else but the theory of electrophilic aromatic substitution developed later by *Pfeiffer* and *Wizinger* and perfected by *Ingold*.



(24)

The catalytic action of metal halides such as zinc chloride or antimony pentachloride was also recognized in 1926 as a general principle [7]. These halides, like many other electron-accepting compounds, are ansolvo acids (now known as Lewis acids). "Complex formation", *i.e.* reaction with the nucleophilic centers of water, alcohol, or carboxylic acids, leads to strong protonic acids.



Thus aluminum alkoxides react with alcohols to form alkoxy-acids, the acidic protons of which can be esterified with diazomethane. It is possible in this way to convert alcohols (which do not react as such with diazomethane) into methyl ethers [8]. The catalytic action of zinc chloride in the inversion of sugars or in the elimination of water from alcohols is also explained by the formation of dissociable "esters" of complex zinc acids. Many salts of such acids have been prepared. *Meerwein* also explained the solubility of aluminum hydroxide in

[5] *H. Meerwein* u. *K. van Emster*, Ber. dtsch. chem. Ges. *55*, 2500 (1922).

[6] Angew. Chem. *38*, 815 (1925).

[7] *H. Meerwein*, Schriften der Königsberger Gelehrtengesellschaft *3*, 129 (1926); Liebigs Ann. Chem. *455*, 227 (1927).

[8] *H. Meerwein* and *G. Hinz*, Liebigs Ann. Chem. *484*, 1 (1931).

alkalis by the formation of salts of complex hydroxo acids.

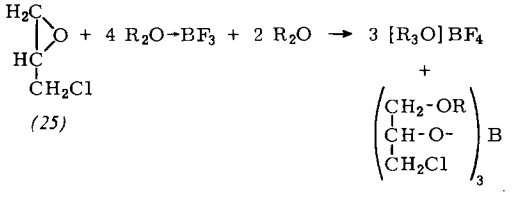
Just as the O–H bond in alcohols can be activated by complex formation with ansolvo acids, so the C=O double bond can be polarized and hence activated by complex formation. Whereas acetone does not react with diazomethane, its molecular complexes with water, alcohols, or lithium chloride react rapidly with diazomethane to form epoxides together with homologous ketones [9]. *Eugen Müller* recently developed these findings into a synthesis of homologous cyclic ketones.

These experiments also led *Meerwein* to study the photochemical decomposition of diazomethane in solution. Together with *Rathjen* and *Werner* [10] he found that the methylene formed can insert into any C–H bond, and so, *e.g.* from diethyl ether, produce a mixture of homologous ethers. This insertion is typical of "hot" carbenes. The formation of tricyclene *(20)* from camphor hydrazone *(19)* is an intramolecular variant of this reaction.

With benzene, on the other hand, the ring is expanded to form tropilidene, a result that prompted several research groups to carry out intensive investigations on the tropilidene-norcaradiene isomerization.

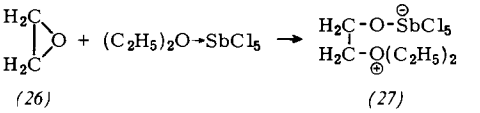
Among the complexing agents mentioned earlier, boron trifluoride occupies a special place because of its small molar volume [11]. Its numerous addition compounds, which were studied by *Meerwein*, are characterized by exceptional stability. The boron trifluoride hydrates and alcoholates behave as strong acids, the compounds with ethers resemble the esters of mineral acids, and those with esters the acid anhydrides. These relations made possible many catalytic reactions such as esterifications, condensations, rearrangements, and polymerizations, but these cannot be discussed here. Instead we shall consider in more detail the role of boron trifluoride in the preparation of tertiary oxonium salts.

Probably one of the most fruitful of *Meerwein*'s discoveries was that of the trialkyloxonium salts, jointly with *Kroning* in 1937 [12]. These long-sought analogues of quaternary ammonium and tertiary sulfonium salts were obtained unexpectedly when epichlorohydrin *(25)* was treated with boron trifluoride etherate.

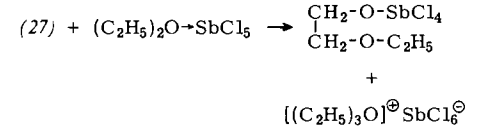


*(25)*

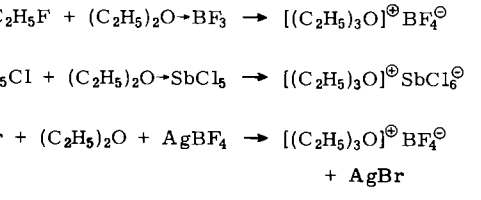
The mechanism of this complex reaction was later elucidated, and will be illustrated here for the somewhat simpler reaction of ethylene oxide *(26)* with the etherate of antimony pentachloride. The first step is cleavage of the oxirane ring to form a zwitterion *(27)*, which transfers an ethyl residue, as a cation, from the oxygen onto a second molecule of $SbCl_5$ etherate.



*(26)* *(27)*



A simpler reaction, but a preparatively less useful one because of its slowness, is that of ethyl fluoride with boron trifluoride etherate. Here, the energy loss on formation of the triethyloxonium ion is compensated by the energy gain accompanying formation of the stable $BF_4^{\ominus}$ anion. Other routes include the reaction of ethyl chloride with $SbCl_5$ etherate, and particularly the reaction of ethyl bromide in ether with silver fluoroborate. The mixture of ethyl bromide and $AgBF_4$ has also proved eminently useful for other alkylations [13].



The trialkyloxonium salts, which superficially are very similar to the tetraalkylammonium salts, are the strongest alkylating agents known. They react as expected for "free" alkyl cations; they are, in fact, stabilized alkyl cations in the same sense that the hydroxonium ion is a stabilized proton. For this reason nearly all simple anions are alkylated immediately, so that trialkyloxonium cations are stable only when accompanied by stable complex anions.

Many paths led to new discoveries from the trialkyloxonium salts. *Meerwein* opened up these paths essentially only after his retirement, *i.e.* at an age when creativity is declining rapidly. Fifteen valuable and lucidly written papers, all published after his 70th birthday, and the last after his 85th, showed that his genius was not dimmed by old age. A few examples may again suffice:

Ethers are alkylated by trialkyloxonium salts to form other oxonium salts. Thus the simplest route to trimethyloxonium salts is *via* the mixed oxonium salt formed by ethylation of dimethyl ether. An alkyl cation also adds readily to the oxygen atom of tetrahydrofuran *(28)*.

[9] *H. Meerwein* and *W. Burneleit*, Ber. dtsch. chem. Ges. *61*, 1840 (1928); *H. Meerwein, Th. Bersin*, and *W. Burneleit, ibid. 62*, 999 (1929).

[10] *H. Meerwein, H. Rathjen*, and *H. Werner*, Ber. dtsch. chem. Ges. *75*, 1610 (1942).

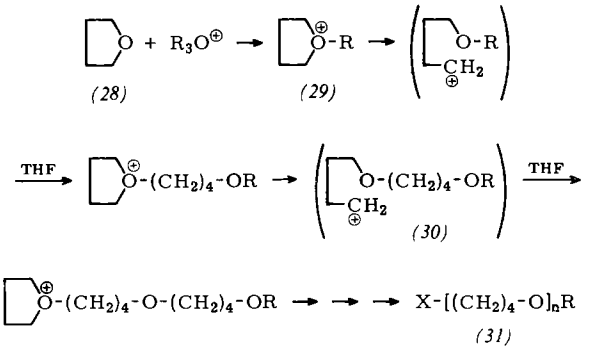
[11] *H. Meerwein*, Ber. dtsch. chem. Ges. *66*, 411 (1933); *H. Meerwein* and *W. Pannwitz*, J. prakt. Chem. [2] *141*, 123 (1934); *H. Meerwein* and *D. Vossen, ibid. 141*, 149 (1934).

[12] *H. Meerwein, G. Hinz, P. Hoffmann, E. Kroning*, and *E. Pfeil*, J. prakt. Chem. [2] *147*, 257 (1937); *H. Meerwein, E. Battenberg, H. Gold. E. Pfeil*, and *G. Willfang, ibid. 154*, 83 (1939).

[13] *H. Meerwein* and *K. Wunderlich*, Angew. Chem. *69*, 481 (1957); *H. Meerwein, V. Hederich*, and *K. Wunderlich*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *291*,581 (1954).

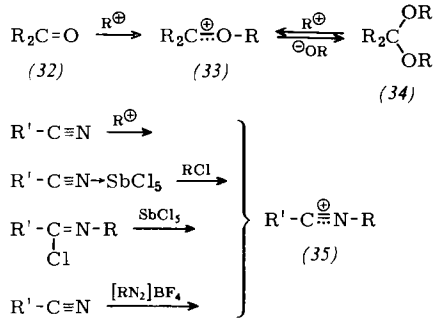
[14] *H. Meerwein, D. Delfs*, and *H. Morschel*, Angew. Chem. *72*, 927 (1960).

The resulting mixed oxonium salt *(29)* can alkylate a second molecule of THF, while itself undergoing ring scission, to form a new oxonium salt *(30)*, which can then alkylate a third THF molecule. The reaction continues in this way with formation of macromolecular ethers. The chain is terminated by addition of a foreign nucleophile, *e.g.* a halide ion derived from the complex anion. The chain lengths of the resulting polyethers therefore depend on the stability of the complex anions present. The trialkyloxonium salts used as initiators may be prepared *in situ*. This is a typical cationic polymerization, all the steps of which have been elucidated [14].



*(28)* *(29)* *(30)* *(31)*

Ketones *(32)* are alkylated by oxonium salts to give carboxonium salts *(33)* [15], the cations of which are stabilized by resonance. Their reactivity is determined by the carbonium limiting form. They react with alkoxides to give acetals *(34)*. Conversely, they can be obtained with trialkyloxonium salts from the acetals; the alkyl cation removes an alkoxide ion from the acetal to form an ether.



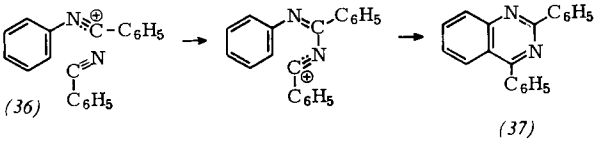
*(32)* *(33)* *(34)* *(35)*

Nitriles can similarly be converted into nitrilium salts *(35)* [16]. *Meerwein* later found further methods for the preparation of this new class of compounds. The antimony pentachloride adducts of nitriles react with alkyl chlorides to form nitrilium salts. These are also formed from *N*-substituted imide chlorides with $SbCl_5$, *N*-arylnitrilium salts being formed when the nitrogen carries an aryl substituent. However, nitriles also can be arylated directly with diazonium fluoroborates. Finally, acylnitrilium salts are obtained when acyl chlorides react with molecular compounds of nitriles with metal chlorides. In most cases, however, two molecules of nitrile react with one molecule of acyl chloride to form salts with very marked resonance stabilization.

[15] *H. Meerwein, K. Bodenbrenner, P. Borner, F. Kunert,* and *K. Wunderlich*, Liebigs Ann. Chem. *632*, 38 (1960).

[16] *H. Meerwein, P. Laasch, R. Mersch,* and *J. Spille*, Chem. Ber. *89*, 209 (1956).

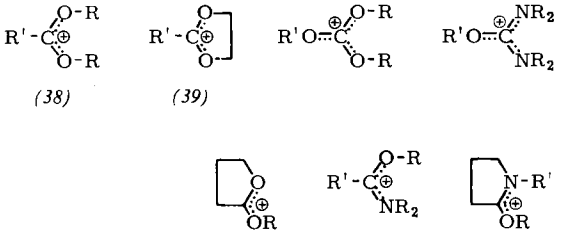
*N*-Arylnitrilium cations *(36)* containing at least one free *ortho* position in the benzene ring react readily with a second molecule of nitrile to form quinazolines *(37)* [17]. The course of the synthesis, in which neither the nitrilium salts nor the imide chlorides used in their production need be prepared as such, can be seen from the following scheme:



*(36)* *(37)*

Diphenylquinazoline is obtained in 86% yield in a single-stage reaction from benzanilide, benzonitrile, thionyl chloride, and aluminum chloride.

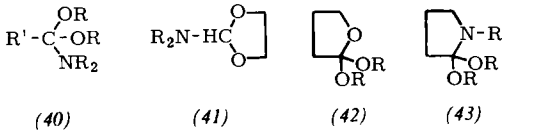
In compounds containing several nucleophilic centers, the alkyl cation, like the proton, reacts in such a way as to give the cation with the greatest resonance stabilization. The most important types of salts prepared from such compounds are shown in Scheme 1 [18]. They are obtained by alkylation of esters of carbonic acid, lactones, amides, lactams, or substituted thioureas with trialkyloxonium salts. The first two types, *(38)* and *(39)*, can also be obtained by abstraction of alkoxide ions from ortho-esters with alkyl cations. The dioxolenium salts *(39)* are particularly stable, probably because of their necessarily planar structure.



*(38)* *(39)*

Scheme 1. Carboxonium salts prepared from compounds containing several nucleophilic centers.

The constitution of these salts was determined by reaction with alkoxide; the products in every case were derivatives of ortho-acids, compounds *(40)–(43)* being of a new type.



*(40)* *(41)* *(42)* *(43)*

The great significance of the numerous reactions with alkyl cations lies in the fact that these are models for acid-catalysed reactions. Whereas the products resulting from protonation of the various substrates cannot usually be isolated, the alkylation products can be readily isolated in the form of stable salts [19].

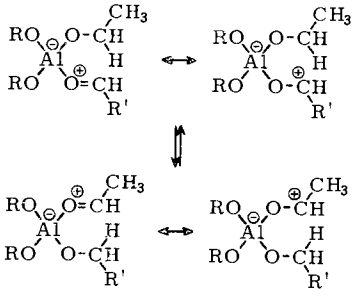
[17] *H. Meerwein, P. Laasch, R. Mersch,* and *J. Nentwig*, Chem. Ber. *89*, 224 (1956).

[18] *H. Meerwein*, Angew. Chem. *63*, 480 (1951); *H. Meerwein, W. Florian, N. Schön,* and *G. Stopp*, Liebigs Ann. Chem. *641*, 1 (1961).

[19] *H. Meerwein*, Angew. Chem. *68*, 356 (1956); *H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt,* and *J. Spille*, Chem. Ber. *89*, 2060 (1956).

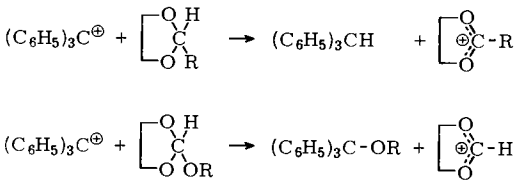
In conclusion let us consider a few reactions having the common feature of the transfer of a hydride ion (and in many cases of an alkoxide or cyanide ion) onto a carbonium ion. These include the well-known Meerwein-Ponndorf reaction, discovered by *Meerwein* and *Schmidt* [20] in 1925 and later extended by *Ponndorf* and *Verley*.

This reaction involves the exchange of oxidation states between an aldehyde or ketone and a primary or secondary alcohol under the catalytic action of an aluminum alkoxide. This forms a complex with the carbonyl component; the "activation by complex formation" consists in the formation of a latent electrophilic center on the carbonyl C-atom, to which the hydride ion migrates, presumably by a cyclic mechanism:



The reverse of this reaction has also become important as the Oppenauer oxidation.

A still more versatile class of reactions is that of the intermolecular anion shifts [21]. The acceptors are carbonium or diazonium ions; on loss of the anion, the donor is converted into a resonance-stabilized cation. The last of these reactions [22] is noteworthy in that the well-known reduction of diazonium salts is carried out with ethers or acetals instead of alcohols. The yields are appreciably better, since no phenol ethers can be formed as by-products.



Much of *Meerwein*'s work has only been hinted at in this survey and much (*e.g.* the Meerwein reaction, *i.e.* the arylation of α,β-unsaturated nitriles, esters, ketones, *etc.*, with diazonium salts [23]) has not even been mentioned. However, it is not the volume, but the substance of his work that is important, *i.e.* the perception of the courses of many reactions, the discovery of ionic processes in organic chemistry, the recognition of the role of complexing agents as catalysts and initiators, and the extension of our knowledge of the carbonium, oxonium, and diazonium ions. *Meerwein* is justifiably regarded as one of the originators of theoretical organic chemistry. He also showed that nothing is of greater practical use than a good theory, since his own theory led him to many new methods, including even industrial processes.

The description of *Meerwein*'s scientific work and the reference to his extensive literary activity also sheds some light on his personality, but the picture gleaned in this way is not complete. To appreciate fully the infectiousness of his enthusiasm one must have discussed with him and listened to his lectures, in which every sentence was clearly formulated, and which held his audience from beginning to end. This is how he will be remembered by all his friends, colleagues, and students. May the flame of enthusiasm for our science that he has kindled in all of them be handed on to future generations like an Olympic flame.

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Translated by Express Translation Service, London

[20] *H. Meerwein* and *R. Schmidt*, Liebigs Ann. Chem. *444*, 221 (1925).

[21] *H. Meerwein, K. Wunderlich*, and *K. Zeuner*, Angew. Chem. *74*, 807 (1962); Angew. Chem. internat. Edit. *1*, 613 (1962).

[22] *H. Meerwein, H. Allendörfer, P. Beekmann, F. Kundert, H. Morschel, F. Paweleck*, and *K. Wunderlich*, Angew. Chem. *70*, 211 (1958).

[23] *H. Meerwein, E. Büchner*, and *K. van Emster*, J. prakt. Chem. [2] *152*, 237 (1939).

# Hans Meerwein, the Teacher and the Man

BY PROF. DR. K. DIMROTH, MARBURG (GERMANY) [*]

*Hans Lebrecht Meerwein* died suddenly on October 24th, 1965. Among the few personal belongings found in his office at the University Chemical Laboratories of Marburg was a small black notebook. It lay in the drawer of his desk, together with some of the many medals and awards that had been bestowed upon him during the later years of his life.

This notebook relates his association with the family home in Hamburg, an association that flourished to the end of his days. The entries are inscribed in the beautifully clear hand of his father *Wilhelm Emil Meerwein* whom he always held in high regard. They relate

[*] Address given at a memorial service held at Marburg University on January 15th, 1966.

the history of the Meerwein family. The story unfolds like an exciting novel, telling of his father's development from the student of architecture with only a casual interest in his subject, to the highly respected and honored master-builder and citizen of the Hanseatic city of Hamburg. Having begun this chronicle at the age of 59, *Wilhelm Emil Meerwein* laid down his pen when he was 81 years old, having added to the tale at intervals of five or ten years. The last two pages are written in another hand, evidently after his death, and contain additions based on notes which had come to light.

At the beginning we find a sentence which seems to me so typical of the relationship between different generations as to merit quotation:

> Even though today my children show no great inclination to acquaint themselves with their family's history, may the time come one day when one or the other of them will be glad to learn from the past.

*Hans Meerwein* was 26 when his father wrote these words in 1905. At the beginning of that year he had taken up his first position as an assistant lecturer at the Chemische Institut at Bonn, under Professor *Richard Anschütz*. On the subject of this appointment his father wrote:

> Although the salary was modest I advised him to take the post, since I think that he is better suited to a career in science than to the practical life.

Having spent his youth in Hamburg, *Hans Meerwein* always looked upon it as his home town. His father, who came from a southern part of Germany, first settled there in 1873, setting up business as an architect in partnership with *Bernhard Hanssen*, his friend from student days. It was through the latter that he met his future wife, *Hanssen*'s sister-in-law *Mathilde Schmilinsky*, whom he married in 1877. Her maternal grandfather had owned a well-known iron foundry and the family had been long established in Hamburg. Its name is familiar to its citizens through a generous foundation, unfortunately deprived during World War II of the large orphanage built by the elder *Meerwein*, as well as through the Schmilinsky-Strasse, named in honor of the founder, an uncle of *Meerwein*'s mother.

While *Hans Meerwein* was still at school at the Hamburger Gelehrtenschule Johanneum, his father set up for him a small chemical laboratory. Here at home he was able, as he himself related afterwards, to carry out all the fundamental experiments known to chemists of that time. Nevertheless, when he graduated from school in 1898, he did not go immediately to a university, but first spent three semesters at the Wiesbaden College of Chemistry run by *Heinrich* and *Wilhelm Fresenius*, where he studied analytical theory and practice. There he obtained a basis which proved to be invaluable for his later work. The careful development of simple methods of qualitative and quantitative analysis characterizes much of *Hans Meerwein*'s scientific work, and it was precisely this approach which enabled him to gain a clear insight into the often complicated course of chemical reactions.

He enrolled at Bonn University in the summer semester of 1900. Not long afterwards he commenced work for his doctorate with *Georg Schroeter*, who was some ten years older than himself and had only recently qualified as a lecturer. In February 1903, after only six semesters of university work, *Meerwein* successfully defended his thesis "On nitrated β-phenylglutaric acids". After studying for some time in Berlin-Charlottenburg, he returned to Bonn early in 1905, at the invitation of the then director of the Chemische Institut at Bonn, Professor *Richard Anschütz*, to take up the assistant lectureship already referred to.

*Hans Meerwein* remained in Bonn until 1923. For many years he must have moved in a stimulating circle of artists and other high-spirited companions. He frequently looked back with pleasure to this period. Gradually, however, his duties increased. Having qualified in 1908 with his inaugural dissertation "On the condensation reactions of α,β-unsaturated aldehydes", he took over in 1910 the position of his former tutor *Georg Schroeter* who had gone to Berlin as Professor of Chemistry at the Veterinary Academy.

During his years in Bonn *Meerwein* concentrated his work on organic rearrangements, particularly in the terpenes and in camphor derivatives. He taught a great many students, with most of whom he established a firm and lifelong friendship. I shall single out only one of them, *Karl Freudenberg*, who passed the practical laboratory courses under him and who was to be for many years the director of the Chemische Institut at Heidelberg. In honor of *Freudenberg*'s 80th birthday on January 29th, 1966, *Meerwein* dedicated to him a paper entitled "On chlorodimethylsulfonium salts". When sending the manuscript to the editor of Liebigs Annalen der Chemie, Professor *Richard Kuhn*, on January 22nd, 1965 he wrote that it would probably be his last paper. It was published in the 688th volume of Liebigs Annalen on October 7th, 1965, just two weeks before *Hans Meerwein* died. It was indeed the last contribution to this great man's work.

In 1923 *Hans Meerwein* was invited to take the Chair of Chemistry at Königsberg. He accepted the position at a difficult time, when the Institute had become practically ineffectual through the ravages of war and inflation. Nevertheless, he succeeded within a short time in restoring the institute to a high standing. He had a relatively small number of students, many of whom were later to reach high positions in the chemical industry, thanks to the excellent training they had received under him. With their assistance he explored two new domains, and in doing so laid the foundation for his future scientific renown: the theory of "cryptoions" as intermediates of many organic reactions, and the formation of complex ions and acids, the "ansolvo acids", as he called them. The reduction of unsaturated aldehydes, named after him, also dates back to those years; it was developed in collaboration with the chemical industry and for some time used in the production of important pharmaceuticals.

Admittedly, much of *Meerwein*'s work received scant recognition at that time. The great chemists of the period were engaged in the elucidation of natural products. Interest was concentrated on the discovery

of vitamins and hormones and the study of their relationship with the enzymatically catalysed processes in organisms. This may be the explanation for the rejection by a leading scientific journal of one of *Meerwein*'s pioneering papers on the ionic mechanism of many organic reactions, on the grounds that it was too speculative. *Meerwein*, who was never a fighter, yielded, though he never doubted the correctness of his views. He knew that in any case the truth would prevail sooner or later. For many years he published no papers in that periodical and preferred to write for the Journal für Praktische Chemie. Partly for similar reasons, he published his fundamental work on complex anions in the "Abhandlungen der Königsberger Gelehrtengesellschaft," and only parts of this still highly interesting paper appeared in more readily accessible journals at a later date. Consequently, many years passed before he received the recognition that was his due. We must confess with some shame that his work has only been fully appreciated in Germany after the end of World War II, and then largely as a result of the high regard in which he was held by American chemists, who consider him as one of the founders of modern organic chemistry. *Meerwein* was fortunate enough to live to witness this change.

Nevertheless, his reputation even in those early years was such that in 1928 he was almost simultaneously offered a professorship at the Universities of Leipzig and Marburg. It seems typical of the man that he gave preference to the smaller university, where he had fewer distractions to fear from administrative and representative duties.

His scientific achievements as a successor to *Karl von Auwers* in the 23 years during which he was head of the Chemische Institut at Marburg, and in the 13 years which followed his retirement from his chair, are unique. To the very end of his life he continued to develop original ideas, and only three weeks before his death he engaged a new post-doctoral assistant at his laboratory with the intention of approaching an old problem, connected with his dissertation, using new concepts and methods.

The discovery of the oxonium salts, the polymerization of tetrahydrofuran and consequently the discovery of cationic polymerization, the discovery of nitrilium salts, the use of carbonium ions instead of protons, which led to new syntheses and reactions of acetals, lactams, and orthoesters, the reactions of alkyl halides with silver fluoroborate or those of diazomethane and aromatic diazonium compounds, are just some of the many topics he studied.

In his teaching capacity, *Hans Meerwein* introduced generations of students to chemistry and guided their progress in their daily laboratory work. His fascinating lectures, supported by brilliant demonstrations, were an unforgettable experience. He had mastered the knack of building up suspense in his listeners to the point when, usually in a startling and unexpected manner, the solution to the problem struck them as if of its own accord.

He advised his students and co-workers also to use the element of surprise in their lectures. It was better, he said, to lecture less frequently, but then to present to the audience new and unexpected material.

Whenever a chemist attracted *Meerwein*'s attention by his originality and acumen, he invariably received the fullest measure of encouragement. The scientific achievements of many young chemists received his support, frequently even without their being aware of it. He did everything he could to bring on the rising generation of chemists, never hesitating to recommend gifted and even very young men for responsible and challenging positions.

To this period at Marburg also belongs the rebuilding of the Chemistry Laboratory after the last war. A new building had been approved at about the time of his appointment. However, by the time he had completed the plans, prepared with all the talent inherited from his father, it was too late: the political circumstances at the universities after 1933 led to a decline in student numbers, and to the rescinding of the earlier approval. Thus it happened that the bold plans for the building were never put into practice. Nevertheless he did have the opportunity of demonstrating his architectural skill, albeit on a much more modest scale, during the rebuilding of the Institute after its destruction in World War II. Thanks to his splendid planning, the new Marburg laboratory was for many years considered as one of the foremost with regard to design and equipment. Even today, it is only lack of space which necessitates the replacement of the present facilities by a new building at another location.

On numerous occasions *Meerwein* has been concerned with literary work falling somewhat outside his own field. The first instance was when he succeeded *Schroeter* in the preparation of the 11th edition of *Richter-Anschütz*, the most comprehensive textbook of organic chemistry of its day. After the last war he worked with *Eugen Müller*, *Otto Bayer*, and *Karl Ziegler* on the new edition of Houben-Weyl, Methoden der Organischen Chemie. Twenty volumes have appeared to date, and only those intimately involved in the work know the full extent of his own efforts. We are indebted to him not only for many useful suggestions, but also for a number of contributions on his own particular fields of interest. As with all his published work, they are models of clarity and precision. He continued working on this project to the last: on his desk were found new drafts for a chapter on condensation reagents, which never ceased to interest him and which had been the subject of much thought and discussion with others.

I have not yet referred to his last work. It was found hidden among other and quite unrelated papers in his otherwise meticulously ordered office. *Meerwein*, who was always glad to talk about his current work, who never missed an opportunity to discuss the problems which occupied his mind, spoke to no one about this last manuscript. It is a comprehensive account of his own life's work. This account, on which he worked to the last day of his life and the last pages of which, just as his father's chronicle, lay unfinished upon his desk, will be his crowning achievement. It is to appear in

Chemische Berichte, successor to the Berichte der Deutschen Chemischen Gesellschaft, which had once shown a lack of appreciation by rejecting one of his most important papers. In this way the man to whom chemistry was his life and who has more than any other in our time disseminated new ideas among chemists all over the world, has continued his father's work in his own way by dedicating himself to research. In so doing he has created for himself the finest memorial.

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# Scrambling Equilibria and Analysis of Labile Mixtures

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*In this brief review, it is attempted to point up the importance of chemical equilibria in structural inorganic chemistry and to show how the kind and yield of various molecules may be treated quantitatively. Because of the importance of kinetic control in organic chemistry and because the chemistry of carbon compounds is by far the most advanced branch of general and descriptive chemistry, preparative inorganic chemists have often overemphasized the value of reaction-mechanism theory to their studies and have thereby neglected the powerful quantitative approach of thermodynamics which may be used in equilibrated systems. The general theorems for treating in terms of small molecular segments the multitude of equilibria present in families of compounds are surveyed superficially with the hope that the interested reader will turn to the original papers for details. Not only physical-inorganic chemists, but also those interested solely in preparative work can advantageously employ the theoretical ideas discussed.*

## I. Introduction

Reactions involving only carbon compounds are generally kinetically controlled (*i.e.*, the structure of the products is determined by the reaction mechanism). However, compounds having elements other than carbon in the spine of the molecule are often quite labile, so that the amounts and kinds of reaction products may be thermodynamically controlled (*i.e.*, by the position of an equilibrium), with different reaction mechanisms leading to identical products and product distributions. Most oligomeric compounds not based on C–C backbones are easily disrupted and therefore, under suitable conditions, readily undergo "scrambling" reactions involving exchange of parts between the same or adjacent molecules [1]. It is these scrambling reactions that complicate separations, lead to unreliability in elucidation of structure by degradation or synthesis, and cause many preparations of supposedly pure compounds to consist of mixtures of molecules at or near equilibrium with respect to exchange of parts among them.

In these cases the usual postulates as to reaction mechanism are no longer fruitful for explaining reaction products, and must be replaced by the mathematically more complicated approach of thermodynamics and its underlying statistics of molecules (statistical mechanics and stochastic theories of molecular structure and configuration).

[1] *J. R. Van Wazer*, Amer. Scientist *50*, 450 (1962).

Of course, we do not wish to imply that reaction mechanisms are always inapplicable to the rationalization of reaction products in inorganic chemistry. There are a number of areas (*e.g.*, the square-planar platinum complexes) in which the energetics along the reaction coordinate are ideally suited to present-day interpretative techniques of reaction-mechanism theory. However, when reaction products are to be ascribed to kinetic control the examples [2] must be carefully selected when working with compounds based on elements other than carbon.

## II. Techniques of Experimentation and Data Treatment

### 1. Analysis of Mixtures

#### a) Nuclear Magnetic Resonance

During the last 10 years, high-resolution NMR spectroscopy [3] has become a major analytical tool. At present, the most suitable nuclei for quantitative NMR measurements are $^{1}H$, $^{19}F$, and $^{31}P$. Nuclei exhibiting quadrupole moments, such as $^{11}B$, are ill-suited for quantitative assay of mixtures (using the magnetic-field strengths obtainable with non-superconducting magnets) because of excessive line broadening. Problems of line broadening may also be introduced by paramagnetic

[2] *H. Taube*, Chem. Rev. *50*, 69 (1952).

[3] *J. A. Pople, W. G. Schneider*, and *H. J. Bernstein*: High-resolution Nuclear Magnetic Resonance. McGraw-Hill, New York 1959.

impurities, so that the presence of a few p.p.m. of iron in a sample may cause coalescence of important fine structure in the NMR spectrum. The emphasis on hydrogen, fluorine, and phosphorus in practical high-resolution NMR spectroscopy is not as much of a limitation as would appear, since the NMR spectra are often very sensitive to changes in molecular structure occurring many atoms removed from the position of the magnetically active nucleus in the molecule. For example, Fig. 1 shows separate resonance peaks [4] for various values of n in a mixture of dimethyl polysulfates, $CH_3O(SO_3)_nCH_3$. For $n > 9$, resonances for the individual molecules cannot be resolved with the present apparatus. This means that the chemical shift of the hydrogen of a methyl group is appreciably affected by the substitution of carbon for sulfur at a position 21 atoms removed from the hydrogen (one C, then an O, plus nine S alternating with nine O, followed by the sulfur or carbon atom in question).

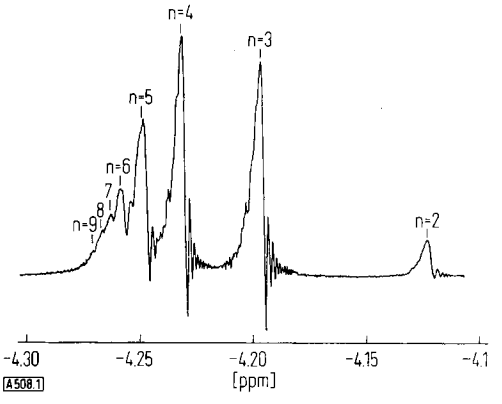



Fig. 1. The $^1$H-NMR spectrum of an equilibrated mixture of dimethyl polysulfates [4], $CH_3O(SO_3)_nCH_3$, taken on a Varian A-60 spectrometer modified to give a sweep width of 25 cps. The composition of this mixture equilibrated at 72 °C is given by a $CH_3$:S mole ratio of 0.22. The resonances for n = 8 and 9 can be reproducibly distinguished.

This ability to see in depth into a molecule [5] enables mixtures of molecules to be assayed in detail if at least some of the monofunctional exchangeable substituents or the molecular backbones or any nonexchangeable groups on the backbone atoms contain hydrogen, fluorine, or phosphorus atoms so arranged that their NMR spectra are not unduly complicated by spin-spin interactions. A methyl group is a particularly valuable substituent in this respect, since all three hydrogens are in chemically equivalent positions and their NMR signals do not show fine structure due to spin-spin splitting by hydrogens within the substituent, such as is found for ethyl or phenyl groups. Likewise, the methylene hydrogens of a benzyl group are suitable for quantitative analysis of mixtures by $^1$H-NMR spectroscopy, since there is inappreciable coupling between these hydrogens and those of the phenyl ring. We have found the following monofunctional substituents, which remain intact throughout most exchange reactions, to be particularly advantageous: H, $CH_3$, $C_6H_5CH_2$, $ClCH_2$, $CH_3O$, $CH_3S$, $(CH_3)_2N$, $(CH_3)_3C$, $(CH_3)_3Si$, F, $F_3C$, and (with poorer results because of the inclusion of an extra intermediate atom) the groups $(CH_3)_3CO$, $(CH_3)_3SiO$, and $CH_3C(O)O$. Certain bridging groups are also very useful in this respect, *e.g.* $CH_3N <$, $CH_2 <$, and $(CH_3)_2Si <$. Since all of the measurements described herein were performed on single-phase liquids or solutions, the resulting data correspond to a total analysis of all the components in the system under study [6].

Equilibria between compounds not containing suitable NMR-active nuclei may be indirectly studied by NMR spectroscopy. Thus the scrambling of, say, isocyano groups with bromine atoms on germanium [*i.e.*, equilibria between compounds of the type $Ge(NC)_iBr_{4-i}$], can be investigated by studying the exchange of these substituents on dimethyl-and monomethylgermanium moieties (which remain intact) and extrapolating the results to the case of methyl-free germanium. By these procedures, it is possible to attack quantitatively such experimentally difficult problems as the molecular constitution of silicate glasses.

The time and temperature required for a particular system to reach equilibrium with respect to scrambling of substituents is determined in a series of pilot experiments. Equilibrium is deemed to be attained when the NMR pattern of the sample remains constant for prolonged times at a given temperature.

NMR spectroscopy may be used to investigate rapidly equilibrating systems, the individual components of which cannot be separated by distillation [7]. However, when the rate of exchange becomes too rapid, the individual resonances coalesce to a single sharp peak which is difficult to interpret in terms of individual components of a mixture [3]. The rates of exchange may, of course, be reduced by lowering the temperature or by dilution with a solvent. Signals separated by about 200 c.p.s. allow a quantitatively analysis for components of short lifetimes (*e.g.* $10^{-3}$ sec) in mixtures. In Fig. 2, $^{19}$F- and $^1$H-NMR spectra are presented for the mixture [7] obtained on equilibrating 1.25 moles of $AsF_3$ with 1 mole of $As[N(CH_3)_2]_3$. This Figure illustrates the good resolution obtained for the widely separated fluorine peaks of the neat liquid as compared to the closely spaced hydrogen resonances which were not resolved sufficiently for quantitative assay until 18–20 parts of a solvent were added. From the widths of the allow a quantitative analysis for components of short of the $^1$H resonances, it is estimated that the rate of exchange of fluorine and dimethylamino groups on arsenic corresponds to an average lifetime of *ca.* $4 \times 10^{-3}$ sec in the neat liquid at room temperature.

### b) Assignment of NMR Signals

There are several general methods for assigning the various NMR peaks of a mixture. First the chemical shifts of the pure starting materials are determined. These data may be

[4] *J. R. Van Wazer, D. Grant,* and *C. H. Dungan,* J. Amer. chem. Soc. *87,* 3333 (1965).

[5] *J. R. Van Wazer* and *D. Grant,* J. Amer. chem. Soc. *86,* 1450 (1964).

[6] *L. C. D. Groenweghe, J. R. Van Wazer,* and *A. W. Dickinson,* Analytic. Chem. *36,* 303 (1964).

[7] *K. Moedritzer* and *J. R. Van Wazer,* Inorg. Chem. *3,* 139 (1964).

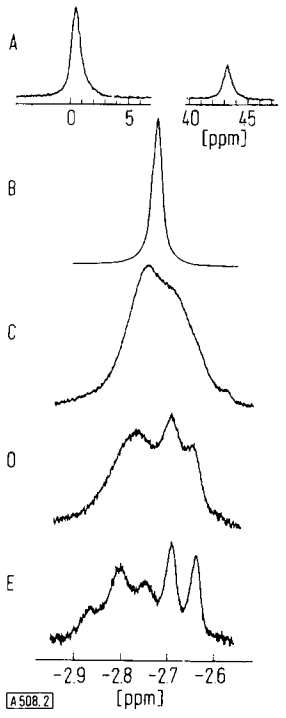



Fig. 2. NMR spectra of an equilibrated mixture [7] of $AsF_2N(CH_3)_2$ and $AsF[N(CH_3)_2]_2$ at 25 °C.

A: $^{19}F$-NMR spectrum of the neat liquid.

B: $^1H$-NMR signals of the methyl groups in the neat liquid.

C: as for B, but with addition of 5 parts $CCl_4$ by volume.

D: as for B, but 10 parts $CCl_4$.

E: as for B, but 18 parts $CCl_4$.

The downfield peak of the $^{19}F$-NMR spectrum and the triplet on the downfield side of the $^1H$-NMR spectra correspond to the $AsF_2N(CH_3)_2$ molecule. The singlet peak at the upfield side in the $^{19}F$ spectrum and the upfield doublet in the $^1H$ spectra correspond to $AsF[N(CH_3)_2]_2$. The doublet and triplet character of the $^1H$ spectra are attributable to spin-spin splitting between the methyl group hydrogens and the fluorine atoms.

Abscissae: Chemical shift relative to trifluoroacetic acid (top) and tetramethylsilane (bottom).

used to identify these compounds when present in a mixture. In a *simple system* involving the exchange of monofunctional substituents only, the chemical shift of a series of related compounds generally changes more or less linearly upon replacement of one substituent by another. In the more complicated systems involving *families* of compounds (*e.g.* in the systems $AsF_3/As_2O_3$ or $(CH_3)_2SiCl_2/[(CH_3)_2SiO]$), NMR signals appear in clusters, which generally indicates that these peaks represent moieties of the same functionality but of different chemical environment. The separations between clusters are often much greater than those between individual peaks within a cluster. In addition, assignments may be based on the order of appearance of new NMR signals when equilibrating large amounts of a compound A with increasing amounts of a compound B. The maximization of the peak areas at certain compositions when comparing a series of spectra of samples having varying mole ratios of the starting components or their increase or decrease with varying over-all composition is also utilized in assigning NMR peaks. In many cases the ratio of the areas of two or more peaks remains constant for different over-all compositions. Peaks exhibiting such a fixed-area relationship generally are readily assignable to certain simple molecules or molecular segments. Kinetic data serve as an additional source of information for peak assignments. In well-filled sealed tubes where no phase separation occurs, the over-all composition must remain fixed from start to finish. Further, in many scrambling reactions certain peaks appear, reach a maximum area, and then disappear at a given over-all composition, whereas at another composition, one of these peaks may be seen under equilibrium conditions.

After all of the resonances have been assigned, one may check the validity of the assignments by material-balance calculations. For single-phase liquids the correct assignments of the NMR peaks will lead to acceptable material balances at any stage of the reaction. In addition, the distribution of atomic or molecular arrangements at equilibrium may be described by a set of equilibrium constants, as exemplified by Eq. (a) below. These constants may be used to calculate a theoretical distribution as a function of the over-all composition.

### c) Other Methods

Raman spectra may also be used for analysis of systems undergoing rapid exchange [8]; however, this method is considerably more restricted than high-resolution NMR spectroscopy and considerable effort is required to obtain quantitative data from the spectra. Gas chromatography [9–11] (see Fig. 3) and mass spectrometry [12, 13]

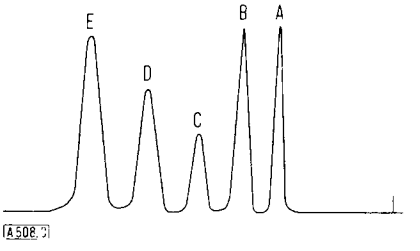



Fig. 3. Gas chromatogram of a mixture [10] of alkyl silicates equilibrated at 120 °C in the system $Si(OCH_3)_4/Si(OC_2H_5)_4$.

A: $Si(OCH_3)_4$

B: $Si(OCH_3)_3(OC_2H_5)$

C: $Si(OCH_3)_2(OC_2H_5)_2$

D: $Si(OCH_3)(OC_2H_5)_3$

E: $Si(OC_2H_5)_4$

A Perkin-Elmer vapor fractometer, Model 154D, having a thermistor-bead thermal-conductivity detector and a digital-integrator printout was employed with a 3 m column filled with 10 % Tween 80 on C-22 firebrick.

have also been employed in the quantitative study of exchange reactions, and microwave spectroscopy holds some promise. The first two of these methods can be used on relatively labile systems since the interacting molecules are rapidly separated from each other in the initial stages of the analysis. Another promising technique for labile systems would be column or thin-film sorption chromatography from a liquid medium at very low temperatures. However, high-resolution NMR spectroscopy appears to be the most generally applicable method for the quantitative study of scrambling reactions between complicated molecules because the relative areas of the peaks are exactly proportional to the relative amounts of the corresponding active nuclei, and because many molecules may be seen "in depth".

[8] *M. L. Delwaulle* and *F. Francois*, C. R. hebd. Séances Acad. Sci. *219*, 64 (1944); *227*, 1229 (1948).

[9] *K. Moedritzer, G. M. Burch, J. R. Van Wazer*, and *H. K. Hofmeister*, Inorg. Chem. *2*, 1152 (1963).

[10] *K. Moedritzer* and *J. R. Van Wazer*, Inorg. Chem. *3*, 268 (1964).

[11] *J. R. Van Wazer* and *K. Moedritzer*, J. inorg. nucl. Chem. *26*, 737 (1964).

[12] *P. D. Zemany* and *F. P. Price*, J. Amer. chem. Soc. *70*, 4222 (1948).

[13] *J. K. Ruff* and *G. Paulett*, Inorg. Chem. *3*, 998 (1964).

Further, one can generally determine within about a day whether or not a given system may adequately be studied by this method, compared to the weeks or months needed to optimize the conditions for chromatographic analyses.

## 2. Theoretical Treatment of Exchange Equilibria

### a) Exchange Equilibria Involving Simple Compounds

Of all equilibrium reactions in a single phase, the scrambling of two or more substituents about a given kind of central atom or non-exchangeable moiety is the simplest type, since this process is merely a rearrangement of covalent bonds – with the total number of σ-bonds of any type remaining constant. Many such reactions have essentially zero enthalpies, being fully entropy-controlled [14,15]. This behavior occurs to the extent to which Pauling-type bond energies are additive [16]. The equilibrium constants of such entropy-controlled scrambling reactions may be calculated from the statistics of random sorting of the substituents. If there are ν sites for exchange on the central atom or moiety, Q, on which two kinds of monofunctional substituents, T and Z, are being exchanged, there are (ν + 1) possible compounds, $QZ_iT_{\nu-i}$, where i = 1, 2, ... (ν + 1), and (ν − 1) independent equilibrium constants of the form:

$$K_i = [QZ_{i+1}T_{\nu-i-1}][QZ_{i-1}T_{\nu-i+1}]/[QZ_iT_{\nu-i}]^2 \qquad (a)$$

where i = 1, 2 ... (ν − 1). Consider, for example, the system $OPCl_3/OPBr_3$ for which Q = (OP), ν = 3, Z = Br, T = Cl and for which the (ν − 1) = 2 independent equilibrium constants are:

$$K_1 = [OPCl_3][OPClBr_2]/[OPCl_2Br]^2 \qquad (b)$$

$$K_2 = [OPCl_2Br][OPBr_3]/[OPClBr_2]^2 \qquad (c)$$

By quantitative $^{31}P$-NMR spectroscopy [15] the values $K_1 = 0.41$ and $K_2 = 0.34$ were found, both of which are not far from the value $K_1 = K_2 = 0.33$ calculated for a random distribution of substituents. Deviations from randomness are also small for the exchange of Br and Cl on other central atoms or moieties, such as carbon [17] ($CCl_4/CBr_4$) and tin [18] ($SnCl_4/SnBr_4$). On the other hand, the scrambling of chlorine atoms with dimethylamino groups on any central atom or moiety [7,10,11] is found to be highly non-random, *i.e.* to have a sizable enthalpy. For example, the enthalpies of formation of $PCl_2[N(CH_3)_2]$ and $PCl[N(CH_3)_2]_2$ from $PCl_3$ and $P[N(CH_3)_2]_3$ are +4.8 and +4.0 kcal/mole, respectively [19], corresponding to *ca.* $10^{-8}$ for the equilibrium constants of the form of Eqs. (b) and (c). For scrambling of substituents on the transition metals [20], there may also be sizable contributions to the enthalpy due to association (an effective increase in ν by use of d-orbitals in the σ-bond structure), since solution non-idealities are reflected in the equilibrium constants.

Simple molecules which consist of exchangeable monofunctional substituents bonded to a central atom or moiety are called *neso*-compounds [*] and their scrambling equilibria are noteworthy for two reasons:

a) When the molecules form approximately ideal solutions, the deviations from randomness of the equilibria offer a good means of characterizing the interactions between two substituents bonded to the same atom or moiety.

b) The findings may be extrapolated to exchanges of parts between more complicated molecules (see next paragraph), since the pertinent thermodynamics generally are little affected by structural variations more than one atom removed from the site of the exchange.

### b) Exchange of Parts Between Complicated Molecules

For inorganic molecules in which the molecular backbone consists of two kinds of atoms alternating with each other ("heteropolymers" [22], including branched and crosslinked molecules) as well as for those based on chains of like atoms ("catenation" or "homopolymers" [22]), any exchange process may be simulated by a series of steps involving the splitting of two molecules each into two pieces or of one molecule into three pieces and interchanging the molecular portions. Chemically meaningful (*i.e.* nontrivial) exchanges can be represented formally by the interchange of a monofunctional substituent for a larger piece of a molecule, the interchange of two pieces differing in size or in atomic arrangement, or ring scission involving affixing the cut ends of another molecule to the cut ends of the cyclic structure. Although it is possible to set up equilibrium constants for interactions among the many molecules of various sizes [straight and branched chains and cyclic molecules (including rings with chain segments on them and perhaps connecting them, fused-ring structures, *etc.*)] which may be in equilibrium with respect to exchange of parts, it is better to simplify the problem so

[*] A term taken from silicate chemistry [21] meaning a small "island" structure (νῆσος = island). In the sense in which *neso* has been employed in equilibrium chemistry, it stands for the smallest member of a family of compounds; *i.e.* methane is the *neso*-compound of the paraffinic hydrocarbons and orthophosphoric acid is the *neso*-compound of the polyphosphoric acids.


[14] *G. Calingaert* and *H. A. Beatty*, J. Amer. chem. Soc. *61*, 2748 (1939).

[15] *L. C. D. Groenweghe* and *J. H. Payne*, J. Amer. chem. Soc. *81*, 6357 (1959).

[16] *H. A. Skinner*, Recueil Trav. chim. Pays-Bas *73*, 991 (1954).

[17] *G. S. Forbes* and *H. H. Anderson*, J. Amer. chem. Soc. *66*, 931 (1944).

[18] *J. J. Burke* and *P. C. Lauterbur*, J. Amer. chem. Soc. *83*, 326 (1961).

[19] *J. R. Van Wazer* and *L. Maier*, J. Amer. chem. Soc. *86*, 811 (1964).

[20] *H. I. Weingarten* and *J. R. Van Wazer*, J. Amer. chem. Soc. *87*, 724 (1965).

[21] *G. W. Morey* in *R. E. Kirk* and *D. Othmer*: Encyclopedia of Chemical Technology. Interscience, New York 1954, Vol. XII, pp. 268–303.

[22] *D. N. Hunter*: Inorganic Polymers. Wiley, New York 1963.

that only the essentials of the large set of resulting equilibrium constants need be considered. Such simplification has recently been treated with the aid of stochastic graph theory [23].

In this treatment it is proved that the host of equilibrium constants involving the many possible interchanges among all of the molecules may be replaced by a much smaller number involving molecular segments (which may be large and overlapping). As in the simple scrambling of the monofunctional substituents of *neso*-compounds (*e.g.* Cl *vs.* Br in mixtures of $CCl_4$ and $CBr_4$), one can compare experimental equilibrium data pertaining to the ring-free molecular segments with theoretical values calculated on the basis of statistical randomness.

A useful concept for discussing deviations from randomness is the reorganizational heat order [23], $\rho$. This

### c) Generalized Treatment of Exchanging Molecules [23]

Let us now consider atoms or moieties Q having $\nu$ sites for exchangeable substituents and fill these sites with either bifunctional (Z) or monofunctional (T) substituents. This model corresponds to a "heteropolymer" [22] and can be applied to the "homopolmers" by letting Z stand for a bond between a pair of Q atoms. By scrambling the Z and T substituents around the Q's, we obtain a set of $(\nu + 1)$ "building units" (shown here by non-stoichiometric formulae), ranging from the $QT_\nu$ *neso*-molecule through the end group $QZT_{\nu-1}$, the middle $QZ_2T_{\nu-2}$, the threeway branched $QZ_3T_{\nu-3}$, to the most branched building unit $QZ_\nu$. Examples of a molecule and its constituent building units are given for $\nu = 4$ and $\nu = 6$ in Fig. 5.

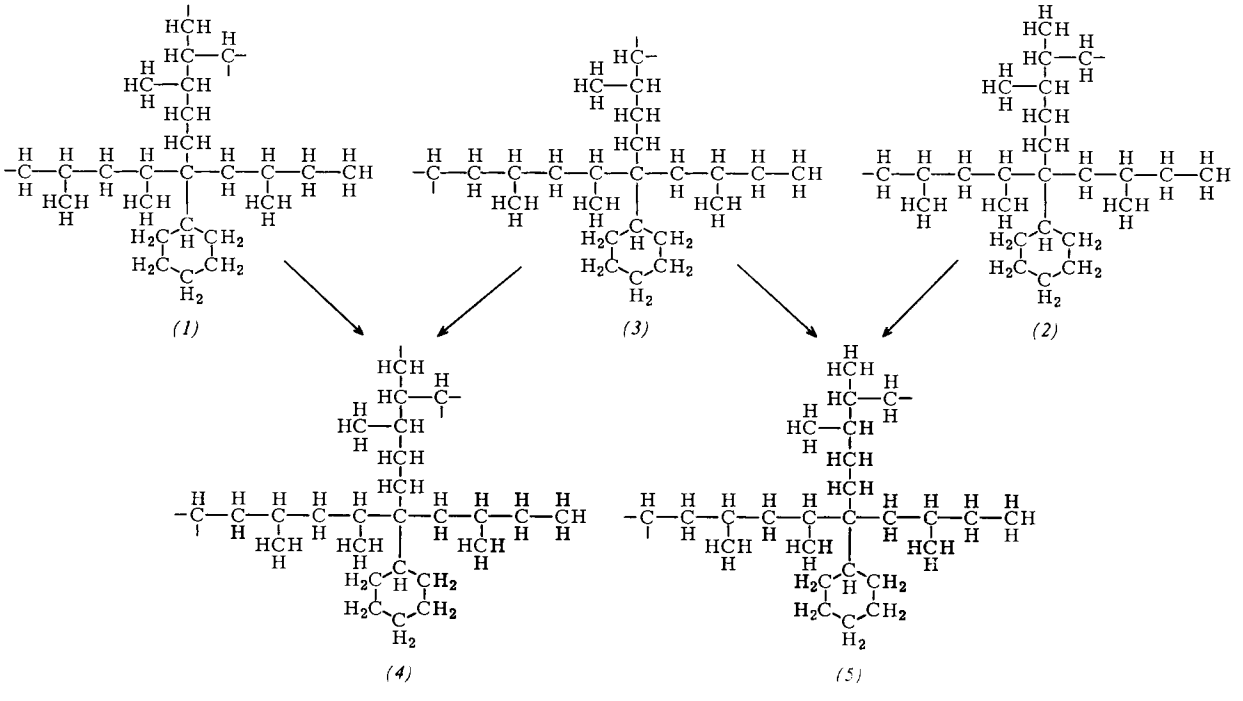



Fig. 4. Example of the application of the mathematical theory of graphs [23] to paraffinic hydrocarbons. If $[(1)][(2)] \neq [(4)][(5)]$, $\rho \geq 11$. If in addition such mergings of all larger graphs which differ only at the boundary result in an equality, then $\rho = 11$.

denotes the number of atoms (or repeating groups of atoms) in the longest block of atoms which is not a random overlay of the next smaller blocks (cf. Fig. 4). When the ring-free portion of a system is random with respect to the sorting of the atoms or other smallest exchangeable units, $\rho$ is zero. In this case, monofunctional substituents interchange randomly with pieces of chains so that for the class of "heteropolymers" there is no energetic distinction between the monofunctional substituents and the bridging atoms with respect to scrambling interchanges, and for "homopolymers" the chain atoms are not thermodynamically distinguishable from the substituents in a sorting process. A widely applicable theoretical treatment is found for $\rho = 1$, where the probability of attachment of an atom or exchangeable moiety is influenced only by its nearest bonded neighbors.

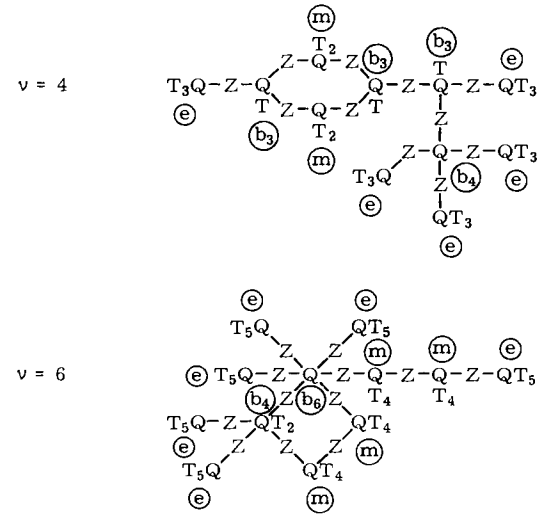



Fig. 5. A molecule in each general system $QT_\nu/Q_2Z_\nu$ [23] corresponding to $\nu = 4$ and $\nu = 6$, with e = end, m = middle, and bj = j-way branched building units.

[23] *D. W. Matula, L. V. D. Groenweghe*, and *J. R. Van Wazer*, J. chem. Physics *41*, 3105 (1964).

For $\rho \leqslant 1$, the equilibria between all molecules and parts of molecules which do not contain rings are completely described by a minimum of $(\nu-1)$ independent equilibrium constants. The set of equilibrium constants described by Eq. (a) (but now involving building units) fully represents the deviations from randomness for the ring-free portion of a system for which $\rho = 1$. For $\rho = 0$, the equilibrium constants $K_i$ have predetermined values [14] and the system is fully entropy-controlled with zero enthalpies for exchange of all parts between any ring-free molecules or ring-free molecular segments. As in the reactions of the *neso*-molecules, $K_i$ may be calculated from the statistics of random sorting of the Z and T substituents on the Q moiety. For $\rho = 1$, the equilibrium constants of Eq. (a) do not correspond to a random arrangement but the resulting building units, $QZ_iT_{\nu-i}$, are randomly arranged in the ring-free molecular structures so that the ring-free system is fully defined by the $(\nu-1)$ constants of Equation (a). For higher values of $\rho$, it is necessary to employ more equilibrium constants involving larger blocks of atoms than appear in the building units of the form $QZ_iT_{\nu-i}$. In such cases, overlapping of these blocks precludes additive stoichiometry. However, for $\rho = 1$, additive stoichiometry may be achieved by dividing the bridging substituents Z in half, so that the building unit previously symbolized by $QZ_iT_{\nu-i}$ may be written in stoichiometric form as $QZ_{i/2}T_{\nu-i}$ and the resulting family of compounds can be represented by the system $QT_\nu/Q_2Z_\nu$.

### d) Infinite Molecules and the Gel Point [24]

In the system $QT_\nu/Q_2Z_\nu$ in which the molecules consist of $\nu$-functional moieties Q connected by bridges Z, with T groups as the monofunctional substituents, infinite or wall-to-wall molecules occur when there are not enough end groups to terminate the tree-like branched-chain molecules resulting from the presence of building units having a functionality of 3 or larger. If the branched building units are not incorporated in a ring, the statistical reasoning shows that for $\rho \leqslant 1$ the total number of end groups will have to be at least 3 per three-way branch, 8 per four-way branch, 15 per five-way branch, and 24 per six-way branch in order to keep the system free of infinite polymers. Ring closure reduces the need for end groups since, by joining two chain segments per ring closure, it is unnecessary to cap off this pair of segments by end groups in order to keep the molecule finite. When the exchange of parts between molecules is rapid, infinite molecules will exhibit flow through a making-and-breaking process. Alternatively, for slow exchange the viscosity of the system will increase precipitously as the critical composition (the "gel point") at which infinite network molecules first appear is approached from the low-molecular-weight side.

### e) Ring-Chain Equilibria [23]

There is as yet no satisfactory theoretical treatment of ring-chain equilibria. Usually just one or two sizes of rings are found in systems in which small cyclic molecules are present at equilibrium. When there are no fused-ring systems, this means that only a few ring-chain equilibrium constants are needed, *viz.* one for each size of ring.

Although specific NMR peaks sometimes may be assigned to cyclic molecules, direct observation often is not possible, and the amounts of ring structures must be determined by difference. Since, as stated above, ring closures effectively make excess end groups, or, in other words, middle groups present in simple rings are effectively removed from the chain population, the presence of simple rings should make the observed amount of the short-chain molecules larger than the amount calculated on the assumption of no cyclic molecules. When $\rho \leqslant 1$ it is therefore possible to estimate the amount of simple ring molecules from the deviation of the observed amount of a short-chain molecule, say the di-chain, from that calculated assuming the absence of rings. Equilibrium constants similar to those of Eq. (a) apply only to the ring-free portion of the molecules, and the presence of simple cyclic molecules causes a continuous increase in such equilibrium constants as the amount of bridging units is increased with respect to the monofunctional substituents. Correcting this increase by subtracting the number of middle groups present in the simple cyclic molecules so as to give a constant value for the equilibrium constant represents another way of estimating the amount of rings when they cannot be directly measured. In either of these methods of indirect estimation of the amount of cyclic molecules, one would expect that the ring-chain equilibrium constants should remain constant within experimental error, and this offers a check of whether one is on the right track.

### f) Rings and Infinite Molecules [23]

The third technique for indirectly estimating ring populations is comparison of the experimentally observed "gel point" with the value calculated on the assumption that no rings are present. If branched building units are incorporated into ring structures which appear as components of finite molecules, the observed "gel point" will occur at an equilibrium composition corresponding to more branched groups than the gel-point composition calculated for the absence of rings. At present, a detailed theory for quantitative calculation of the amount of rings from this type of data is not available. We are developing such a theory using the assumption that the probability of pairs of bonding sites on a given atom in rings is the same as in chains. According to this, it is six times more probable that a fourway branch and three times more probable that a threeway branch group be in a ring than a middle group at the same concentration. We believe that this concept may be combined with numerical values of the ring-chain constants for the various sizes of rings (as evaluated for simple rings composed solely of middle groups) to give a quantitative measure (with proper accounting for volume changes in the reaction) of the relative amounts of all rings, whether or not these rings contain branched building units.

## 3. Kinetic Measurements and Interpretation

Relatively rapid changes at constant temperature in the amount of a given molecular structure can be measured NMR-spectroscopically by scanning back and forth over the corresponding resonance peak and measuring the change in peak area with time. With this technique, points spaced 1–2 minutes apart on a rate curve can be readily obtained. For slow processes at elevated temperatures, it is generally satisfactory to quench a sample quickly, take its spectrum at room temperature, and put it back in the furnace for another period of time. Occasionally we have obtained good results by making up a series of like tubes, each of which is quenched and used for measurement, to give the separate points of the rate curve.

Lifetimes for exchange processes in the range of $10^{-4}$ to *ca.* $10^{-1}$ sec can be estimated from NMR line broad-

[24] *P. J. Flory*: Principles of Polymer Chemistry. Cornell University Press, Ithaca 1953, p. 47.

ening and coalescence [3] (see Fig. 7). When the group bearing the magnetically active nuclei can interchange among several chemically non-equivalent sites, this technique yields an average value for the exchange lifetime. Estimations of the over-all order of a reaction can be made by measuring the variation with solvent concentration of the NMR line broadening.

A serious problem in treating kinetics of equilibrium processes is the number of independent steps involved. Thus in an all-*neso* system in which two kinds of substituents are exchanged (through four-center intermediates) on a central moiety having $\nu$ exchangeable sites, there are $\nu(\nu-1)$ second-order rate constants needed to describe the system. In some examples in which there are no problems in gathering data on the $(\nu+1)$ *neso*-compounds involved, it is difficult to establish even the order of the constituent reactions, much less to prove the mechanism.

## III. Examples of Chemical Systems

The study of single-phase liquid systems carried out thus far in our laboratory has been directed at the elucidation of four questions:

a) If two substituents are exchanged on a given central atom, how far will the resulting equilibrium deviate from that corresponding to random sorting of the substituents? Most of the work done to answer this question has been carried out with *neso*-compounds, but the data on all-*neso* systems will not be reviewed here.

b) What reorganizational heat order is required for an adequate quantitative treatment of equilibrium data involving families of molecules and what is the quickest and most satisfactory experimental way for obtaining these data?

c) At the composition where one would expect to obtain relatively long chains, how much are these chains shortened through formation of rings; *i.e.* what are the ring-chain equilibrium constants and can they be predicted?

d) How fast is equilibrium achieved, and can this rate be predicted either through reaction-mechanism theory or otherwise?

In the following discussion, we shall emphasize work done to answer questions b) and c).

Any family of compounds, the molecules of which can interchange parts with each other, can be discussed in terms of a chemical system between the *neso*-molecules, $QT_\nu$, and the compounds, $Q_2Z_\nu$, corresponding to the completely branched structures. Thus the family of aliphatic hydrocarbons may be treated in terms of exchange of hydrogen atoms for neighboring carbon atoms on a given carbon so that the system ranges from the *neso*-compound, $CH_4$, to the completely crosslinked structure, which is diamond. Thus the paraffin family is described by the system $CH_4/[C]$ (diamond) [1,23]. Similarly, the methyl polyborates [25] in which equilibrium is achieved by exchange of methoxy groups for bridging oxygen atoms around a boron atom is described by the system $(CH_3O)_3B/B_2O_3$ and the family of sodium polyphosphates [26] by the system $Na_3PO_4/P_2O_5$; these two families of compounds may be represented even more broadly by $(CH_3)_2O/B_2O_3$ and $Na_2O/P_2O_5$. Where groups do not readily exchange, *e.g.*, the two hydrogen atoms per carbon atom in the polyoxymethylenes and the single alkyl group per silicon in the polymonoalkylsiloxanes, we take the same approach. Thus the polyformaldehyde chains obtained by exchanging hydroxy groups with bridging oxygen atoms [27] are encompassed by the system $CH_2(OH)_2/[CH_2O]$ or more broadly by the system $H_2O/[CH_2O]$, and the polymonoalkylsiloxanes [28] by $CH_3SiX_3/[CH_3SiO_{3/2}]$.

### 1. Arsenic(III) Compounds

The families of compounds represented by the system $AsX_3/As_2O_3$ have been studied by NMR spectroscopy [29–31] and by ebullioscopy and cryoscopy [32]. In the NMR work, interpretable data were obtained for over-all X:As mole ratios ranging from 3 to 1; the colligative studies were necessarily restricted to mole ratios between 3 and 2.5.

#### a) Polyarsenous Oxide Fluorides [29]

For X = F, the $^{19}$F-NMR spectra of mixtures of nine different compositions gave 90 data points corresponding to the relative areas of the ten resonances per composition. These resonances correspond to various arrangements of the four types of building units:

| $AsF_3$ | $F_2AsO_{1/2}-$ | $FAs(O_{1/2}-)_2$ | $As(O_{1/2}-)_3$ |
|---|---|---|---|
| *neso*, *n* | end, *e* | middle, *m* | three-way branch, *b* |

One resonance signal is due to $AsF_3$; three resonances are attributable to end groups, that is to (i) an end group attached to another in the molecule $F_2AsOAsF_2$, as well as (ii) an end attached to a middle, and (iii) an end attached to a branch point in larger molecules. These may be denoted by **e***e*, **e***m*, and **e***b*, where the directly observed group, **e**, is shown in boldface type. Likewise, the remaining six resonances are attributed to middle groups corresponding to the various ways *e*, *m*, and *b* can be arranged around the observed middle group, **m**; *i.e.*, *e***m***e*, *e***m***m*, *e***m***b*, *m***m***m*, *m***m***b*, *b***m***b*. A typical spectrum showing all ten of these resonances is presented in Fig. 6.

At this point it might be of interest to review the technique used to arrive at the assignments given in Fig. 6.

[25] *H. K. Hofmeister* and *J. R. Van Wazer*, J. inorg. nucl. Chem. *26*, 1201 (1964).

[26] *J. R. Van Wazer*: Phosphorus and its Compounds. Interscience, New York 1958, Vol. I. p. 754–765.

[27] *K. Moedritzer* and *J. R. Van Wazer*, J. physic. Chem., in press; see also *P. Skell* and *H. Suhr*, Chem. Ber. *94*, 3316 (1961).

[28] *K. Moedritzer* and *J. R. Van Wazer*, work in progress.

[29] *J. R. Van Wazer*, *K. Moedritzer*, and *D. W. Matula*, J. Amer. chem. Soc. *86*, 807 (1964).

[30] *M. D. Rausch*, *J. R. Van Wazer*, and *K. Moedritzer*, J. Amer. chem. Soc. *86*, 814 (1964).

[31] *J. R. Van Wazer*, *K. Moedritzer*, and *M. D. Rausch*, J. chem. Physics *42*, 3302 (1965).

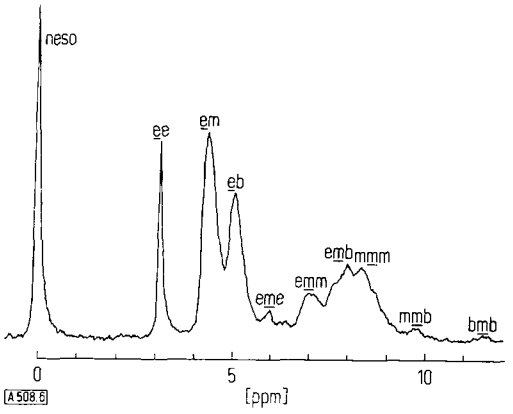



Fig. 6. $^{19}$F-NMR spectrum of a mixture equilibrated at 120 °C in the system [29] $AsF_3/As_2O_3$; over-all F:As mole ratio = 1.25. The symbols e, m, and b refer to end, middle, and branch structure-building units, respectively, and the group giving the particular resonance is underlined. Data obtained on a Varian HR-60 spectrometer at 56.444 Mc/sec and sample spinning in 5 mm precision tubes. The chemical shift reference is $AsF_3$, with field strength increasing from left to right.

When only small amounts of $As_2O_3$ are added to $AsF_3$ and the mixture is equilibrated, the product will be all or nearly all the end-end molecule, $F_2AsOAsF_2$, and therefore the first new peak to appear at F:As ratios near 3:1 is assigned to **ee**. The next peaks to appear on further decrease of the F:As ratio (dissolution of more $As_2O_3$) are due to the *eme* molecule. Here two signals are expected, one representing end groups next to the central middle group, **em**, and another (having one quarter of the area) representing the middle between the two end groups, *e***m***e*. Thus the general location of resonances for end and middle groups are established in relation to that of the *neso*-compound $AsF_3$ which is easily identifiable by its chemical shift. Further increase of the relative amounts of $As_2O_3$ in these mixtures results in longer chain molecules, such as *emme*, *emmme*, *etc.*, and also in branched species. The branch groups cannot be detected by $^{19}$F-NMR directly but their relative concentration can be calculated from the NMR data and the composition of the mixture. Even though the numbers of branch points are obtained by difference, the material balances still give a good check of the peak assignments, since the number of branches must increase monotonically with decreasing F:As mole ratio. The presence of branches leads to another type of end-group resonance corresponding to an end group next to a branch group, **eb**. There are also a series of different middle groups in longer chains, such as ***emm*** and ***mmm***, and the middle groups next to branch groups, ***emb***, ***mmb***, and ***bmb***.

The appearance of three signals resulting from end groups and six from middle groups indicates that the $^{19}$F chemical shift of a particular building unit depends only on the nature of the building units directly attached to it; building units one removed from these do not cause a resolvable effect.

The areas of the three peaks assigned to end groups reach a maximum value near the composition F:As = 2:1, and those of the middle groups increase from the composition 3:1 to that of 1:1.

Although the NMR peak for the *neso*-compound, $AsF_3$, stands out by itself, the regions where end and middle groups absorb are close together; but considering the sharpness of the peaks and the separations between them, the assignment in Fig. 6 appears reasonable. The validity of this assignment is established [29] by the material-balance calculations, together with the equilibrium constants ($K_1$ and $K_2$, discussed below), and the good agreement of the group of 90 NMR peak areas with the values calculated on the basis of random sorting of the building units into molecules.

Fig. 6 shows that the *neso* and **ee** peaks are sharp, as expected for molecules not undergoing rapid exchange. By this criterion, the *e***m***e* peak should also be sharp, but it is so small in the spectrum shown that its sharpness is lost in the noise. The **em** peaks and **eb** peaks are broad because there are various arrangements farther out in the molecule which would show up as separate peaks if the resolution were better (*i.e.* the *e***m** arrangement may be present in structures such as *e***m***e*, *e***m***me*, *e***m***be*$_2$, *etc.*). Throughout most of the composition range between the pure *neso*-molecule and the gel point, the end structures predominate so that the peaks corresponding to ends are the principal ones in the majority of this kind of NMR spectrum. Except for the *e***m***e* and *e***m***m* arrangements, even more structural variations are encountered for peaks involving middle groups, with the greatest number of possible arrangements corresponding to the ***bmb*** peak which is generally the most broad or diffuse. The odd shape of the *e***m***b* peak in Fig. 6 probably represents rather large weighting of some of these more distant arrangements as compared to others.

From the 90 pieces of information corresponding to the nine different compositions studied by $^{19}$F-NMR, the values of the equilibrium constants

$$K_1 = [neso][\text{middles}]/[\text{ends}]^2 \quad \text{(d)}$$

$$K_2 = [\text{ends}][\text{branches}]/[\text{middles}]^2 \quad \text{(e)}$$

were found to be $K_1 = 0.33 \pm 0.06$ (standard deviation) and $K_2 = 0.31 \pm 0.02$. These constants are very similar to those of Eqs. (b) and (c). It was originally stated [29] that the number of rings in the system above the gel point is insignificant. However, later quantitative calculations with these equilibrium constants have shown that the relative amount of the *ee* molecule is a quite insensitive measure of the amount of ring structures.

### b) Colligative Measurements

Cryoscopic and ebullioscopic measurements have recently been discussed by *Thilo* and *Flögel* [32]. The theoretical treatment is identical to that given for $\rho = 1$ in our publications. The equilibrium constants, $1/K_n$, for the reactions

$$As_nO_{n-1}Cl_{n+2} + As_2OCl_4 \rightleftharpoons As_{n+1}O_nCl_{n+3} + AsCl_3 \quad \text{(f)}$$

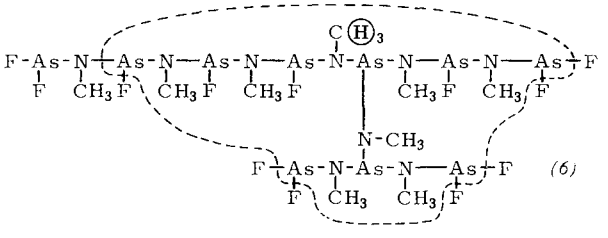
can be shown to be constant and identical for all values of n only on the assumption that the reorganizational heat order, $\rho$, is unity and that branches are disallowed. Simple mathematical manipulation also shows that, with no branches, four times the $K_s$ or K given by *Thilo* and *Flögel* is equal to the $K_1$ in the form of Eq. (a), so that the colligative measure-

[32] *E. Thilo* and *P. Flögel*, Z. anorg. allg. Chem. *329*, 244 (1964).

ments offer a simple way of determining one, *viz.* $K_1$, of the $(\nu-1)$ equilibrium constants, $K_i$, describing the equilibria in the chain portion of the system, assuming $\rho = 1$. Since the number of branches and of rings in the composition region accessible to study by cryoscopic and ebullioscopic measurements is necessarily small, even in those cases where ring-chain equilibria favor cyclic molecules, the discussion by *Thilo* and *Flögel* in terms of only unbranched chains is a reasonable approximation in the composition range which they studied.

### c) Poly(fluoroarsenous methylimides)[30]

This family of compounds corresponding to the system $AsF_3/As_2(NCH_3)_3$ is particularly interesting in that the chemical shift of the hydrogen of a methylimino bridge is sensitive to the arrangement of fluorine atoms and methylimino bridges on the neighboring arsenic atoms. A very complicated spectrum results in which 18 resonances are distinguishable. This means that the chemical shift of the encircled hydrogens [formula *(6)*] gives information about the arrangement of all atoms within the dotted line.



*(6)*

### d) Exchange Rates[29–31]

From the broadening and coalescence of the NMR peaks with increasing temperature, as exemplified by Fig. 7, the lifetime for the exchange of fluorine atoms,

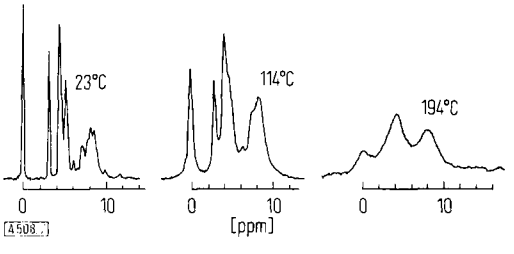
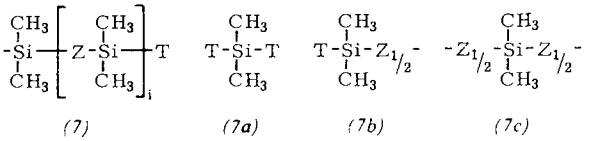



Fig. 7. $^{19}$F-NMR spectra as a function of temperature for an $AsF_3/As_2O_3$ mixture [29]; over-all F:As mole ratio 1.25. Conditions as in Fig. 6.

methoxy groups, or methylimino bridges between chemically different sites may be measured, together with the activation energy for the process. The exchange lifetimes of molecules based on arsenic atoms bridged with either oxygen atoms or methylimino groups are found to be small fractions of a second at room temperature. The corresponding activation energy is also small, being only several kcal/mole. Since slow flow is observed beyond the gel point in the $AsF_3/As_2O_3$ system, and the activation energy for flow is the same as that for exchange of fluorine atoms between different sites, it is evident that in systems where the molecules exchange parts at a rapid rate, flow of even infinitely large molecules can occur through such exchange.



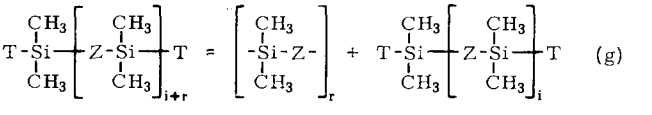
For molecules having the structure *(7)*, where T is an exchangeable substituent such as a halogen, methoxy, dimethylamino, *etc.*, and Z is a bridging oxygen[33], sulfur[34], or methylimino group[35], there will be an equilibrium between *neso*-molecules *(7a)*, end groups *(7b)*, and middle groups *(7c)*, corresponding to one constant, $K_1$, as given by Eq. (a) with $\nu = 2$ and Q = $(CH_3)_2Si$. In addition, the middle groups may combine to give rings. These systems of molecules are readily studied by means of the $^1$H-NMR signals of the dimethylsilicon moiety.



*(7)* *(7a)* *(7b)* *(7c)*

### a) Equilibrium with Cyclic Structures

Ring-chain equilibria are particularly interesting in these systems. The equilibrium (g) was found to be more strongly shifted in the direction of cyclic molecules with Z being successively oxygen, methylimino, and sulfur:



(g)

where for the chain molecules $\rho \approx 1$; the subscript r denotes the number of silicon atoms in the ring.

At 120 °C, the equilibrium constant corresponding to Eq. (g) is about 0.5 moles/l for Z = O, 40 for Z = $NCH_3$, and 2000 moles/l (estimated) for Z = S, where T = Cl and r = 3. As might be expected, there is a rather large enthalpy change connected with the equilibria between small cyclic molecules. For Z = S, there is an enthalpy difference of −3.3 kcal per Si atom for the conversion of three dimeric into two trimeric rings. Many more quantitative data of this type are needed in order to allow prediction of whether rings or chains will dominate in a particular system.

### b) α,ω-Dichloropolydimethyl-*N*-methylsilazanes[35]

In equilibrium mixtures of chain and ring compounds corresponding to T = Cl and Z = $NCH_3$ in *(7)* the distribution of molecules can be characterized from theNMR signals of the methyl groups on the silicon as well as from that of the methyl group on the bridging nitrogen. A typical spectrum is shown in Fig. 8, from which it

[33] *K. Moedritzer* and *J. R. Van Wazer*, J. Amer. chem. Soc. *86*, 802 (1964).

[34] *K. Moedritzer, J. R. Van Wazer*, and *C. H. Dungan*, J. chem. Physics *42*, 2478 (1965).

[35] *J. R. Van Wazer* and *K. Moedritzer*, J. chem. Physics *41*, 3122 (1964).

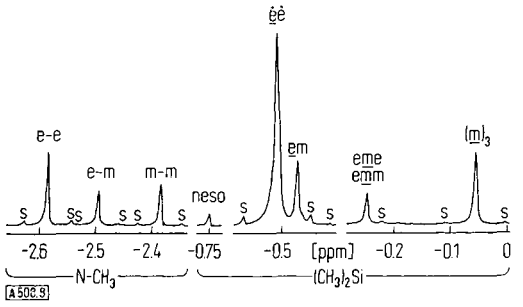



Fig. 8. $^1$H-NMR spectrum of a mixture [35] of molecules equilibrated at 120 °C in the system $(CH_3)_2SiCl_2/[(CH_3)_2Si(NCH_3)]$; over-all $Cl:(CH_3)_2Si$ mole ratio 0.78. Data obtained on a Varian A-60 spectrometer at 60.000 Mc/sec with sample spinning in precision tubes and a sweep width of 50 cps full scale. The symbol s refers to $^{29}$Si satellites, corrections for which must be made when they are buried under neighboring peaks.

can be seen that the resonances corresponding to the methylimino bridge are considerably downfield from those corresponding to the dimethylsilicon moiety. The relative areas of certain peaks in these spectra are fixed. Thus the *e*—*e* resonance corresponds to the single methyl of the bridging $CH_3N$ group, whereas the **ee** signal comes from the four methyl groups of the pair of dimethylsilicon moieties in the molecule so that the areas of these peaks must always be in the ratio of 1:4. Likewise, the *e*—*m* resonance is again due to a single methyl group whereas the **em** resonance results from the two methyl groups on the terminal silicon atom. The *m*—*m* resonance in the spectrum of Fig. 8 corresponds to both chains and rings, hence its area must be half the sum of the areas of the peaks denoted as *e***m***e* and *e***m***m* plus $(\mathbf{m})_3$.

### c) Kinetic Data

The kinetics of the reaction between equimolar amounts of silicon in a ring compound and in the *neso*-molecule is shown [33] in Fig. 9 for X = Cl and Z = O. The same information is presented [35] in Fig. 10 for X = Cl and $Z = NCH_3$. The fact that the kinetic pattern in Fig. 9 is considerably more complicated than that in Fig. 10 is attributable to a difference in the rate of the first step

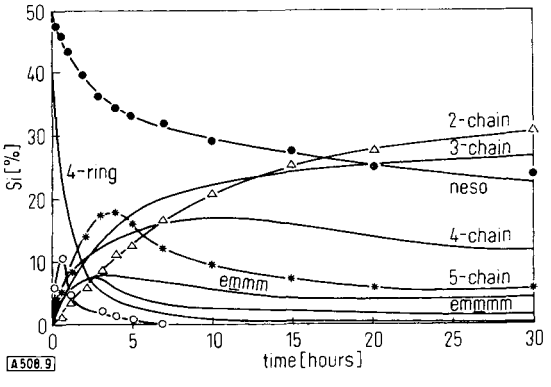



Fig. 9. Variation with time of the distribution of total silicon present in various molecules or building units during equilibration [33] at 200 °C of a mixture of one mole of dichlorodimethylsilane with 1/4 mole of octamethylcyclotetrasiloxane using 0.5 wt.-% $AlCl_3$ as catalyst. To avoid confusion, experimental points are shown only for the *neso*-compound (●), the di-chain (△), the penta-chain (*), and the large molecules (big rings or long-chains) (○).

(whereby the *neso*-compound reacts with the ring to give a chain) as compared to the rates of succeeding steps. When $Z = NCH_3$, this reaction is slower than the succeeding reactions whereby the *neso* and chain compounds equilibrate; when Z = O, this reaction is at least as rapid as the succeeding ones.

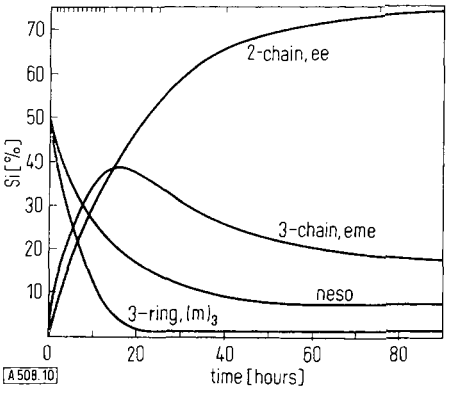



Fig. 10. Variation with time of the percentage of total silicon present in various molecules during equilibration [35] at 120 °C of a mixture of one mole of dichlorodimethylsilane with 1/3 mole of nonamethylcyclotrisilazane. The marks along the top of this figure denote the times at which the data were obtained.

In siloxanes [33] (Z = O) the interaction of tetrameric rings to give larger rings (octameric, dodecameric, *etc.*) or long chains terminated by trace amounts of ends (perhaps impurities) is the process occurring at the beginning of the reaction:

j (4-ring) → large rings or long chains

The early and prominent maximum noted for the five-membered chains shows that the following reaction is also initially prominent:

*neso*-compound + 4-ring → 5-chain

The rapid diminution in the amount of long chains or large rings after passing through a maximum is most probably attributable to:

*neso*-compound + long chains or large rings → shorter chains

The subsequent diminution of the amount of five-membered chains is caused by several reactions such as:

5-chain + *neso*-compound → 2 (3-chain)

or perhaps

5-chain + 3 *neso*-compound → 4 (2-chain)

After about 15 hours under the experimental conditions of Fig. 9 all of the different species of molecules are in the process of exchanging parts with each other so that any theoretical explanation of the right-hand end of the curves of Fig. 9 must involve reactions between many different molecules, as must be the case at the final dynamic equilibrium. For further examples, see [36–40].

[36] *D. Grant* and *J. R. Van Wazer*, J. Amer. chem. Soc. *86*, 3012 (1964).

[37] *M. D. Rausch* and *J. R. Van Wazer*, Inorg. Chem. *3*, 761 (1964).

[38] *H. K. Hofmeister* and *J. R. Van Wazer*, J. inorg. nucl. Chem. *26*, 1209 (1964).

[39] *N. E. Aubrey* and *J. R. Van Wazer*, J. Amer. chem. Soc. *86*, 4380 (1964).

## IV. Concluding Remarks

### 1. Summary

In this brief review, we have attempted to point up the importance of chemical equilibria in structural inorganic chemistry and to show how the kind and yield of various molecules may be treated quantitatively. Because of the importance of kinetic control in organic chemistry and because the chemistry of carbon compounds is by far the most advanced branch of general and descriptive chemistry, preparative inorganic chemists have often overemphasized the value of reaction-mechanism theory to their studies and have thereby neglected the powerful quantitative approach of thermodynamics which may be used in equilibrated systems. The general theorems for treating in terms of small molecular segments the multitude of equilibria present in families of compounds have been surveyed superficially with the hope that the interested reader will turn to the original papers for details. In these days of high-speed computers, not only physical-inorganic chemists, but also those interested solely in preparative work can advantageously employ the theoretical ideas discussed above.

### 2. Future Developments

#### a) Theory

Atomic-interaction theories are being developed for correlation and prediction of the deviations from randomness in the equilibria involving chains. Work is also under way on the theoretical basis of ring-chain equilibria and the time needed to reach equilibrium in various systems. The concept of order of environment within molecules can be extended to the interpretation of what might be called atomically additive properties, such as density, refractive index, or bulk magnetic susceptibility. In addition, we are studying several examples of the effect of solution nonideality on deviations from randomness in equilibria.

#### b) Analysis

New and improved analytical techniques for assaying molecules in mixtures are surely to be expected in a reasonably near future. In particular, nuclear magnetic resonance spectrometers of very high resolution will become available with improvements in field-strength uniformity of superconducting magnets. These should allow one to see molecules in considerably greater depth than is possible today, as well as to extend practical high-resolution NMR to samples having the natural abundance of chemically interesting nuclei such as $^{13}C$, $^{15}N$, $^{29}Si$, $^{77}Se$, $^{111}Cd$ or $^{113}Cd$, $^{119}Sn$, $^{125}Te$, $^{195}Pt$, $^{199}Hg$, and $^{207}Pb$, all of which have spin $1/2$. Moreover, with very high field strengths, it will be possible to measure much more rapid exchange rates and to observe uncoalesced resonances under conditions where either exchange or quadrupole broadening now makes the spectra difficult and sometimes impossible to interpret. Another way of increasing the range of elements that can be studied by NMR is to use isotopic enrichment of those magnetically suitable nuclei which are naturally present in low abundance (*e.g.* $^{29}Si$).

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German version: Angew. Chem. *78*, 401 (1966)

[40] *K. Moedritzer* and *J. R. Van Wazer*, Inorg. Chem. *3*, 943 (1964).

# Structures and Reactions of Organic ate-Complexes

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*Some years ago, Wittig [1] pointed out that ate-complexes are characterized by anionic activation of the substituents attached to the central atom. The behavior of these compounds thus contrasts with that of the onium-complexes [2] studied by Meerwein, which are characterized by cationic activation of the ligands. These two types of complexes form together two complementary aspects of organic coordination chemistry [5].*

## A. Introduction

ate-Complexes, according to *Wittig* [1], are compounds having the structure $M_{n-z}[ZR_n]$, in which a complex anion $[ZR_n]^{(n-z)-}$ is associated with a cationic partner (such as an electropositive metal). The name "ate-complex" was chosen because in chemical nomenclature complex anions are given a name having the suffix "-ate" [3, 4]. The positive center in onium-complexes

[1] *G. Wittig*, Angew. Chem. *70*, 65 (1958).

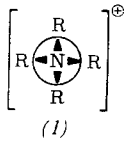
[2] Cf. *E. Müller*: Neuere Anschauungen der organischen Chemie. Springer, Berlin 1957, p. 132–142.

[3] "Nomenclature of Inorganic Chemistry." J. Amer. chem. Soc. *82*, 5523 (1960); *H. Remy*, Angew. Chem. *71*, 515 (1959).

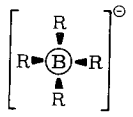
[4] *D. F. Martin* and *B. B. Martin*: Coordination Compounds. McGraw-Hill, New York 1964.

[5] Metal-carbon π-complexes are excluded from the following discussion.

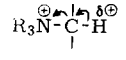
[*e.g. (1)*] contributes to the cationic activation of the ligands by an inductive effect. On the other hand, the negative charge in the ate-complexes [*e.g. (2)*] activates all the substituents anionically by an inductive effect which may facilitate the removal of a ligand as an anion or may lead to an increase in the mobility of hydrogen as hydride on a carbon $\alpha$ or $\beta$ to the central atom.

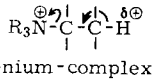


*(1)*

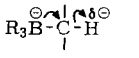


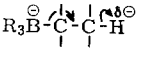
*(2)*



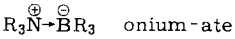


onium-complex





ate-complex



*(3)* onium-ate-complex

It is also to be expected that in coordination compounds with an "onium-ate" structure [*e.g. (3)*], which result from the combination of a Lewis acid with a Lewis base, the reactivities of the ligands may be substantially altered by adduct formation.

The ligands are anions or molecules exhibiting donor properties, usually owing to the presence of a lone pair of electrons. Complex formation is related to the tendency of the central atom to assume the energetically favorable electronic configuration of the nearest inert gas. However, the tendency towards complex formation and the stability of the complexes depends also on the charge and size of the groups and on the bond energy of, for example, the new metal-carbon bond, which can also be appreciably affected by other factors, such as the interaction between the d-orbitals of the metal and the p-orbitals of the ligand [5].

## B. Complex Organolithium Compounds

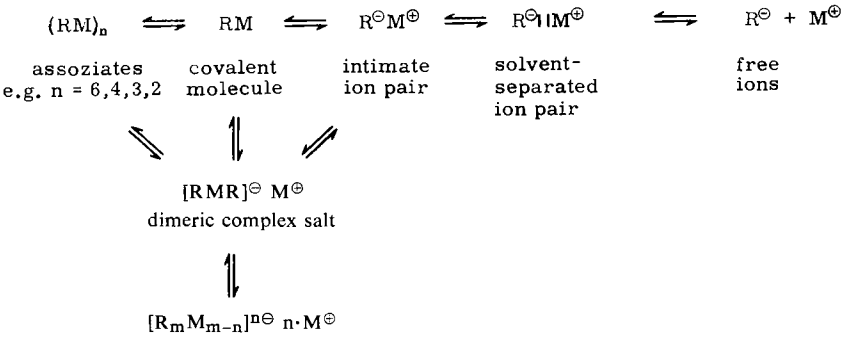
### 1. General

Organolithium compounds RLi (R = alkyl, aryl) exist in solution as associates $(RLi)_n$, where n can vary widely depending on the concentration, the solvent, and the nature of the group R [6–10]. The ability of lithium ions in aqueous solution to form complexes according to

$$Li^+ + X^{n-} \rightleftharpoons [LiX]^{(n-1)-}$$

was discovered by *Schwarzenbach* [11] during investigations on complexes with iminoacetic acid derivatives.

*Wittig* [8] discussed the dimerization of phenyl-lithium in ether in terms of self-complexing with formation of the ate-complex *(4)*. In this case, however, as is also found by molecular-weight determinations on the analogous triphenylzincate, triphenylberyllate, and tetraphenylborate complexes, the lithium ions remain predominantly in the vicinity of the complex anion. In solvents of relatively low dielectric constants (ether, acetone), solvation is sufficient only for the formation of ion pairs and higher aggregates [12]. Ion associates of this nature are very common [13a], and even organometallic compounds which exist in ether mainly as ion pairs have very low dissociation constants [13b]. The association, self-complexing, ionization, and dissociation of organometallic derivatives of alkali metals generally involve many steps, and can according to *Ebel* be represented as follows [13c, 13d]:




Predominantly "free" ions are to be expected only in dilute aqueous solutions of lithium or sodium tetraphenylborate [13e].

$[C_6H_5{-}Li{-}C_6H_5]Li$ *(4)* $Ca[Al(i\text{-}OC_3H_7)_4]_2$ *(5)* $Cu[Al(OC_2H_5)_4]_2$ *(6)*

It is also found in several cases that when two different alkoxides combine, dissociation is not promoted but

[6] See *G. E. Coates*: Organo-Metallic Compounds. Methuen, London 1960.

[7] *Fr. Hein* and *H. Schramm*, Z. physik. Chem. *151*, 234 (1930).

[8] *G. Wittig*, *F. J. Meyer*, and *G. Lange*, Liebigs Ann. Chem. *571*, 167 (1951).

[9] *T. L. Brown* and *M. T. Rogers*, J. Amer. chem. Soc. *79*, 1859 (1957).

[10] *K. B. Piotrovsky* and *M. P. Ronina*, Doklady Akad. Nauk SSSR *115*, 737 (1957); Chem. Abstr. *52*, 3476f (1958).

[11] *G. Schwarzenbach*, *A. Willi*, and *R. O. Bach*, Helv. chim. Acta *30*, 1303 (1947).

[12] *E. S. Gould*: Mechanism and Structure in Organic Chemistry. Holt, Rinehart & Winston, New York 1959, pp. 102, 580.

[13a] Cf. *F. Basolo* and *R. G. Pearson*: Mechanisms of Inorganic Reactions. Wiley, New York 1958, pp. 376–385.

[13b] See, for example, *D. G. Hill*, *J. Burkus*, *S. M. Luck*, and *C. R. Hauser*, J. Amer. chem. Soc. *81*, 2787 (1959).

[13c] *H. F. Ebel*, Tetrahedron *21*, 699 (1965).

[13d] For the detection of carbanionic ion pairs, see *E. De Boer*, Advances in Organometallic Chemistry, Academic Press, New York 1964, vol. 2, p. 115; *T. E. Hogen-Esch* and *J. Smid*, J. Amer. chem. Soc. *87*, 669 (1965).

[13e] On the conductivity of these tetraphenylborates in water, see *W. Rüdorff* and *H. Zannier*, Z. Naturforsch *8b*, 611 (1953).

suppressed. Thus in contrast to the calcium alkoxides, the complex *(5)* can be vacuum distilled without decomposition, and copper tetraethoxyaluminate *(6)* even dissolves (probably as the monomer) in benzene[14].

## 2. Crystal Structure and Association in the Gas Phase and in Nonpolar Solvents

X-ray analyses of crystalline ethyl-lithium[15] showed that the molecules form pairs of layers held together by van der Waals forces, which can be relatively easily displaced with respect to one another. These double layers are built up from $(C_2H_5Li)_4$ units, each of which consists of two strongly associated ethyl-lithium dimers. The four lithium atoms form an almost regular tetrahedron, which has a methylene group situated above each face. Since ethyl-lithium may be regarded as an electron-deficient compound, bonds of this type are probably also responsible for the complex crystal structure. The carbon-lithium bond in this case is largely covalent[16], as is manifested also in the low electrical conductivity[17] and the small dipole moment[18].

t-Butyl-lithium exists in benzene and in hexane as the tetramer. On the basis of spectroscopic studies, this tetramer was assumed to have a tetrahedral structure, in which the four lithium atoms and the four α-carbon atoms of the t-butyl groups occupy the vertices of two interpenetrating tetrahedra[19]. The complex is thought to be held together by four equivalent four-center electron-deficient bonds:

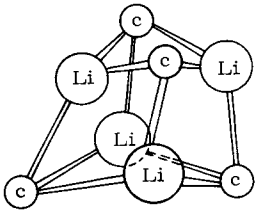



Fig. 1. Structural unit of tetrameric t-butyl-lithium [19].

This structure, which is similar to that of tetrameric tetramethylplatinum[20], has also been proposed by *Brown*[21] for the tetramer present in ethyl-lithium vapor and in solutions. The mass spectrum of saturated ethyl-lithium vapor[22] at 80–95 °C shows it to consist predominantly of $Li_6R_6$ and $Li_4R_4$ units in roughly equal concentrations. The structure therefore probably is cyclic, since there would be no reason for the predominance of hexameric and tetrameric units if the structure were linear:

$$C_2H_5{-}Li \ldots C_2H_5{-}Li \ldots C_2H_5{-}Li$$

*(7)*

In the hexameric lithium compound, which also predominates in solution (ethyl-lithium and n-butyl-lithium are hexameric both in benzene and in cyclohexane[21,23,24]), the six lithium atoms are thought to form a nucleus in a chair form, with the alkyl groups situated on the periphery of the structure[25]. Each lithium atom is again bonded to three carbon atoms and *vice versa*. The four-center bond involves an $sp^3$-orbital of the carbon, together with the orbitals of three lithium atoms, and each lithium atom is involved in three such bonds.

The strong inclination of organolithium compounds to form associates can be attributed to the tendency of lithium to fill its empty 2p-orbitals, which have only a slightly higher energy than the 2s-level[13c].

Information about the structures of organolithium compounds has also been obtained from infrared spectra[26,27]. The asymmetric and symmetric C–H stretching vibrations of methyl-lithium are displaced to lower wave numbers; this phenomenon is generally found with bridging methyl groups[28]. In agreement therewith, both bridging methylene groups with the characteristic decrease in frequency *and* non-bridging terminal methyl groups are found in ethyl-lithium. However, frequency shifts of this type do not appear to be confined to compounds with electron-deficient structures. A similar situation is found for the α-methylene groups of tetraalkylborates[29]; here the displacement of the C–H stretching frequency may be due to the inductive effect of boron.

## 3. Organolithium Compounds in Basic Media

It has long been known that organolithium compounds are much more reactive in solvents such as ether than in hydrocarbons[6], and many attempts have been made to elucidate the degree of association of these compounds and their interactions with these solvents[8]. The addition of even relatively small quantities of a Lewis base (ether, *etc.*) has a marked influence on the behavior of lithium alkyls in hydrocarbons[30–32], as was shown

[14] *H. Meerwein* and *Th. Bersin*, Liebigs Ann. Chem. *476*, 113, 138 (1929).

[15] *H. Dietrich*, Acta crystallogr. *16*, 681 (1963). *E. Weiss* and *E. A. C. Lucken* found a similar situation in the case of methyl-lithium (J. organomet. Chemistry *2*, 197 (1964).

[16] *G. Fraenkel, D. G. Adams*, and *J. Williams*, Tetrahedron Letters, *1963*, 767 assign an ionic character of about 20% to the C-Li bond on the basis of NMR studies. From theoretical considerations, *H. F. Ebel* [13c] gives a value of 27% for methyl-lithium. A much higher value is given in *L. Pauling*: The Nature of the Chemical Bond. Cornell University Press, Ithaca, N.Y., 2nd Edit., 1948.

[17] Fused ethyl-lithium does not conduct electricity: *Fr. Hein, E. Petzchner, K. Wagler*, and *F. A. Segitz*, Z. anorg. allg. Chem. *141*, 161 (1924).

[18a] *M.T. Rogers* and *A. Young*, J. Amer. chem. Soc. *68*, 2748 (1946).

[18b] *M.T. Rogers* and *T.L. Brown*, J. physic. Chem. *61*, 336 (1957).

[18c] *V. N. Vasil'eva, T. V. Talalaeva, E. N. Gur'yanova*, and *K. A. Kocheskov*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1960*, No. 9, 1549–1552; Chem. Abstr. *55*, 6971f (1961). Values between 0.8 and 1.5 D were found for the dipole moments of several alkyl-lithium molecules, depending on the concentration and the solvent. Appreciably higher values are expected for ion pairs such as are formed by lithium perchlorate in dioxane [18a].

[19] *M. Weiner, G. Vogel*, and *R. West*, Inorg. Chem. *1*, 654 (1962).

[20] *R. E. Rundle* and *J. H. Sturdivant*, J. Amer. chem. Soc. *69*, 1561 (1947).

[21] *T. L. Brown, D. W. Dickerhoof*, and *D. A. Bafus*, J. Amer. chem. Soc. *84*, 1371 (1962).

[22] *J. Berkowitz, D. A. Bafus*, and *T. L. Brown*, J. physic. Chem. *65*, 1380 (1961).

[23] *D. Margerison* and *J. P. Newport*, Trans. Faraday Soc. *59*, 2058 (1963).

[24] *T. L. Brown, R. L. Gerteis, D. A. Bafus*, and *J. A. Ladd*, J. Amer. chem. Soc. *86*, 2135 (1964).

[25] A structure of this type is also supported by the ease with which an ethyl radical is split off during the ionization, and by the extremely high appearance potential of the lithium cation.

[26] *R. West* and *W. Glaze*, J. Amer. chem. Soc. *83*, 3580 (1961).

[27] *J. Goubeau* and *K. Walter*, Z. anorg. allg. Chem. *322*, 58 (1963).

[28] *T. L. Brown* and *M. T. Rogers*, J. Amer. chem. Soc. *79*, 1859 (1957).

[29] *R. Damico*, J. org. Chemistry *29*, 1971 (1964).

[30] *D. Y. Curtin* and *W. J. Koehl jr.*, J. Amer. chem. Soc. *84*, 1967 (1962).

[31] *D. E. Applequist* and *D. F. O'Brien*, J. Amer. chem. Soc. *85*, 743 (1963).

[32] *J. F. Eastham* and *G. W. Gibson*, J. Amer. chem. Soc. *85*, 2171 (1963).

by the discovery [33a, b] of a solvated dimer $(n\text{-}C_4H_9Li)_2 \cdot (C_2H_5)_2O$, the structure of which is shown in Fig. 2.

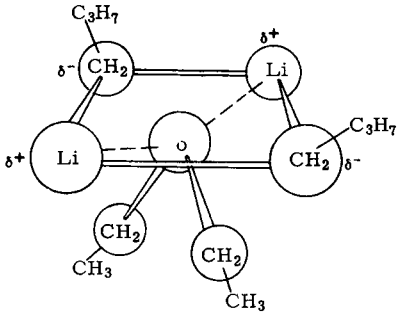


Fig. 2. Structure of a butyl-lithium/diethyl ether adduct [33a].

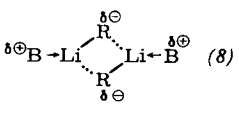
When ether is added to a solution of n-butyl-lithium in hexane, the vapor pressure of the ether decreases below that found in the absence of butyl-lithium, and the dielectric constant of the solution increases considerably, until the quantity of ether equivalent to the 2:1 complex has been added. In the NMR spectrum, the position of the α-methylene proton signal of the butyl-lithium changes only until all the n-butyl-lithium has been converted into the 2:1 complex; the addition of more ether has no further effect, so that any further changes in the reactivity of the organometallic component are probably due simply to a general solvent effect [33a].

On the basis of NMR studies on complexes of 9-fluorenyl-lithium with tetrahydrofuran and with 1,2-dimethoxy-ethane, *Dixon* [33c] recently concluded that the lithium cation and the coordinated Lewis bases (THF or dimethoxy-ethane) lie above the plane of the aromatic carbanion.

The Lewis-acidic character of the alkyl-lithium polymers is shown also by complex formation between ethyl-lithium and triethylamine in benzene, which was detected by *Brown* [24] from the dielectric constants and freezing-point depressions of the solutions.

This result is best explained in terms of an initial addition of one or two molecules of amine to the hexameric lithium compound; this weakens and breaks the bond framework, forming tetrameric and dimeric ethyl-lithium units. These in turn coordinate with triethylamine, so that a sequence of complex equilibria can exist, depending on the concentration of the base. If the arrangement of the six lithium atoms in the hexamer is assumed to be octahedral, the ethyl groups attached can occupy only six of the eight octahedral faces, and the amine can therefore add on to the two remaining faces.

Although no details about the hybridization of the lithium orbitals are known at present, it may be assumed that in multi-center bonds of this type, one or two orbitals of each lithium atom remain empty, and these are available for the addition of a donor which leads to dissociation of the hexamer, tetramer, *etc.* Any complex formation with an electron donor, *e.g.* the in dimer *(8)*, causes considerable anionic activation of the



*(8)*

alkyl groups, thereby increasing the reactivity of the alkyl-lithium compounds.

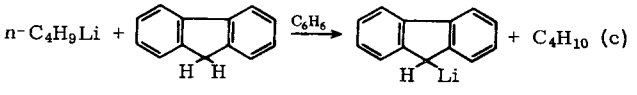
On the basis of NMR data, *Fraenkel* [16] assumed that ethyl-lithium, ethylmagnesium bromide, and diethylmagnesium exist in ethereal solutions as strongly associated salts of carbanions; this prompted further spectroscopic studies on organolithium compounds [24], but these failed to produce any evidence for the presence of solvated ion pairs. However, NMR spectroscopy does not appear to be a very sensitive method for the detection of organometallic compounds having different degrees of association or solvation [13, 16, 24, 61].

Kinetic studies show, on the other hand, that the reactions of organolithium compounds are preceded by dissociation equilibria [31, 32, 34]; this supports the view that the monomer is the reacting species, although it may be present only in small concentrations.

The rate r of the metalation of fluorene with n-butyl-lithium in benzene is found to obey the relation (a), *i.e.* the actual reaction is preceded by the formation of the monomer in the equilibrium (b).

$$r = k[n\text{-}C_4H_9Li)_6]^{1/6}\,[\text{fluorene}] \qquad (a)$$

$$(n\text{-}C_4H_9Li)_6 \rightleftharpoons 6\,n\text{-}C_4H_9Li \qquad (b)$$



*Waack* and *West* [34d] recently showed that benzyl-lithium, allyl-lithium, and phenyl-lithium also react as the monomers in the metalation of triphenylmethane in tetrahydrofuran [34e]. The relative reactivities:

benzyl-lithium > allyl-lithium > n-butyl-lithium > phenyl-lithium > vinyl-lithium > methyl-lithium

indicate that the rate-determining step in the metalation is a nucleophilic attack on the hydrogen of the substrate.

## 4. Complexes with Lithium Halides and Organometallic Compounds of Alkali Metals

The most important organolithium complexes, apart from those with amines and ethers (among which the complexes of dioxane with aryl-lithium derivatives are noteworthy for their low solubility and their ease of isolation [33b, 35]), are those formed with lithium halides and organometallic compounds of other alkali metals.

Salt-free solutions of lithium compounds are more reactive than solutions containing salt; this fact is often

[33a] *Z. K. Cheema, G. W. Gibson,* and *J. F. Eastham,* J. Amer. chem. Soc. *85,* 3517 (1963).

[33b] See also *T. V. Talalaeva, M. M. Nad,* and *K. A. Kocheskov,* Doklady Akad. Nauk SSSR *109,* 101 (1956); Chem. Abstr. *51,* 1962f (1957).

[33c] *J. A. Dixon, P. A. Gwinner,* and *D. C. Lini,* J. Amer. chem. Soc. *87,* 1379 (1965).

[34a] *D. F. Worsfold* and *S. Bywater,* Canad. J. Chem. *38,* 1891 (1960).

[34b] *A. G. Evans* and *D. B. George,* J. chem. Soc. (London) *1961,* 4653.

[34c] *A. G. Evans* and *N. H. Rees,* J. chem. Soc. (London) *1963,* 6039.

[34d] *R. Waack* and *P. West,* J. Amer. chem. Soc. *86,* 4494 (1964).

[34e] The same is true of styryl-lithium: *S. Bywater* and *D. J. Worsfold,* Canad. J. Chem. *40,* 1564 (1962).

[35] *N. G. Chernova* and *B. M. Mikhailov,* Zhur. Obschei Khim. *25,* 2280 (1955); Chem. Abstr. *50,* 9365f, 11996i (1956); J. gen. Chem. USSR *25,* 2249 (1956); *B. M. Mikhailov* and *N. G. Chernova,* Zhur. Obschei Khim. *29,* 222 (1959); Chem. Abstr. *53,* 21843h (1959).

utilized in metalations and polymerizations [36–38]. *Wittig* and *Lange* [36a] obtained the crystalline phenyl-lithium/LiBr 2:1-adduct from solutions of phenyl-lithium in ether containing LiBr, and *Glaze* and *West* [39] isolated adducts of lithium halides and alkyl-lithium compounds. The ratio RLi:LiBr in the adduct depends on its preparation, but the products appear to be mixtures of LiBr with 1:1 complexes. The butyl-lithium/LiBr adduct is hydrolysed rapidly by water, but reacts only slowly with atmospheric oxygen. When suspended in pentane, this complex gives a negative Gilman color test [40]; a positive test is obtained only with its dissociation products formed by addition of ether. Thus organolithium compounds can be deactivated to substances that are easily handled, and from which the active reagent can be regenerated by addition of ether.

The deactivation is probably due to the fact that LiBr is a stronger Lewis acid than organolithium compounds and so forms coordination compounds that are more stable than the complexes of RLi with itself. However, it is not yet settled whether these adducts have ionic structures such as *(9)* or *(10)*, or whether they are electron-deficient compounds.

$[RLiX]^{\ominus}Li^{\oplus}$ *(9)* $[Li_2R]^{\oplus}X^{\ominus}$ *(10)*

Using ethyl-lithium/lithium ethoxide complexes, *Brown* [40a] showed that, unlike ethers and amines, alkoxides do not cause appreciable dissociation of the ethyl-lithium hexamer into more reactive species. Corresponding remarks could also apply to the unreactive RLi/LiBr adducts.

The efficiency of *e.g.* phenyl-lithium as an initiator in the anionic polymerization of styrene depends on the quantity of lithium halide added, and this fact has been used for the detection of the 1:1 complex RLi·LiBr and for the determination of the equilibrium constant K [38,40b].

$$K = \frac{[R\text{-}Li\cdot LiX]}{[R\text{-}Li]\,[LiX]}$$

K = 13.5 l/mole (20 °C; THF; R = $C_6H_5$; X = Br)

K = 115 l/mole (20 °C; THF; R = $CH_2{=}CH-$; X = Br)

The complexes of organolithium compounds with organosodium, organopotassium, and organocesium compounds, which were discovered by *Wittig* [41], have acquired some preparative importance. Their preparation is based on the fact that the dimer of phenyl-lithium in ether [7,8] may be formulated as a complex ion pair *(4)*, in which one lithium atom acts as the coordination center, the other as the cationic partner of the negative complex ion. It should therefore be possible to replace $Li^+$ by another metal cation without affecting the complex character; this was confirmed by the isolation of the colorless complex *(11)*, which is sparingly soluble in ether.

$[C_6H_5{-}Li{-}C_6H_5]Na\cdot(C_2H_5)_2O$ *(11)*

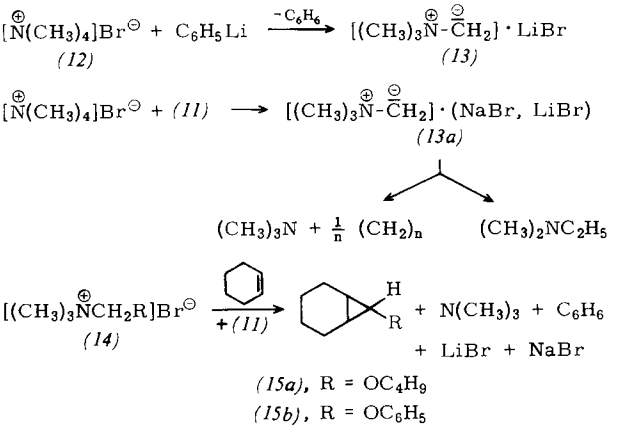
Whereas ether is rapidly decomposed by phenylsodium, the complex *(11)*, which is obtained from phenyl-lithium, diphenylmercury, and sodium or from chlorobenzene, sodium, and phenyl-lithium, is stable in ether for some days. The stability of these 1:1-complexes decreases rapidly from lithium to cesium as cation.

Solutions of *(11)* in ether stabilize phenylsodium, probably because the sodium ions of *(11)* greatly reduce the solubility of phenylsodium. The decomposition of phenylsodium can therefore be prevented by the addition of an ethereal solution of LiBr, which gives rise to the complex *(11)* in accordance with the reactions [42]:

$$C_6H_5Na + LiBr \rightarrow C_6H_5Li + NaBr \quad (d)$$
$$C_6H_5Li + C_6H_5Na \rightarrow (11)$$

Complexes with alkyl-lithium compounds can also be prepared. The limit of applicability of ether assolvent is reached with the particularly reactive sodium dibutyl-lithiate. The reactivities of the complexes are between those of the organolithium and the organosodium compounds themselves, and they have proved particularly useful for the metalation of diphenylmethane and triphenylmethane, anisole, 1,3-dimethoxybenzene, diphenyl sulfide, triphenylamine, and triphenylphosphine. In the metalation of anisole with *(11)* to *o*-methoxyphenyl-lithium, a conversion of 71 % is obtained in two days, whereas salt-free phenyl-lithium gives only 17 % conversion in the same period.

Phenyl-lithium and ammonium salts *(12)* react to form ammonium ylides [43,44], which are stabilized by coordination with LiBr to give *(13)*. On the other hand,




[36a] *G. Wittig*, Angew. Chem. *62*, 232 (1950).

[36b] *G. Wittig* and *E. Benz*, Chem. Ber. *91*, 873 (1958).

[37] *R. Huisgen* and *W. Mack*, Chem. Ber. *93*, 332 (1960), detected 1:1 complexes of lithium piperidide and lithium halides, and determined their dissociation constants.

[38] *R. Waack* and *M. A. Doran*, Chem. and Ind. *1964*, 496.

[39] *W. Glaze* and *R. West*, J. Amer. chem. Soc. *82*, 4437 (1960); Chem. Engng. News *1960*, No. 43, p. 40.

[40] *H. Gilman* and *F. Schulze*, J. Amer. chem. Soc. *47*, 2002 (1925). This Gilman color test is based on the preparation of a di- or triphenylmethane dye from Michler's ketone and RM.

[40a] *T. L. Brown*, *J. A. Ladd*, and *G. N. Newman*, J. organomet• Chemistry *3*, 1 (1965).

[40b] See also *F. J. Welch*, J. Amer. chem. Soc. *82*, 6000 (1960).

[41a] *G. Wittig*, *R. Ludwig*, and *R. Polster*, Chem. Ber. *88*, 294 (1955).

[41b] *G. Wittig* and *F. Bickelhaupt*, Chem. Ber. *91*, 865 (1958).

[41c] *G. Wittig* and *E. Benz*, Chem. Ber. *91*, 873 (1958).

[42] German Pat. 1003731 (March 7th, 1957), BASF Ludwigshafen; inventor: *G. Wittig*; Chem. Abstr. *53*, 16064b (1959).

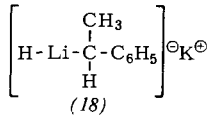
[43] *G. Wittig* and *R. Polster*, Liebigs Ann. Chem. *599*, 1, 13 (1956).

[44] On the structure of trimethylammonium methylide, see *H. Daniel* and *J. Paetsch*, Angew. Chem. *76*, 577 (1964).

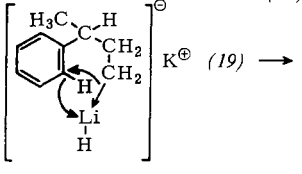
the ylide *(13a)* obtained in the same manner, but with *(11)* as proton acceptor, decomposes into polymethylene and trimethylamine, or undergoes a Stevens rearrangement to form ethyldimethylamine, since NaBr is a much weaker complexing agent than LiBr. This behavior has been used in two cases for the formation of cyclopropane rings. Thus *(11)* and *(14)* react in the presence of cyclohexene to give 7-n-butoxy-*(15a)* or 7-phenoxy-norcarane *(15b)* [45].

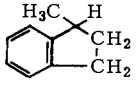
*Eberhardt* [46] used the ate-complexes *(16)* and *(17)* (prepared from potassium hydride or potassium + butyl-lithium) as catalysts for the reaction of ethylbenzene with ethylene. Whereas neither potassium hydride nor n-butyl-lithium reacts with ethylbenzene at room temperature, *(16)* reacts immediately with liberation of butane, the solution turning red and *(18)* being formed. The latter adds to ethylene to form *(19)*, which undergoes ring closure to give 1-methylindane *(20)* with loss of hydride from the aromatic ring. The complex hydride *(21)* adds to ethylene to give a new alkyl-hydride complex *(22)*, which in turn reacts with ethylbenzene to begin the cycle once again. In addition to products of higher molecular weight, a total of 70 % of 1-methylindane *(20)* and sec-butylbenzene is obtained [the latter product resulting from the hydrolysis of *(19)*] from ethylene and ethylbenzene.

$K[HLiC_4H_9]$ *(16)* $\qquad$ $K[(C_4H_9)_2Li]$ *(17)*

*(16)* + $CH_3\text{-}CH_2\text{-}C_6H_5 \longrightarrow C_4H_{10}$ + 

*(18)*

*(18)* + $C_2H_4 \longrightarrow$  *(19)* $\longrightarrow$

*(20)*  + $[LiH_2]K$ *(21)*

*(21)* + $C_2H_4 \longrightarrow K[HLiC_2H_5]$ *(22)* $\longrightarrow$ etc.

## C. Complex Organoberyllium Compounds

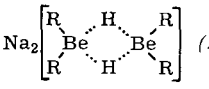
Elements of Groups II and III of the periodic table have an even greater tendency than lithium to form dimeric and polymeric electron-deficient structures in organometallic compounds and hydrides, and have a pronounced Lewis acid character. With organometallic compounds of alkali metals they form ate-complexes, and with electron donors such as amines, phosphines, and ethers they form adducts $R_nZ \leftarrow Z'R_m$.

In complexes with alcohols and secondary amines, the combination of cationic activation of a hydrogen atom in the donor part of the molecule with anionic activation of an alkyl group in the acceptor part leads to extreme readiness to undergo eliminations. Thus *(23)* loses methane to form *(24)*, which contains an N–Be–N–Be–N–Be ring [47].

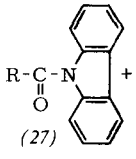
$$3\,(CH_3)_2\overset{\ominus}{B}e\text{–}\overset{\oplus}{N}H(CH_3)_2 \xrightarrow{44^\circ C} 3\,CH_4 + [CH_3Be\text{–}\ddot{N}(CH_3)_2]_3$$

*(23)* $\qquad$ *(24)*

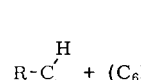
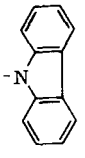
ate-Complexes of dialkylberyllium derivatives have also been obtained by the action of sodium hydride on dimethylberyllium and on diethylberyllium; the product is probably *(25)* [48a]. Complex salts of diethylberyllium with alkali metal fluorides and cyanides have also been reported [48b].

 *(25)*

In 1952, *Wittig* and *Hornberger* [49] obtained lithium hydridodiphenylberyllate *(26)* by fusion of diphenylberyllium with lithium hydride; they studied the complex (which can provide one hydride ion for reduction) to establish its suitability for the conversion of acyl chlorides into aldehydes. This reduction can be carried out *via* the amide *(27)*, which is obtained from the acyl chloride and carbazole; however, higher yields are obtained with other complex hydrides such as lithium tetrahydridoaluminate, lithium hydrido-tri-n-butoxyborate, and lithium hydridodiphenylzincate. This method was used for the preparation of unsaturated polyene aldehydes, such as cinnamaldehyde and 9-phenylnona-2,4,6,8-tetraenal.

 + $Li[HBe(C_6H_5)_2]$

*(27)* $\qquad$ *(26)*

$\longrightarrow$  + $(C_6H_5)_2Be$ + 

With the aid of an electron-attracting system, it is possible to draw the lone electron pair on the nitrogen into a cyclic π-electron system, so increasing the rate of nucleophilic additions to the carbonyl group. This principle led independently to simple syntheses of aldehydes by the action of lithium tetrahydridoaluminate on *N*-methylanilides [50], acyl imidazolides [51], and acyl pyrazolides [52]. Aldehydes are now

[45] *D. Krauß*, Dissertation, Universität Heidelberg, 1963; *G. Wittig* and *D. Krauß*, Liebigs Ann. Chem. *679*, 34 (1964).

[46] *G. G. Eberhardt*, J. org. Chemistry *29*, 643 (1964).

[47] *G. E. Coates*, *F. Glockling*, and *N. D. Huck*, J. chem. Soc. (London) *1952*, 4512. Cf. the corresponding behavior of analogous trialkylaluminum and trialkylgallium compounds [6].

[48a] *G. E. Coates* and *G. F. Cox*, Chem. and Ind. *1962*, 269; *N. A. Bell* and *G. E. Coates*, Proc. chem. Soc. (London) *1964*, 59.

[48b] *W. Strohmeier* and *F. Gernert*, Chem. Ber. *95*, 1420 (1962).

[49] *G. Wittig* and *P. Hornberger*, Liebigs Ann. Chem. *577*, 11 (1952).

[50] Review: *F. Weygand*, *G. Eberhardt*, *H. Linden*, *F. Schäfer*, and *J. Eigen*, Angew. Chem. *65*, 525 (1953).

[51] *H. A. Staab*, Angew. Chem. *74*, 407 (1962), Angew. Chem. internat. Edit. *1*, 351 (1962); *H. A. Staab* and *H. Bräunling*, Liebigs Ann. Chem. *654*, 119 (1962).

[52] *W. Ried* and *F. -J. Königstein*, Liebigs Ann. Chem. *622*, 37 (1959); *W. Ried*, *G. Deuschel*, and *R. Koteiko*, *ibid. 642*, 121 (1961).

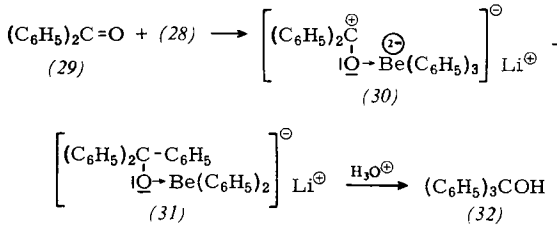
easily accessible by the reaction of amides, nitriles, or acyl chlorides with complex aluminum hydrides[53,54].

Diphenylberyllium reacts with phenyl-lithium to form lithium triphenylberyllate[8] *(28)*. This compound is very stable, suffers practically no decomposition in solution, gives a negative Gilman color test at room temperature[40], and does not metalate fluorene. The rate of metalation of fluorene shows that the tendency of the adducts $[(C_6H_5)_3Z]^{\ominus}Li^{\oplus}$ to dissociate into phenyllithium and diphenylmetal increases in the order:

$$[(C_6H_5)_3Be]Li < [(C_6H_5)_3Zn]Li < ([C_6H_5)_3Mg]Li < [(C_6H_5)_3Cd]Li < [(C_6H_5)_2Hg + C_6H_5Li]$$

*(28)*

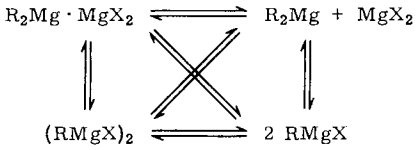
As in inorganic complexes[55], the stability of the complex decreases as the size of the central atom increases. Although *(28)* is inert towards fluorene *(i.e.* it does not dissociate to give phenyl-lithium), it reacts with benzophenone *(29)* to give triphenylmethanol *(32)* in 45 % yield; one must therefore conclude that the ate-complex *(28)* as a whole reacts with the ketone. In contrast to $[(C_6H_5)_4B]Li$, the central atom of *(28)* does not possess a complete octet of electrons in the outer shell; this deficiency can be compensated by addition to the carbonyl oxygen atom to form *(30)*, (yellow, halochromism, cf. Section F. 6):



A molecular-weight determination shows that the ate-complex *(28)* is partially associated in ether. In 1,2-dimethoxyethane at 100 °C, however, it appears to dissociate into phenyl-lithium and diphenylberyllium, since the solution can be used for the metalation of fluorobenzene, so permitting the generation of dehydrobenzene[56].

## D. Complexes of Organomagnesium Compounds

Organomagnesium compounds are extremely important in organic syntheses[6,57,58]. The constitution of Grignard compounds has been the subject of many discussions in recent years, and this question is still not settled[16,59–63c]. Knowledge available at present indicates that the following equilibria are possible, and that the positions of these equilibria depend on the groups R and X (Cl, Br, I), on the solvent, and on the concentration.



The kinetics of the reactions of organomagnesium compounds with ketones are very difficult to interpret because of the problems associated with the constitution of the organometallic compounds[64–69].

*Smith* and *Su*[68a] found simple relationships by following spectroscopically the reaction of 2,4-dimethyl-4′-(methylthio)benzophenone with methylmagnesium bromide, which leads to a 1:1-complex absorbing at 355 mμ. The equilibrium constant K (6.2 l/mole) for complex formation was determined, but it was impossible to distinguish between the kinetic schemes (e) and (f).

$$\text{Ketone} + CH_3MgBr \overset{K}{\rightleftharpoons} \text{1:1-complex} \xrightarrow{k} \text{product}\ [68b] \qquad \text{(e)}$$

$$\text{1:1-Complex} \overset{K}{\rightleftharpoons} \text{ketone} + CH_3MgBr \xrightarrow{k} \text{product} \qquad \text{(f)}$$

*House*[67,69] studied the mechanism of the addition of diethylmagnesium and ethylmagnesium bromide to ketones in the hope of elucidating the factors which in-

[53] *H. C. Brown*: Hydroboration. W. A. Benjamin, New York 1962.

[54] *H. C. Brown* and *C. J. Shoaf*, J. Amer. chem. Soc. *86*, 1079 (1964); *H. C. Brown* and *C. P. Garg*, *ibid.* *86*, 1085 (1964); *H. C. Brown* and *A. Tsukamoto*, *ibid.* *86*, 1089 (1964).

[55] *Fr. Hein*: Chemische Koordinationslehre. S. Hirzel, Leipzig 1954.

[56] *H. Rabold*, Dissertation, Universität Heidelberg, 1963.

[57] *M. S. Kharasch* and *O. Reinmuth*: Grignard Reactions of Nonmetallic Substances. Prentice Hall, New York 1954.

[58] *E. G. Rochow*, *D. T. Hurd*, and *R. N. Lewis*: The Chemistry of Organometallic Compounds. Wiley, New York 1957.

[59] *R. E. Dessy*, *G. S. Handler*, *J. H. Wotiz*, and *C. A. Hollingsworth*, J. Amer. chem. Soc. *79*, 3476 (1957); *R. E. Dessy* and *G. S. Handler*, *ibid.* *80*, 5824 (1958); R. E. Dessy, J. org. Chemistry *25*, 2260 (1960).

[60] *G. D. Stucky* and *R. E. Rundle*, J. Amer. chem. Soc. *85*, 1002 (1963); *86*, 4825 (1964); *L. J. Guggenberger* and *R. E. Rundle*, *ibid.* *86*, 5344 (1964).

[61] *E. C. Ashby* and *W. E. Becker*, J. Amer. chem. Soc. *85*, 118 (1963); *E. C. Ashby* and *M. B. Smith*, *ibid.* *86*, 4363 (1964); *E. C. Ashby*, *ibid.* *87*, 2509 (1965).

[62] *A. D. Vreugdenhil* and *C. Blomberg*, Recueil Trav. chim. Pays-Bas *82*, 453, 461 (1963).

[63] *R. E. Dessy*, *S. E. J. Green*, and *R. M. Salinger*, Tetrahedron Letters *1964*, 1369.

[63a] *D. O. Cowan*, *J. Hsu*, and *J. D. Roberts*, J. org. Chemistry *29*, 3688 (1964).

[63b] *E. Weiß*, Chem. Ber. *98*, 2805 (1965).

[63c] *M. B. Smith*, and *W. E. Becker*, Tetrahedron Letters *1965*, 3843.

[64] *J. Miller*, *G. Gregoriou*, and *H. S. Mosher*, J. Amer. chem. Soc. *83*, 3966 (1961); *D. O. Cowan* and *H. S. Mosher*, J. org. Chemistry *27*, 1 (1962).

[65] *N. M. Bikales* and *E. J. Becker*, Chem. and Ind. *1961*, 1831; *S. J. Storfer* and *E. J. Becker*, J. org. Chem. *27*, 1868 (1962); *N. M. Bikales* and *E. J. Becker*, Canad. J. Chem. *41*, 1329 (1963).

[66] *M. Anteunis*, J. org. Chemistry *26*, 4214 (1961); *27*, 596 (1962).

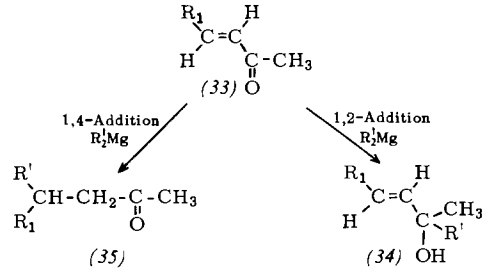
[67] *H. O. House*, *D. D. Traficante*, and *R. A. Evans*, J. org. Chemistry *28*, 348, 355 (1963).

[68a] *S. G. Smith*, Tetrahedron Letters *1963*, 409; *S. G. Smith* and *G. Su*, J. Amer. chem. Soc. *86*, 2750 (1964).

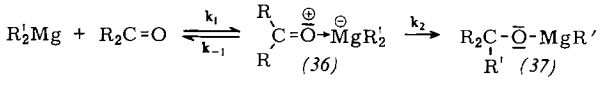
[68b] A similar mechanism was also proposed by *N. M. Bikales* and *E. J. Becker*, Canad. J. Chem. *41*, 1329 (1963), for the addition of methylmagnesium bromide (which was, however, formulated as the dimer) to benzophenone in tetrahydrofuran.

[69] *H. O. House* and *H. W. Thompson*, J. org. Chemistry *28*, 360 (1963).

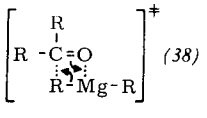
fluence the ratio of 1,2- to 1,4-addition to α,β-unsaturated ketones. On the one hand, the reaction order appears to be the same for both types of addition; on the other, $MgBr_2$ does not accelerate the addition of diethylmagnesium or ethylmagnesium bromide to diethyl ketone, nor does it affect the ratio of 1,2- to 1,4-addition in the reaction with *trans*-pent-3-en-2-one *(33)*, $R_1 = CH_3$, or *trans*-4-phenylbut-3-en-2-one *(33)*, $R_1 = C_6H_5$, to form *(34)* or *(35)*.



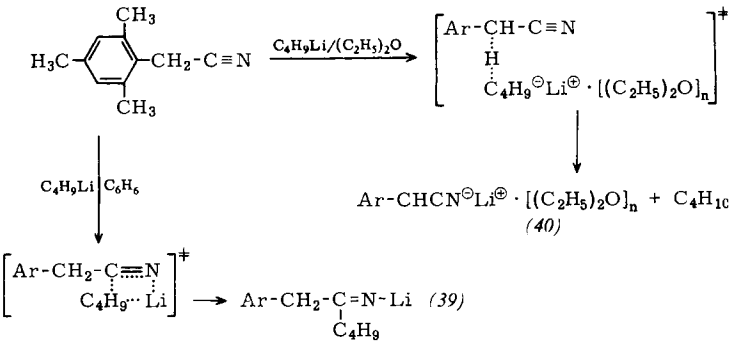

*House's* results [67] are compatible with reversible addition of the magnesium compound to form a complex *(36)*, which then rearranges to give the alkoxide *(37)*. In the system diisopropyl ketone/diethylmagnesium, a transient color that could be due to *(36)* has in fact




been observed; however, spectroscopic measurements have not been possible owing to the high rate of the reaction. *Smith's* results [68] also point to complexes of the type *(36)* as intermediates in which an alkyl residue can easily migrate from the negative magnesium to the carbon; however, since mechanisms (e) and (f) cannot at present be distinguished, direct addition to form *(37)* cannot be completely ruled out. *(38)* has been suggested as a possible transition state in this reaction. The normal

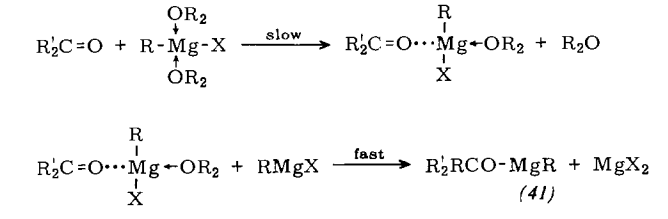



1,2 addition of organomagnesium compounds to C=O (as well as to C≡N and C=N) bonds would then, according to *Dessy* and *Paulik* [70], involve "assisted four-center mechanisms". In many reactions, nucleophilic or electrophilic assistance is provided by coordination in a part of the molecule adjacent to the reaction center. In the reactions discussed here, the coordination of the nucleophilic heteroatom (O,N) to the metal could assist the attack of the alkyl group R on the carbon to form a new C–C bond. Thus the ability of the organometallic compound to donate a carbanion to another reactant is increased, *i.e.* the anionic activation is intensified by formation of an ate-complex [1]. Coordinative assistance may also be provided by the solvent, as can be seen from the difference in the behavior of butyl-lithium in benzene and in ether [reaction to form preferentially *(39)* or *(40)*] [70, 71].



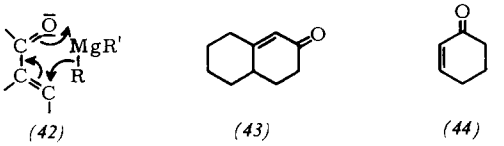

*Ashby* and *Smith* [61] regard the transition state *(38)* as unlikely, and offer the following possible explanations (among others) for the difference in the reactivities of $R_2Mg$ and RMgX and for the appreciable decline in the reaction rate after 50 % conversion in the addition to ketones:

$$2\ RMgX \rightleftharpoons (RMgX)_2$$




The displacement of one molecule of the ether from the complex is regarded as rate-determining, and compound *(41)* would then react more slowly than the Grignard reagent.

It has often been suggested that the 1,4-addition of Grignard compounds to unsaturated ketones involves a six-membered cyclic transition state *(42)*. However, doubt has also been cast on this proposal, since cyclic unsaturated ketones with a *transoid* arrangement of the conjugated system, *e.g.* *(43)* and *(44)*, give comparable quantities of 1,4-adduct [69, 72a]. The addition mechanism is thought to be similar to that of the Michael addition [69].




Ether and dioxane adducts [6] of organomagnesium compounds, as well as an ate-complex *(45)* obtained from diphenylmagnesium and phenyl-lithium, are also known [8]. Although *(45)* dissociates into its components in ether, it appears in some cases to react in the undissociated form. Thus reaction with benzalaceto-

[70] *R. E. Dessy* and *F. Paulik*, J. chem. Educat. *40*, 185 (1963).

[71] *W. J. O'Sullivan, F. W. Swamer, W. J. Humphlett*, and *C. R. Hauser*, J. org. Chemistry *26*, 2306 (1961).

[72a] *F. C. Whitmore* and *G. W. Pedlow*, J. Amer. chem. Soc. *63*, 758 (1941); *E. R. Alexander* and *G. R. Coraor*, *ibid. 73*, 2721 (1951); *R. N. Lewis* and *I. R. Wright*, *ibid. 74*, 1253 (1952).

phenone *(46)* results almost exclusively in 1,4-addition with formation of β,β-diphenylpropiophenone *(47)*, whereas phenyl-lithium adds predominantly in the 1,2-position [8].

$$\underset{(46)}{C_6H_5\text{-}CH{=}CH\text{-}CO\text{-}C_6H_5} + \underset{(45)}{Li[Mg(C_6H_5)_3]} \longrightarrow$$

$$Li^{\oplus}\left[(C_6H_5)_2CH\text{-}CH{=}\underset{\ominus}{C}\text{-}C_6H_5 \;\; \underset{OMg(C_6H_5)_2}{}\right] \xrightarrow{H_3O^{\oplus}}$$

$$\underset{(47)}{(C_6H_5)_2CH\text{-}CH_2\text{-}CO\text{-}C_6H_5}$$

## E. Complexes with Elements of Groups Ib and IIb as the Central Atom

ate-Complexes of all three Group Ib elements are known [72b]. Yellow methylcopper, obtained from methyl-lithium and CuI, is insoluble in ether; when a second mole of methyl-lithium is added, the compound is decolorized and dissolves, owing probably to the formation of lithium dimethylcuprate(I) *(48)* [73]. The diamagnetic complex acetylides *(49)* and *(50)* studied by *Nast* and *Pfab* [74] can be isolated, but they are extremely readily hydrolysed.

| $Li[Cu(CH_3)_2]$ | $K_2[Cu(C{\equiv}C{-}R)_3]$ | $K[Cu(C{\equiv}C{-}R)_2]$ |
|---|---|---|
| *(48)* | *(49)* | *(50)* |

R = H, $CH_3$, $C_6H_5$

No such coordination compounds of bivalent copper can be isolated, since copper(II) ions [75] enter into coupling reactions with both alkynyl and cyanide ions in liquid ammonia. It has been shown that only some of the copper ions are initially reduced to the diphenylethynylcuprate(I) anion *(51)*, accompanied by the formation of diphenylbutadiyne *(52)*.

$$3\,[Cu(NH_3)_4]^{2+} + 6\,IC^{\ominus}{\equiv}C\text{-}C_6H_5 \xrightarrow{NH_3}$$

$$\underset{(51)}{[\overset{II}{Cu}(NH_3)_4]^{2+}[\overset{I}{Cu}(C{\equiv}C\text{-}C_6H_5)_2]^{-}{}_2 \cdot (NH_3)_x} + \underset{(52)}{C_6H_5\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C_6H_5}$$

Compound *(51)*, which gives a green solution, loses ammonia when the solvent is evaporated, and is oxidized further to *(52)*. The unstable violet (x = 12) and green (x = 2) complexes *(53)* can be isolated with ethylenediamine ("en").

$$(51) \longrightarrow 3\;Cu\text{-}C{\equiv}C\text{-}C_6H_5 + (x+4)NH_3 + 1/2\;(52)$$

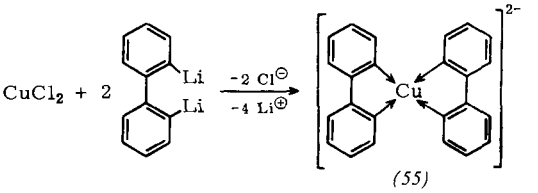
$$[Cu(en)_2]\,[Cu(C{\equiv}C\text{-}C_6H_5)_2]_2 \cdot (NH_3)_x \quad (53)$$

ate-Complexes *(54)* are involved also in the formation of open-chain and cyclic poly-*o*-phenylenes such as *o*-bi-, *o*-tetra-, and *o*-hexaphenylene [76] from 2,2′-dilithiobiphenyl and transition metal chlorides, since the products depend on the nature of the metal, the number of benzene rings in the coupling product often being equal to the coordination number of the metal.

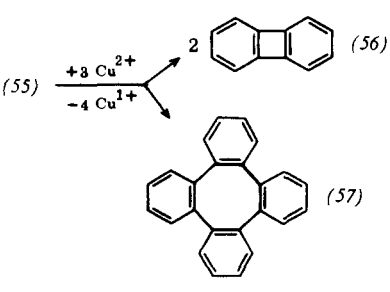
$$M^{2+} + n\,biph^{2-} \rightarrow [M(biph)_n]^{(2n-2)-} \xrightarrow{+(n-1)\,M^{2+}} n\,M + (biph)_n$$

*(54)*

This is confirmed by mechanistic studies carried out by *Wittig* and *Klar* [77] on the action of Cu(II) and Cu(I) salts. The reaction of $CuCl_2$ with 2,2′-dilithiobiphenyl (molar ratio 2:1) to give a 60 % yield of *o*-tetraphenylene *(57)* and 3 % of *o*-biphenylene *(56)* can be explained in terms of a copper(II) ate-complex *(55)*. Under the influence of further copper(II) ions, *(55)* undergoes oxidative coupling to form the cyclopolyenes *(56)* and *(57)*.




*(55)*




The products of the reaction of cuprous chloride with 2,2′-dilithiobiphenyl, which proceeds *via* the complexes *(58)* and *(59)*, include after hydrolysis not only *o*-quaterphenyl (the principal product), but also *o*-tetraphenylene and *o*-octiphenyl, since *(59)* either suffers hydrolysis or undergoes further oxidative coupling.

The organocopper complexes were detected by iodolysis, 55 % of 2,2‴-diiodo-*o*-quaterphenyl being obtained from ether-soluble *(59)*. The ate-complex *(59)* must be very stable, since in the absence of excess copper ions, it gives good yields on reaction with iodine even after two weeks.

[72b] In many cases, the rather unstable organometallic derivatives of the elements of this group are stabilized by addition of donors (phosphines, amines, *etc.*).

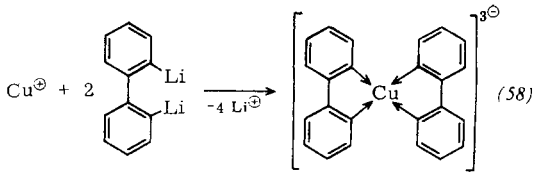
[73] *H. Gilman, R. G. Jones,* and *L. A. Woods,* J. org. Chemistry *17*, 1630 (1952).

[74] *R. Nast* and *W. Pfab,* Chem. Ber. *89*, 415 (1956).

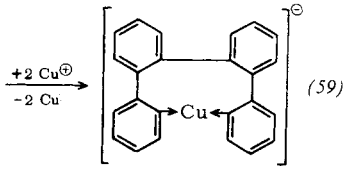
[75] On the mechanism of the oxidation of R–C≡C–H with Cu(II) ions, see *F. Bohlmann, H. Schönowsky, E. Inhoffen,* and *G. Grau,* Chem. Ber. *97*, 794 (1964).

[76] *G. Wittig* and *G. Lehmann,* Chem. Ber. *90*, 875 (1957).

[77] *G. Wittig* and *G. Klar,* unpublished work; *G. Klar,* Dissertation, Universität Heidelberg, 1963. Similar complexes have also been observed with $MnCl_2$ and $FeCl_3$.



(58)



(59)

Other complexes that have recently been synthesized are lithium diphenylaurate(I) *(60)* [78], potassium dialkynylargentate(I) *(61)* [79] and potassium dialkynylaurate(I) *(62)* [79]. A complex of trivalent gold containing an organic ligand, *i.e.* sodium trichlorophenylaurate(III), was described as early as 1931 [80].

| $Li[Au(C_6H_5)_2]$ | $K[Ag(C{\equiv}C{-}R)_2]$ | $K[Au(C{\equiv}C{-}R)_2]$ |
|---|---|---|
| *(60)* | *(61)* | *(62)* |
| $R = H, CH_3, C_6H_5$ | | $R = C_6H_5$ |

Compounds *(61)* and *(62)*, which are strong electrolytes in liquid $NH_3$, are colorless, readily hydrolysable complexes, the ligands of which can be readily replaced by cyanide ion.

The stability of anionic complexes of organomercury, organocadmium, and organozinc complexes increases markedly in that order. Not only were diethylzinc and ethylzinc iodide among the first organometallic compounds described [81], but the first ate-complex, sodium triethylzincate *(63)*, was prepared by *Wanklyn* in about 1858 from diethylzinc and sodium [82].

$$3\,(C_2H_5)_2Zn + 2\,Na \rightarrow Zn + 2\,Na[Zn(C_2H_5)_3]$$

*(63)*

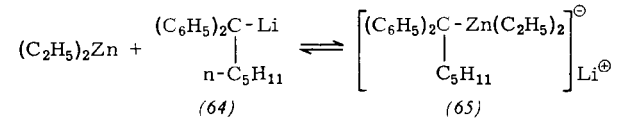
Compounds of the types $M[ZnR_3]$ and $M_2[ZnR_4]$ can be prepared either by the action of a strongly electropositive metal on the organozinc compound or from the components RM and $R_2Zn$ [8, 49, 83]. Conductivity measurements [7, 17, 84] provided important information about the behavior of alkali metal alkyls dissolved in other metal alkyls. Whereas ethylsodium is infusible and ethyl-lithium is non-conducting, whether alone or in benzene, all the alkali metal alkyls studied conduct electricity when dissolved in diethylzinc, the molar conductivities decreasing in the following order:

$$KC_2H_5 > NaC_2H_5 \gg LiCH_3 > LiC_2H_5 > LiC_6H_5$$

Though electrolysis ultimately leads to the decomposition of diethylzinc, it can be shown that an equilibrium must exist in accordance with (g), but not in accordance with (h).

$$Zn[Na(C_2H_5)_3] \overset{(h)}{\rightleftharpoons} NaC_2H_5 + (C_2H_5)_2Zn \overset{(g)}{\rightleftharpoons} Na[Zn(C_2H_5)_3]$$

The molar conductivity is of the order expected for a salt largely associated to ion pairs in a solvent of low dielectric constant [85]. From spectroscopic studies on the ate-complex *(65)* obtained from 1,1-diphenyl-n-hexyl-lithium *(64)* and diethylzinc, *Waack* and *Doran* [86] obtained information about the dissociation constant, the bond energy, and the change in charge on complex formation.



*(64)* *(65)*

Addition of diethylzinc to the deeply colored solution of *(64)* in tetrahydrofuran ($\lambda_{max}$ = 496 mμ) leads to a decrease in extinction and to the appearance of a new maximum ($\lambda_{max}$ = 375 mμ) due to *(65)*. The reversibility of complex formation was demonstrated by removal of the diethylzinc from the equilibrium with butyl-lithium; the equilibrium constant was found to be 103 l/mole in THF/hexane at room temperature, and the energy of the new carbon-zinc bond is estimated to be about 19 kcal/mole.

NMR studies show that the complex formation *(64)* → *(65)* leads to a displacement of the aromatic proton signals to lower fields, while the signals due to the methylene protons of the ethyl groups attached to the zinc are displaced to higher fields. With the aid of an empirical relationship [87] between the change in electron density and the resulting change in chemical shift, it can be estimated that on adduct formation, the electron density on the benzene rings in *(64)* decreases by about 0.36, while a corresponding increase takes place in the diethylzinc moiety in *(65)*. This excess negative charge probably is localized mainly on the zinc.

The phenyl complexes of zinc and cadmium [8] also dissociate in solution, the rate of metalation of fluorene increasing in the order:

$$[(C_6H_5)_3Zn]Li < [(C_6H_5)_7Zn_2]Li_3 < [(C_6H_5)_3Cd]Li$$

*(66)* *(67)* *(68)*

The less acidic fluorobenzene is not metalated by *(66)*, even at 100 °C [56]. The most stable of these adducts,

[78] *A. Weiß*, personal communication.

[79] *R. Nast* and *H. Schindel*, Z. anorg. allg. Chem. *326*, 201 (1963); *R. Nast* and *U. Kirner*, *ibid. 330*, 311 (1964).

[80] *M. S. Kharasch* and *H. S. Isbell*, J. Amer. chem. Soc. *53*, 3053 (1931).

[81] *E. Frankland*, J. chem. Soc. (London) *2*, 263 (1848/49).

[82] *J. A. Wanklyn*, Liebigs Ann. Chem. *107*, 125 (1858); *108*, 67 (1858); *111*, 234 (1859); *140*, 211 (1866).

[83] *A. v. Grosse*, Chem. Ber. *59*, 2646 (1926); *H. Gilman* and *L. A. Woods*, J. Amer. chem. Soc. *67*, 520 (1945); *J. de Postin*, C. R. hebd. Séances Acad. Sci. *223*, 1006 (1946); *D. T. Hurd*, J. org. Chemistry *13*, 711 (1948); *R. Nast* and *R. Müller*, Chem. Ber. *91*, 2861 (1958); *K. Issleib* and *H. O. Fröhlich*, Chem. Ber. *95*, 375 (1962).

[84] *Fr. Hein*, Z. Elektrochem. angew. physik. Chem. *28*, 469 (1922); *Fr. Hein* and *Fr. A. Segitz*, Z. anorg. allg. Chem. *158*, 153 (1926).

[85] See [6], p. 24. For the conductivity of ethyl-lithium in diethylzinc as a function of the concentration, see [7] and *G. Jander* and *L. Fischer*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *62*, 971 (1958).

[86] *R. Waack* and *M. A. Doran*, J. Amer. chem. Soc. *85*, 1651, 2861, 4042 (1963).

[87] *T. Schaefer* and *W. G. Schneider*, Canad. J. Chem. *41*, 966 (1963).

*(66)*, is monomeric in ether, while *(67)* undergoes partial dissociation to phenyl-lithium and *(66)* under these conditions. Molecular-weight determinations on diphenylmercury alone and in the presence of phenyl-lithium confirm previous chemical experience that organomercury compounds have no appreciable tendency to form complexes. However, complex anions have been obtained with trifluoromethyl ligands on mercury as the central atom [88].

## F. Complexes of Organoboron and Organoaluminum Compounds

### 1. Alkylborates

The stability of the ate-complexes reaches a maximum with Group III elements such as boron and aluminum, since here the addition of electron donors to $ZR_3$ always completes the octet in the outermost shell of the central atom Z. Moreover, in the series $Li[Li(C_6H_5)_2]$, $Li[Be(C_6H_5)_3]$, and $Li[B(C_6H_5)_4]$, the strength with which the phenyl groups are bound increases with the valence and charge of the central atom, *i.e.* in the order $Li < Be < B$.

The chemistry of organoboron and organoaluminum compounds, particularly of the hydrides and alkyl derivatives, has been described in numerous reviews and monographs, which naturally also devote due space to the coordination chemistry of boron [6,53,89–92] and of aluminum [6,93–96].

Trialkyl- and triarylboranes have a strong tendency to complete their octet by coordination. More than 100 years ago *Frankland* [97] found that trimethylborane reacts with ammonia and potassium hydroxide solutions, and in this way he probably prepared (but did not isolate) the first organic borate complex:

$$(CH_3)_3B + KOH \rightarrow K[(CH_3)_3BOH] \quad (69)$$

The alkylborates are readily obtainable, generally either from trialkylboranes, alkyl halides, and sodium [Eq. (i)] [98] or from trialkylboranes and organometallic compounds of alkali metals [Eq. (j)] [29,89,99]. ate-Complexes are also obtained by the action of complex borohydrides on olefins and acetylenes [98b,100].

$$(CH_3)_3B + CH_3Cl + 2\,Na \xrightarrow{-NaCl} Na[B(CH_3)_4] \quad (i)$$

$$R{-}M + B(CH_3)_3 \longrightarrow M[B(CH_3)_3R] \quad (j)$$

$$Na[R_3BH] + CH_2{=}CH{-}R' \longrightarrow Na[R_3B{-}CH_2{-}CH_2{-}R'] \quad (k)$$

$$Na[R_3BH] + HC{\equiv}CR' \longrightarrow Na[R_3B{-}C{\equiv}C{-}R'] + H_2 \quad (l)$$

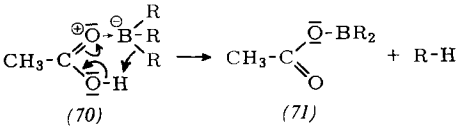
Some of these complexes have unusual properties, such as solubility in benzene [*e.g.* $LiB(CH_3)_3C_2H_5$] and low melting points [*e.g.* $NaB(C_2H_5)_3H$] [99] so that, as in certain aluminum complexes [94,96], structures containing electron-deficient bonds may have to be considered as well as salt-like structures. The alkali metal tetraalkylborates, which are extremely unstable in air, were characterized by conversion into the more stable tetramethylammonium and tetrabutylphosphonium derivatives, which are sparingly soluble in water [29].

The transfer of negative charge from the boron to the ethyl groups in the ate-complex $Li[B(C_2H_5)_4]$ is reflected in the NMR spectrum, where the signals due to the α-methylene groups are located upfield by 0.5 p.p.m. from that of tetramethylsilane [29,100a]. In oxonium salts, on the other hand, the signals due to the α-methyl or α-methylene protons occur at considerably lower τ values in comparison with the analogous neutral compounds [100b].

The borates $M[BR_4]$ are stable in pure water, but are rapidly hydrolysed on addition of acetic acid; however, only 25 % of the expected quantity of hydrocarbon is liberated rapidly, the remainder being released more slowly. The hydrolysis appears to involve fast protonation of $M[BR_4]$ with loss of one mole of alkane [Eq. (m)], followed by slow hydrolysis of the trialkylborane [Eq. (n)] (cf. also [53,101,102]). In reaction (n), the carbonyl oxygen of the acid probably becomes coordinated to the boron to form *(70)*, and the proton then makes an intramolecular attack on an anionically activated alkyl group. Since *(71)* has a

$$M[BR_4] + CH_3COOH \xrightarrow{fast} MOAc + R_3B + RH \quad (m)$$

$$R_3B + 3\,CH_3COOH \xrightarrow{slow} 3\,RH + B(OAc)_3 \quad (n)$$



*(70)* *(71)*

[88] *H. J. Emeléus* and *J. J. Lagowski*, J. chem. Soc. (London) *1959*, 1497.

[89] *M. F. Lappert*, Chem. Reviews *56*, 959 (1956).

[90] *H. C. Brown* in *H. Zeiss*: Organometallic Chemistry. Reinhold, New York 1960, p. 150.

[91] *E. Schenker*, Angew. Chem. *73*, 81 (1961).

[92] *R. Köster*, Angew. Chem. *75*, 1079 (1963), Angew. Chem. internat. Edit. *3*, 174 (1964).

[93] *K. Ziegler et al.*, Liebigs Ann. Chem. *629*, (1960).

[94] *K. Ziegler* in *H. Zeiss*: Organometallic Chemistry. Reinhold, New York 1960, p. 194.

[95] *K. Ziegler*, Angew. Chem. *71*, 623 (1959); *72*, 829 (1960); *76*, 545 (1964).

[96] *H. Lehmkuhl*, Angew. Chem. *75*, 1090 (1963), Angew. Chem. internat. Edit. *3*, 107 (1964).

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[98a] *K. Ziegler* and *H. Hoberg*, Angew. Chem. *73*, 577 (1961).

[98b] *J. B. Honeycutt, Jr.* and *J. M. Riddle*, J. Amer. chem. Soc. *83*, 369 (1961).

[99] *J. R. Johnson, H. R. Snyder*, and *M. G. van Campen, Jr.*, J. Amer. chem. Soc. *60*, 115 (1938); *H. J. Schlesinger* and *H. C. Brown, ibid. 62*, 3429 (1940); *H. C. Brown, H. J. Schlesinger, J. Sheft*, and *D. M. Ritter, ibid. 75*, 192 (1953); *D. T. Hurd*, J. org. Chemistry *13*, 711 (1948).

[100] *P. Binger* and *R. Köster*, Tetrahedron Letters No. 4, *1961*, 156; *1965*, 1901.

[100a] Cf. also *A. G. Massey, E. W. Randall*, and *D. Shaw*, Spectrochim. Acta *20*, 379 (1964); *21*, 263 (1965).

[100b] *F. Klages, J. E. Gordon*, and *H. A. Jung*, Chem. Ber. *98* 3748 (1965).

[101] *D. Ulmschneider* and *J. Goubeau*, Chem. Ber. *90*, 2733 (1957).

[102] *H. Meerwein* and *H. Sönke*, J. prakt. Chem. [2] *147*, 251 (1937); *J. Goubeau, R. Epple, D. Ulmschneider*, and *H. Lehmann*, Angew. Chem. *67*, 710 (1955); *H. C. Brown* and *K. Murray*, J. Amer. chem. Soc. *81*, 4108 (1959); *L. Toporcer, R. E. Dessy*, and *S. J. E. Green, ibid. 87*, 1236 (1965).

smaller tendency than *(70)* to coordinate with another molecule of acid, further hydrolysis proceeds more slowly.

The trialkylboranes[53,103] and the complexes $M[BR_4]$[29] are rapidly oxidized by oxygen. The oxidation of trialkylboranes with aqueous alkaline hydrogen peroxide, which also involves a borate complex *(72)* as an intermediate[53], is important for the conversion of olefins into alcohols by hydroboration. This mechanism, involving the anionic migration of an alkyl group R from boron to oxygen, is in agreement with the retention of configuration that is always observed.

$$R_3B + {}^{\ominus}|O-O-H \longrightarrow [R_3B-O-O-H]^{\ominus} \xrightarrow{-OH^{\ominus}} R_2BOR \text{ etc.}$$

*(72)*

However, an oxidation mechanism of this type is unlikely with the borates $M[BR_4]$, since here the central atom is fully coordinated. Moreover, the oxidation of lithium tetrabutylborate, which leads mainly to n-butanol, does not proceed by dissociation into butyl-lithium and tributylborane. It has been suggested, therefore, that oxygen is inserted directly into the boron-carbon bond, or that a hydroperoxide is formed on the α-carbon atom of the butyl group[29].

The anionic activation of the ligands in ate-complexes may lead not only to a reversible dissociation into the donor and acceptor pair, but also, owing to the transfer of charge from the boron to the adjacent carbon atom in $M[BR_4]$, this carbon atom should tend to lose hydrogen as hydride.

The reverse process, *i.e.* the removal of a proton from the α-carbon atom of onium-complexes, led *Wittig*[43,104] to the "ylides". Thus the inductive attraction of electrons by the central atom in ammonium and phosphonium salts facilitates the formation of anions in the presence of strong proton acceptors, leading *e.g.* from *(12)* and *(73)* to trimethylammonium methylide[44] and methylenetriphenylphosphorane *(74)*, respectively, the parent compounds of the ammonium and phosphonium ylides.

$$\left[(C_6H_5)_3P-\underset{\underset{H}{|}}{\overset{\overset{H}{|}}{C}}-H\right]^{\oplus} Br^{\ominus} \xrightarrow[-LiBr,\ -C_6H_6]{+C_6H_5Li}$$

*(73)*

$$(C_6H_5)_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2 \longleftrightarrow (C_6H_5)_3P=CH_2$$

*(74)*

The Hofmann degradation of quaternary ammonium salts with organolithium compounds also proceeds by initial formation of an ylide *(75)*, followed by β-elimination, *i.e.* it may be regarded as an α′,β-elimination[43,105,106].

$$(CH_3)_2\overset{\oplus}{N}(\overset{\alpha'}{CH_2}\overset{\ominus}{})(H)(H\text{-}\overset{\alpha}{C}\overset{\beta}{C}H_2\text{-}CH_3) \longrightarrow (CH_3)_3N + CH_3\text{-}CH{=}CH_2$$

*(75)*

The deprotonation of the *N,N*-dimethylpyrrolidinium system *(76)* may result in a Grob fragmentation[107] of the ring system[108].

$$\underset{H_3C}{\overset{X^{\ominus}}{\overset{H}{\underset{H}{\overset{\oplus}{N}}}}}\underset{CH_3}{} \xrightarrow[-C_6H_6,\text{-LiBr}]{+C_6H_5Li} \left[\underset{H_3C}{\overset{H}{\underset{H}{\overset{\oplus}{N}}}}\underset{CH_3}{}\right]^{\ominus} \longrightarrow \underset{CH_2}{\overset{CH_2}{\|}} + \underset{CH}{\overset{CH_2}{\|}}\underset{N(CH_3)_2}{}$$

*(76)*

*Jäger* and *Hesse*[109], on the other hand, treated lithium tetrabutylborate *(77)* with hydride acceptors such as benzyl chloride, benzhydryl chloride, and triethyloxonium fluoroborate.

$$Li^{\oplus}\left[(C_4H_9)_3B-\underset{\underset{\delta^-H}{|}}{\overset{\overset{H}{|}}{C}}-C_3H_7\right]^{\ominus} + C_6H_5CH_2Cl \xrightarrow{-LiCl}$$

*(77)*

$$C_6H_5-CH_3 + (C_4H_9)_3\overset{\ominus}{B}-\overset{\oplus}{C}H-C_3H_7$$

*(78)*

The "inverse" ylide *(78)*, in which the positive charge is situated on the carbon and the negative charge on the boron, could not be isolated, but the final products are consistent with its occurrence as an intermediate[109a]. The boron ylide *(78)* undergoes intramolecular anionotropic rearrangement, with migration of a butyl group, to form di-n-butyl-(1-propylpentyl)borane *(79)*, which is capable of undergoing eliminations (to form dibutylborohydride and 3- and 4-octenes) and additions[110].

$$\underset{C_4H_9}{\overset{(C_4H_9)_2B^{\ominus}\text{-}\overset{\oplus}{C}H\text{-}C_3H_7}{\longrightarrow}} \longrightarrow (C_4H_9)_2B-\underset{C_4H_9}{\overset{C_3H_7}{\underset{H}{C}}}$$

*(78)* *(79)*

Thus the final product obtained from *(79)* is a mixture of 3-octene and 4-octene, together with octanols formed by oxidation during the hydrolysis. The stabilization of *(78)* by conversion into *(79)* may be regarded as the counterpart of the Stevens rearrangement of nitrogen ylides.

*Köbrich* and *Merkle*[110a] recently rearranged the borate salt *(79a)*, *via* the supposed boron ylide intermediate

[103] *S. B. Mirviss*, J. Amer. chem. Soc. *83*, 3051 (1961); *L. Parts* and *J. T. Miller Jr.*, Inorg. Chem. *3*, 1483 (1964).

[104] Reviews: *G. Wittig*, Experientia *12*, 41 (1956); Angew. Chem. *68*, 505 (1956); *U. Schöllkopf*, *ibid.* *71*, 260 (1959); *A. Maercker*: Organic Reactions. Vol. *14*, p. 270. Wiley, New York, 1965.

[105] *F. Weygand*, *H. Daniel*, and *H. Simon*, Chem. Ber. *91*, 1691 (1958).

[106] Review: *A. C. Cope* and *E. R. Trumbull*, Org. Reactions. Wiley, New York 1960, Vol. 11, p. 317.

[107] *C. A. Grob*, Experientia *13*, 126 (1957).

[108a] *F. Weygand* and *H. Daniel*, Chem. Ber. *94*, 1688 (1961).

[108b] *G. Wittig* and *W. Tochtermann*, Chem. Ber. *94*, 1692 (1961).

[108c] *H. Daniel*, Liebigs Ann. Chem. *673*, 92 (1964).

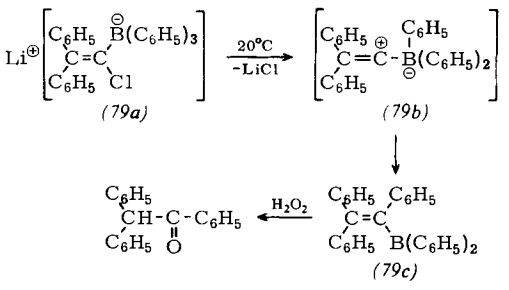
[109] *H. Jäger* and *G. Hesse*, Chem. Ber. *95*, 345 (1962).

[109a] Aluminum ylides are discussed by *H. Hoberg*, Angew. Chem. *77*, 1084 (1965); Angew. Chem. internat. Edit. *4*, 1088 (1965).

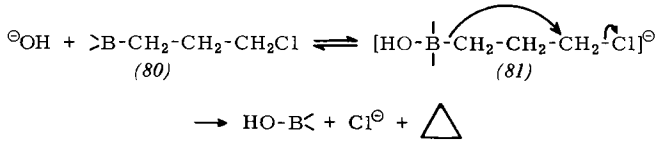
[110] *H. C. Brown* and *B. C. Subba Rao*, J. Amer. chem. Soc. *81*, 6434 (1959).

[110a] *G. Köbrich* and *H. R. Merkle*, personal communication.

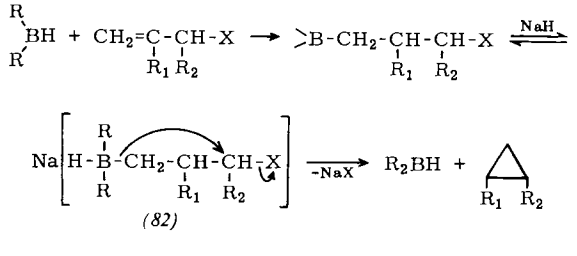
*(79b)*, to the isomer *(79c)*, as indicated by subsequent oxidation to benzhydryl phenyl ketone:



Another example of the reactions of alkylborate complexes is the elegant synthesis of cyclopropane derivatives by *Hawthorne*'s method [111]. In this synthesis, 3-halopropylboranes *(80)* (obtainable by hydroboration of allyl halides) are converted into cyclopropane derivatives by treatment with aqueous alkali metal hydroxide; the product obtained from allyl chloride is cyclopropane itself. The presence of a base is essential to ensure fast reaction, since the increased anionic activation of the alkyl group in the complex *(81)* facilitates the displacement of the chloride ion from the γ-carbon atom. *Binger* and *Köster* [100] improved this synthesis of three-membered rings by the use of sodium hydride. Since the dialkylborane used for hydroboration in the



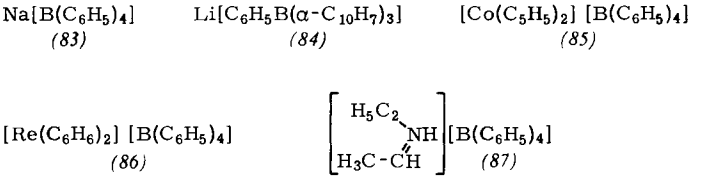
first step is regenerated on cleavage of the ate-complex *(82)*, the overall reaction corresponds to the formation of a three-membered ring system from sodium hydride and an allyl compound.



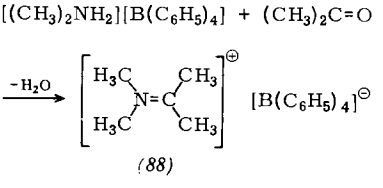
## 2. Arylborates

The most important of the arylborate complexes is sodium (or lithium) tetraphenylborate (Kalignost) *(83)* [112], since this reagent precipitates potassium, rubidium, cesium, silver, thallium, ammonium, and phosphonium cations from aqueous solution, in which the borate complex is completely stable [113].

The complex salt *(84)*, which is readily obtainable from tri-α-naphthylborane and phenyl-lithium, also precipitates many cations ($NR_4$, K, Cs, Rb, Ag, Pb, Hg, Fe), the borates of which being even less soluble than the tetraphenylborates [114]. Thus organic amines in concentrations of 1 mg/10 ml of water can be quantitatively determined with *(84)*, but not with Kalignost. The latter can also be used for the isolation of cationic metal-aromatic π-complexes, as has been shown in the cases of the bis(cyclopentadienyl)cobalt(III) *(85)* [115] and dibenzenerhenium(I) *(86)* [116] complexes. Moreover, the immonium cations [117], which are very unstable even as the tetrafluoroborates and hexachloroantimonates, can be protected against hydrolysis by fast precipitation from aqueous solution with Kalignost [see *(87)*].



Stable immonium tetraphenylborates of this type, *e.g.* *(88)*, can also be obtained directly from alkylammonium tetraphenylborates and ketones or aldehydes [108b, 117].



Reactive cations in general can exist only in the presence of complex anions with very low polarizabilities and low nucleophilic strengths (cf. also triethyloxonium fluoroborate). For example, the first stable tetraphenylbismuthonium salt was isolated as the tetraphenylborate [118].

An interesting group of arylborates comprises the spiro compounds such as *(89)*, which are extremely stable and can be prepared either from 2,2'-dilithiobiphenyl [119] or by decomposition of the complex *(90)* [120]. Asymmetric

[111] *M. F. Hawthorne* and *J. A. Dupont*, J. Amer. chem. Soc. *80*, 5830 (1958); *M. F. Hawthorne, ibid. 82*, 1886 (1960).

[112] *G. Wittig, G. Keicher, A. Rückert*, and *P. Raff*, Liebigs Ann. Chem. *563*, 110 (1949); *G. Wittig* and *A. Rückert, ibid. 566*, 101 (1950); *G. Wittig* and *P. Raff, ibid. 573*, 195 (1951).

[113] *P. Raff* and *W. Brotz*, Z. analyt. Chem. *133*, 241 (1951); *H. Flaschka, ibid. 136*, 99 (1952); *H. W. Spier*, Biochem. Z. *322*, 467 (1952); *A. Heyrovsky*, Chem. Listy *54*, 360 (1960); Chem. Abstr. *54*, 12900b (1960); Analytica chim. Acta *22*, 405 (1960); Chem. Abstr. *54*, 13973c (1960); Z. analyt. Chem. *173*, 301 (1960).

[114] *J. Rabiant, J. Renault*, and *J. A. Gautier*, C. R. hebd. Séances Acad. Sci. *254*, 1819 (1962).

[115] *E. O. Fischer* and *R. Jira*, Z. Naturforsch. *8b*, 327 (1953).

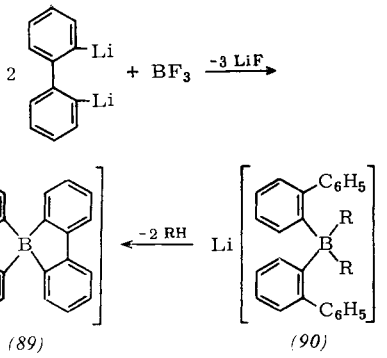
[116] *E. O. Fischer* and *A. Wirzmüller*, Chem. Ber. *90*, 1725 (1957).

[117] *N. Wiberg* and *K. H. Schmid*, Angew. Chem. *76*, 381 (1964), Angew. Chem. internat. Edit. *3*, 444 (1964).

[118] *G. Wittig* and *K. Clauß*, Liebigs Ann. Chem. *578*, 136 (1952).

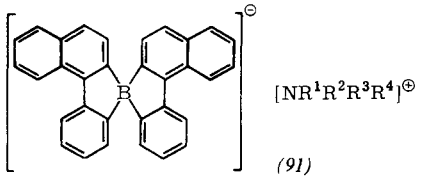
[119] *G. Wittig* and *W. Herwig*, Chem. Ber. *88*, 962 (1955).

[120] *R. Köster* and *G. Benedikt*, Angew. Chem. *75*, 419 (1963), Angew. Chem. internat. Edit. *2*, 323 (1963).



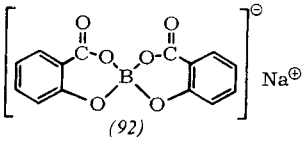
(89) (90)

substitution of such borospiranes leads to optical antipodes, as *Torssell*[121] showed by resolution of *(91)* with an optically active ammonium salt.



(91)

The coordination compound *(92)* containing four boron-oxygen bonds was resolved by *Boeseken* 40 years ago (cf.[121]).



(92)

The stability of *(83)* towards hydrolysis can be further increased by replacement of a phenyl group with a cyanide group as in sodium triphenylcyanoborate *(93)*[112], which is decomposed by aqueous acid only at

$$Na^{\oplus}[(C_6H_5)_3B^{\ominus}\text{-}C{\equiv}N|] \longleftrightarrow [(C_6H_5)_3B^{\ominus}\text{-}C^{\oplus}{=}\underline{\underline{N}}^{\ominus}]^{\ominus}Na^{\oplus}$$

(93)

100 °C. The withdrawal of electrons from the boron atom to the positively charged carbon atom leads to extra reinforcement of the boron-phenyl bonds, and the attack of a proton on this bond during acid hydrolysis becomes more difficult.

In lithium cyanotrihydridoborate *(94)*, the cyano group again decreases the activity of the hydrogen as hydride[112, 122], so that *(94)* does not react with excess of hydrocyanic acid, even at 100 °C. Whereas lithium tetrahydridoborate is slowly decomposed even by water, and decomposes rapidly in the presence of acids, *(94)* liberates hydrogen only when warmed in concentrated mineral acid solutions (quantitatively at 100 °C). Recently prepared

$$Li[BH_4] + HCN \xrightarrow[100°C]{(C_2H_5)_2O} Li[H_3B\text{-}C{\equiv}N] \quad (94)$$

$Li[(C_6H_5)_3BR]$

*(95)*, R = $CH{=}CH_2$

*(96)*, R = $CH_2\text{-}CH{=}CH_2$

$Li[B(CH{=}CH_2)_4]$ *(97)*

[121] *K. Torssell*, Acta chem. scand. *16*, 87 (1962).

[122] *G. Wittig* and *P. Raff*, Z. Naturforsch. *6b*, 225 (1951).

complexes include the vinyl and allyl compounds *(95)* to *(97)*[123].

According to *Meerwein*[124], esters of boric acid react with alcohols to form complex alkyloxo acids *(98)*, which are much more strongly acidic than the alcohols and can be titrated with bases. Complexes of this type, in which an alcohol has been converted into a relatively strong acid by complex formation, are formed with Lewis acids of many elements[2, 55].

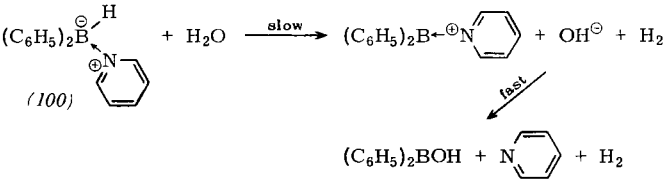
$$(RO)_3B + HOR' \rightarrow H[(RO)_3BOR'] \quad (98)$$

An interesting problem was that of the possibility of achieving a formal dissociation of the benzene molecule into a proton and a complex anion by a suitable sequence of reactions, *i.e.* whether lithium tetraphenylborate could be converted into the corresponding acid *(99)*.

$$\underset{(83)}{Li[B(C_6H_5)_4]} \xrightarrow[-LiCl]{HCl/H_2O} \underset{(99)}{[H_3O]^{\oplus}} + [B(C_6H_5)_4]^{\ominus}$$

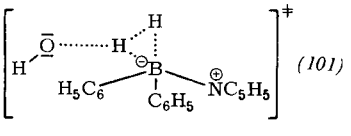
When a cold aqueous solution of *(83)* is acidified, all of the added acid can be back-titrated with bases; when the addition is carried out in the warm, however, it leads to rapid formation of triphenylborane and benzene[112]. It appears from kinetic studies[125] that a benzene ring in the tetraphenylborate anion suffers electrophilic attack by a proton with formation of a zwitterionic complex, which then decomposes into benzene and triphenylborane. Thus acid hydrolysis of tetraphenylborate proceeds by the same mechanism as the cleavage of phenylboronic acid into benzene and boric acid, which is known as a "protodeboronation"[126].

Hydrolysis of the pyridine-diphenylborane adduct in acetonitrile leads to diphenylborinic acid, hydrogen,



(100)

and pyridine[127]. On the basis of the kinetic isotope effects observed in the hydrolysis of the deuterated complex ($k_H/k_D$ = 1.52) and in the deuterolysis ($k_H/k_D$ = 6.9) a transition state *(101)*, corresponding to electrophilic substitution on the carbon, was proposed[128].



(101)

[123] *D. Seyferth* and *M. A. Weiner*, J. Amer. chem. Soc. *83*, 3583 (1961); J. org. Chemistry *26*, 4797 (1961).

[124] *H. Meerwein* and *Th. Bersin*, Liebigs Ann. Chem. *455*, 227 (1927); *476*, 113 (1929).

[125] *J. N. Cooper* and *R. E. Powell*, J. Amer. chem. Soc. *85*, 1590 (1963).

[126] *H. G. Kuivila* and *K. V. Nahabedian*, J. Amer. chem. Soc. *83*, 2159, 2164, 2167 (1961).

[127] *M. F. Hawthorne* and *E. S. Lewis*, J. Amer. chem. Soc. *80*, 4291, 4293, 4296 (1958).

[128] *S. Winstein* and *T. G. Traylor*, J. Amer. chem. Soc. *78*, 2597 (1956); *A. N. Nesmejanov* and *A. E. Borisov*, Tetrahedron *1*, 158 (1957). — Review: *G. Köbrich*, Angew. Chem. *74*, 453 (1962), Angew. Chem. internat. Edit. *1*, 382 (1962).

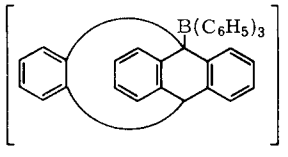
### 3. Complexes with Tritylsodium

The ate-complexes obtained from tritylsodium with Lewis acids such as triphenylborane, triphenylaluminum, and diphenylberyllium occupy a special position since, owing to steric factors, some of these complexes dissociate strongly in accordance with Eq. (o), as is shown by the bright red color of their solutions [129, 133, 135].

$$Na[(C_6H_5)_3C\text{-}Z(C_6H_5)_n] \rightleftharpoons (C_6H_5)_3CNa + (C_6H_5)_nZ \qquad (o)$$

Z = B, Al, Be

Since the tritylsodium-triphenylborane adduct is colored even in the crystalline state, it was presumed that the electron pair of the trityl anion is not covalently bonded to boron, but is delocalized over the phenyl groups, as in tritylsodium itself [129].



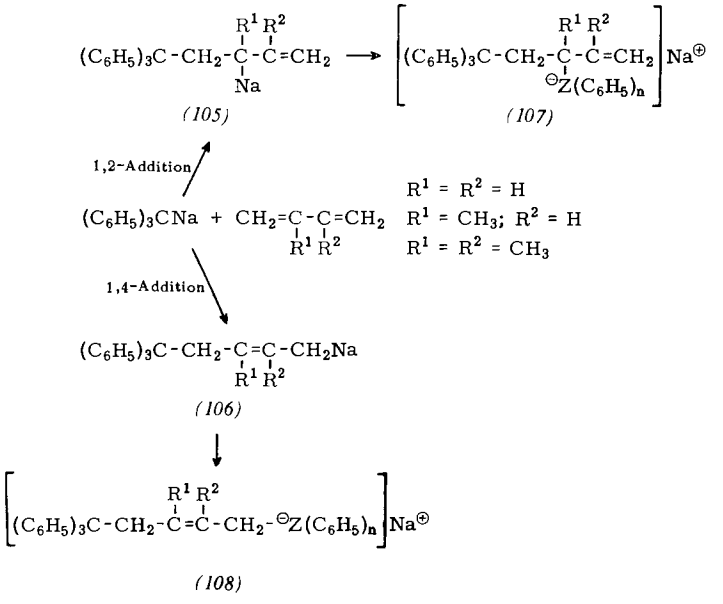

*(102)*

On the other hand, the colorless ate-complex *(102)* obtained from triptycyl-1-lithium and triphenylborane is not detectably dissociated, and is stable even in water [130]. In the colorless triptycyl-1-lithium, mesomeric delocalization of the carbanion electron pair is impossible, in contrast to tritylsodium; moreover, the steric conditions in *(102)* are more favorable for adduct formation. Complexes *(103)* and *(104)* are also relatively stable [131]. The triphenylsilyl group in *(104)* cannot be replaced by a phenyl group by use of phenyllithium.

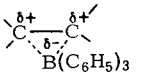
$[(C_6H_5)_3Ge\text{–}B(C_6H_5)_3]Li$ *(103)*

$[(C_6H_5)_3Si\text{–}B(C_6H_5)_3]Li$ *(104)*

Lewis base/Lewis acid pairs such as tritylsodium/triphenylborane, which do not react irreversibly with each other, permit the reaction of, for example, tritylsodium with a suitable substrate to form a new organosodium compound, which can be trapped immediately with triphenylborane. The polymerization of butadiene derivatives with tritylsodium as initiator [132] has been studied in this way; the organometallic compounds formed, *(105)* and *(106)*, do not polymerize by further addition to the diene, but can be trapped as the ate-complexes *(107)* and *(108)* in the presence of Lewis acids $(C_6H_5)_nZ$ (triphenylborane, triphenylaluminum, diphenylberyllium, diphenylmagnesium) [133]. Since the adducts *(107)* and *(108)* and the hydrocarbons formed on hydrolysis can be studied spectroscopically, the proportions of 1,2- and 1,4-addition can be estimated. It is found that as the stability of the ate-complexes *(107)* and *(108)* decreases (B > Al > Be > Mg), the course of the polymerization approaches that followed in the absence of complexing agents.

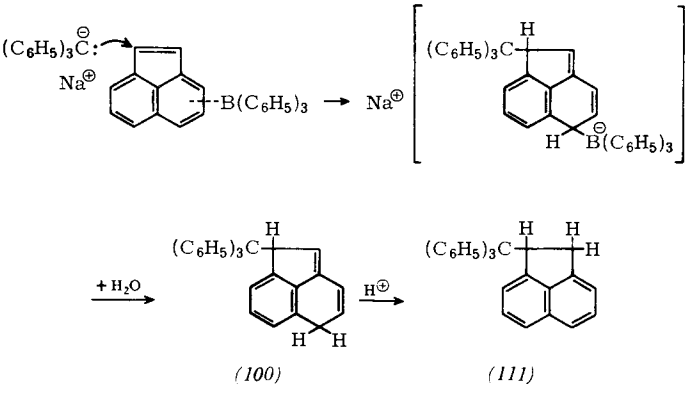



The interesting discovery that the relatively inert 2,3-dimethylbutadiene is not attacked by tritylsodium alone, but forms an adduct *(107)* when triphenylborane is present, and that the dehydrochlorination of vinyl chloride with tritylsodium is accelerated by triphenylborane, indicates that the boron compound promotes reactions at the double bond, possibly by formation of a π-complex *(109)*




*(109)*

The polymerization of acenaphthylene controlled with tritylsodium in the presence of triphenylborane [129] leads, by a supposed 1,6-addition of the Lewis base/Lewis acid pair followed by hydrolysis, to the unsaturated hydrocarbon *(110)*. This rearranges in the presence of acids to 1-tritylacenaphthene *(111)*.




The fact that triphenylborane does not form adducts with bulky organometallic compounds of alkali metals, *e.g.*

[129] *G. Wittig, H. G. Reppe*, and *Th. Eicher*, Liebigs Ann. Chem. *643*, 47 (1961).

[130] *G. Wittig* and *W. Tochtermann*, Liebigs Ann. Chem. *660*, 23 (1962).

[131] *D. Seyferth, G. Raab*, and *S. O. Grim*, J. org. Chemistry *26*, 3034 (1961).

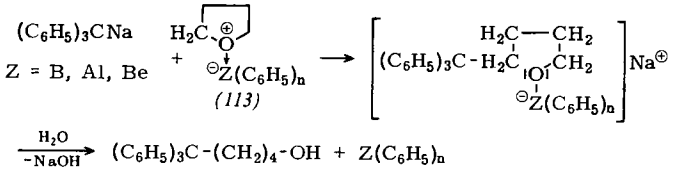
[132] *K. Ziegler* and *L. Jakob*, Liebigs Ann. Chem. *511*, 45 (1934).

[133] *G. Wittig* and *H. Schloeder*, Liebigs Ann. Chem. *592*, 38 (1955); *G. Wittig* and *D. Wittenberg*, *ibid. 606*, 1 (1957).

*(112)*, or that where such adducts are formed they are largely dissociated, permits the formation of C=C double bonds with elimination of metal hydride [1, 134].

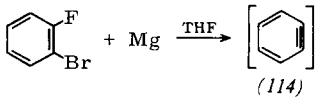
$$(C_6H_5)_2NaC-CH_2-CH_2-CNa(C_6H_5)_2 + 2\,(C_6H_5)_3B \rightarrow$$
*(112)*
$$2\,Na[HB(C_6H_5)_3] + (C_6H_5)_2C{=}CH-CH{=}C(C_6H_5)_2$$

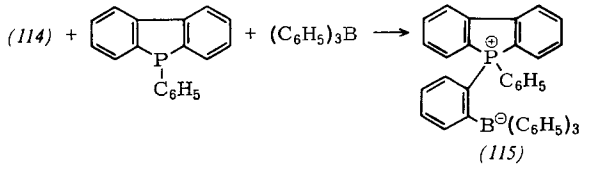
The ability of such acid-base pairs to attack suitable molecules nucleophilically and electrophilically at the same time provides a new method for the cleavage of cyclic ethers such as tetrahydrofuran, 2,5-dihydrofuran, coumaran, and dioxane. In the onium-ate-complex *(113)*,




the ether linkage is weakened to such an extent that nucleophilic attack of tritylsodium on α-carbon atom, which also carries a partial positive charge, leads to ring scission [134, 135].

The Lewis acid/Lewis base pair triphenylborane/2,2′-biphenylylenephenylphosphine has been found useful for the detection of dehydrobenzene; the betaine *(115)* is formed [136].



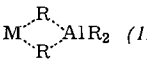




Reviews have appeared on the complex adducts of boranes and boron halides with electron donors [6, 89, 90, 137], as well as on aminoboranes [138] and radical-anions of boron compounds [6].

## 4. Alkylaluminates

*Ziegler* [93–95] and *Lehmkuhl* [96] have recently reviewed alkylaluminium complexes, which have become important also in industrial processes.

Here it need only be emphasized that the low conductivities, the volatilities, and the solubilities in non-polar solvents of the complexes $M_m[AlR_4]_n$ indicate that in addition to ionic structures, structures containing electron-deficient bonds *(116)* must also be considered, depending on the alkali or alkaline-earth cation (particularly where M = $C_2H_5Mg$, Mg, Li, Ca, and Sr) [138a].



*(116)*

$2\,[Al(C_2H_5)_4]^{\ominus}\,[Ca(THF)_2]^{2\oplus}$ *(117)*

The conductivities of molten alkali metal and alkaline-earth metal tetraethylaluminates indicate that the salt-like character increases with the atomic number of M [94, 96].

On solvation of the cation by electron donors, *e.g.* as in *(117)*, the tendency towards ionization is found to increase. Thus the conductivity of calcium tetraethylaluminate can be greatly increased by the addition of tetrahydrofuran [96].

## 5. Arylaluminates

Although lithium tetraphenylaluminate [139] gives a negative Gilman color test [40], it is readily hydrolysed by water, unlike lithium tetraphenylborate. The hydrolysis probably does not proceed *via* an equilibrium between $Li[Al(C_6H_5)_4]$ and free phenyl-lithium + triphenylaluminum, since $Li[Al(C_6H_5)_4]$ does not give carbinols either with benzophenone or with esters of benzoic acid. The ease of hydrolysis of $Li[Al(C_6H_5)_4]$ in comparison with $Li[B(C_6H_5)_4]$ is due partly to size relationships and to the difference in electronegativity between the central atom and carbon. Moreover, intermediates with coordination numbers higher than four are possible in the case of aluminum. $Li[Al(C_6H_5)_4]$ reacts with acyl chlorides such as benzoyl and acetyl chlorides to form ketones (benzophenone and acetophenone). In this case the aluminate complex must react as a whole with the acyl chloride, which probably attacks the aluminum-carbon bond electrophilically.

$$Li[Al(C_6H_5)_4] + R-CO-Cl \xrightarrow[-LiCl,\,-Al(C_6H_5)_3]{} C_6H_5-CO-R$$
$$R = C_6H_5;\ CH_3$$

This example illustrates how the reactivity of an organometallic compound can be either increased or decreased (as shown above for phenyl-lithium, which alone gives carbinols with acyl chlorides) by complex formation; this is referred to by *Wittig* [1] as an "accelerando" or "ritardando" effect.

Whereas in organolithium compounds (see Section B.3) complex solvation of the lithium cation by Lewis bases increases the tendency towards ionization and dissociation, and hence the reactivity, complex formation with a Lewis acid such as triphenylaluminum (which engages the lone electron pair of the potential carbanion) leads to a decrease in reactivity; depending on the nature of the complexing agent, this may result either in retardation or in complete suppression of reactions otherwise characteristic of the lithium compound.

[134] *G. Wittig* and *A. Rückert*, Liebigs Ann. Chem. *566*, 101 (1950); *G. Wittig* and *W. Stilz*, *ibid. 598*, 85, 93 (1956). This elimination is mechanistically the counterpart of the formation of tetraphenylbutadiene from tetraphenylbutane-1,4-diol with acids; see the discussion in [1].

[135] *G. Wittig* and *O. Bub*, Liebigs Ann. Chem. *566*, 113 (1950); *G. Wittig* and *G. Kolb*, Chem. Ber. *93*, 1469 (1960).

[136] *G. Wittig* and *E. Benz*, Chem. Ber. *92*, 1999 (1959).

[137] *F. G. A. Stone*, Chem. Reviews *58*, 101 (1958).

[138] *K. Niedenzu*, Angew. Chem. *76*, 168 (1964), Angew. Chem. internat. Edit. *3*, 86 (1964).

[138a] See also *K. Mach*, J. organomet. Chemistry *2*, 410 (1964).

[139] *G. Wittig* and *G. Keicher*, Naturwissenschaften *34*, 216 (1947); *G. Wittig* and *O. Bub*, Liebigs Ann. Chem. *566*, 113 (1950).

Sodium tetraphenylaluminate was recently prepared from sodium tetraethylaluminate and benzene [Equation (p)]; the anionic displacement of the ethyl groups by phenyl groups is catalysed by sodium alkoxide or phenylsodium, so that the true reactant, *i.e.* phenylsodium, can be continuously replaced as it is consumed [96].

$$Na[Al(C_2H_5)_4] + 4\,C_6H_6 \xrightarrow{NaOR(NaC_6H_5)} Na[Al(C_6H_5)_4] + 4\,C_2H_6 \quad (p)$$

## 6. Triphenylaluminum and Carbonyl Compounds

In contrast to $Li[Al(C_6H_5)_4]$, triphenylaluminum reacts slowly with ketones to form carbinols [139]. When allowed to stand for 16 days at room temperature with benzophenone, it gives triphenylmethanol in 23 % yield [140]. The carbonyl oxygen presumably contributes a lone pair of electrons to complete the electron octet of the aluminum, with rapid and possibly reversible formation of an adduct *(118)*; the rate-determining step is

$$(C_6H_5)_2C^{\oplus}\text{-}\underline{O}\text{-}^{\ominus} + Al(C_6H_5)_3 \rightleftharpoons \left[(C_6H_5)_2C^{\oplus}\text{-}\underline{O}\text{-}Al^{\ominus}(C_6H_5)_3\right] \quad (118)$$

$$\longrightarrow (C_6H_5)_2C(C_6H_5)\text{-}\underline{O}\text{-}Al(C_6H_5)_2 \quad (119)$$

the conversion of this adduct into *(119)* by anionic migration of a phenyl group from the now negatively charged aluminum to the positively charged carbon. This is consistent with the fact that benzaldehyde in boiling xylene reacts with triphenylborane to give diphenylmethanol, though only in moderate yield [141].

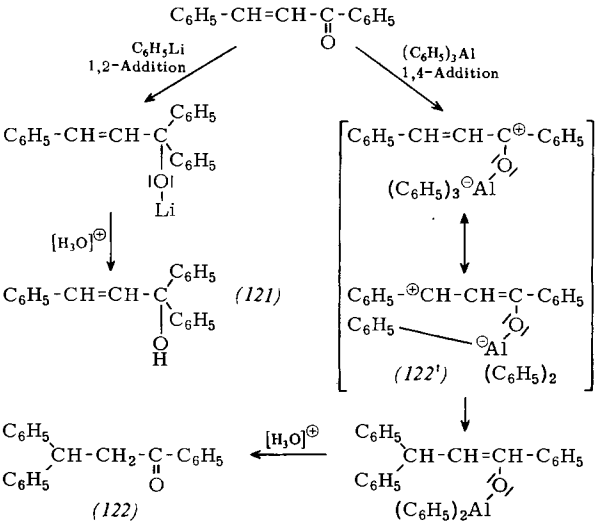
Although the reactions of benzophenone with phenyllithium and with triphenylaluminum (which together form the complex $Li[Al(C_6H_5)_4]$) lead to the same product, *viz.* triphenylmethanol, the reaction with phenyl-lithium (which gives a carbanion more readily) proceeds more rapidly in ether solution. Since the anionic activation of the group R in RLi is generally increased by the addition of donors, a fast and reversible addition of the carbonyl oxygen of ketones to the Li in RLi has been suggested [142].

The initial formation of complexes of the type *(118)* is also indicated by the transient yellow to red color observed during the reaction of triphenylaluminum with ketones such as benzalacetophenone, which indicates resonance-stabilized adducts such as *(120)*.

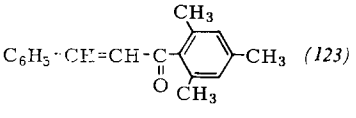
$$C_6H_5\text{-}CH{=}CH\text{-}C^{\oplus}(C_6H_5)\text{-}\underline{O}\text{-}(C_6H_5)_3Al^{\ominus} \longleftrightarrow C_6H_5\text{-}{}^{\oplus}CH\text{-}CH{=}C(C_6H_5)\text{-}\underline{O}\text{-}(C_6H_5)_3Al^{\ominus} \quad (120)$$

Halochromic effects of this type were observed and interpreted by *Pfeiffer* [143] and *Meerwein* [144] for the interaction of aluminum halides and aluminum alkyls with aldehydes and ketones.

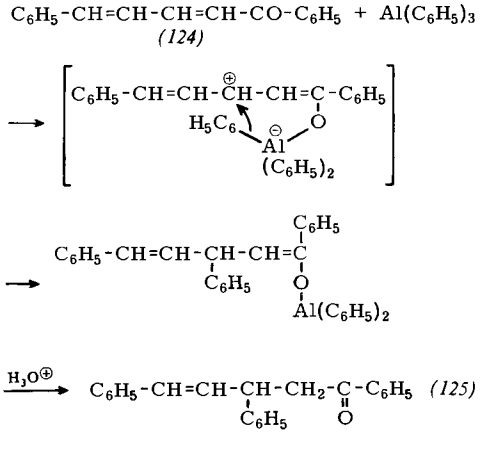
*Wittig* and *Schliesser* [145] studied the addition of phenyllithium and triphenylaluminum to unsaturated aldehydes and ketones in relation to 1,2- and 1,4-addition, *e.g.* to form *(121)* or *(122)*.




Where the carbonyl group is sterically unhindered, as in cinnamaldehyde, both reagents add in the 1,2-position. If, on the other hand, attack on the C=O group is sterically hindered, phenyl-lithium still adds preferentially in the 1,2-position, but $Al(C_6H_5)_3$ adds exclusively in the 1,4-position. When the hindrance is particularly strong, as in 1-mesityl-3-phenylpropenone *(123)*, in which a phenyl anion cannot add to the carbonyl carbon from any direction, both $Al(C_6H_5)_3$ and $LiC_6H_5$ are restricted to 1,4-addition.




In order to check whether the easy 1,4-addition proceeds from an adduct *(122')* *via* a six-membered cyclic transition state, $Al(C_6H_5)_3$ was treated with 1,5-diphenylpenta-2,4-dienone *(124)*. The only product obtained was 1,3,5-triphenylpent-4-enone *(125)*, which is formed by 1,4-addition; no 1,6- or 1,2-addition products were detected.




[140] *H. Gilman* and *K. E. Marple*, Recueil Trav. chim. Pays-Bas *55*, 133 (1936).

[141] *H. Gilman* and *K. E. Marple*, Recueil Trav. chim. Pays-Bas *55*, 77 (1936).

[142] *C. G. Swain* and *L. Kent*, J. Amer. chem. Soc. *72*, 518 (1950); see also *P. D. Bartlett* in *H. Gilman*: Organic Chemistry. Wiley, New York 1953, Vol. 3, p. 96.

[143] *P. Pfeiffer*, *K. Kollbach*, and *E. Haack*, Liebigs Ann. Chem. *460*, 138 (1928).

[144] *H. Meerwein*, *G. Hinz*, *H. Majert*, and *H. Sönke*, J. prakt. Chem. [2] *147*, 226 (1937).

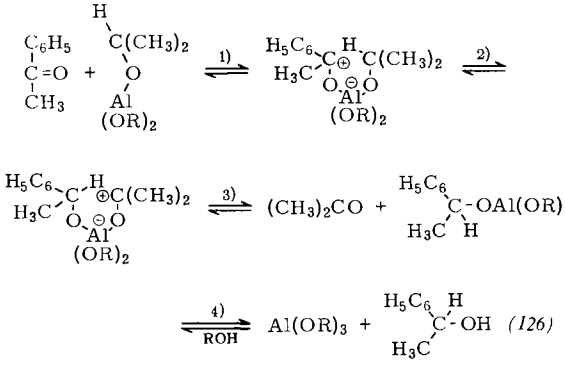
[145] *W. Schliesser*, Dissertation, Universität Tübingen, 1953.

Whereas the results obtained by *House*[67,69] make a six-membered transition state in the 1,4-addition of organomagnesium compounds to unsaturated ketones appear unlikely (see the end of Section D), no 1,4-addition product is obtained in the reaction of $Al(C_6H_5)_3$ with 2-cyclohexenone. The only products, apart from a little of the 1,2-addition product, are polymers. Thus in the case of aluminum, it is necessary to consider the possibility that the 1,4-addition actually takes place *via (122')*, proceeding through a six-membered cyclic transition state.

### 7. Hydride Shifts

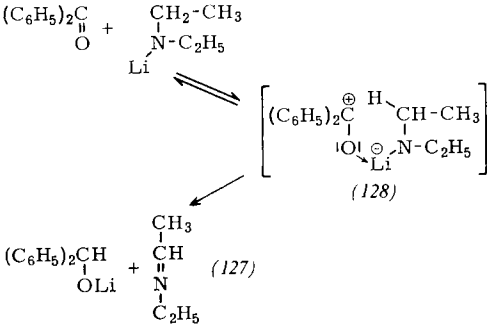
The addition of triphenylaluminum to ketones is closely related in its mechanism to the reduction of carbonyl compounds (and to the Oppenauer oxidation) with triethylaluminum[144], esters of boric acid[146], aluminum alkoxides[147,148], and Grignard compounds[149]. In this reduction, a hydride ion can move from one carbon atom to another because of a favorable steric arrangement and the anionic activation of the hydrogen due to the negative central atom[150]. The reduction with aluminum alkoxides involves the following steps:

1. coordination of the ketone with the monomeric or polymeric alkoxide,
2. hydride shift,
3. separation of the ketone formed in step 2 from the complex,
4. alcoholysis of the mixed alkoxide to form the alcohol obtained.



On the basis of NMR studies, *Shiner* and *Whittacker*[151] postulated fast, reversible complex formation of the trimeric and tetrameric aluminum isopropoxides[152] with acetone in toluene without previous dissociation of the alkoxide into the monomer. The spectroscopically studied formation of 1-phenylethanol *(126)* from acetophenone and trimeric or tetrameric Al-isopropoxide in benzene/isopropanol is much slower than that of acetone; it follows that the rate-determining step in this case is not the hydride shift *(2)*, as is usually assumed, but the alcoholysis of the mixed alkoxide *(4)*.

The question arises of whether the coordinating tendency of lithium is sufficient to induce a redox reaction *via* a coordination step (as is possible with boron, aluminum, and magnesium derivatives). *Wittig*[153] recently used lithium diethylamide to reduce benzophenone to lithium diphenylmethoxide, the secondary amine being converted into the Schiff base *(127)* by "Oppenauer oxidation". Since *(127)* is metalated by lithium diethylamide and adds to excess ketone (directed



aldol condensation[153,154]), the system benzophenone/lithium *N*-benzylanilide, in which secondary reactions of this nature do not occur, was studied kinetically. The formation of the Schiff base was found to be first order with respect to each of the components. Since a transient color, probably due to *(128)*, appears in the course of this reaction, the question again arises of whether the hydride shift takes place *via* an onium-ate-complex *(128)*[155].

The reducing action of metalated amines was already known from the reductive dehalogenation of a number of aryl halides[156–159], and the oxidation product, *i.e.* the Schiff base, had even been isolated in one case[157a]. However, the nucleophilic displacement of the halide ion by a hydride ion, as was previously postulated[156b,157b], seems less likely than the transfer of lithium hydride to dehydrobenzene.

[146] *H. Wuyts* and *A. Duquesne*, Bull. Soc. chim. Belgique *48*, 77 (1939); Chem. Abstr. *33*, 7274³ (1939); *H. G. Kuivila, S. C. Slack*, and *P. K. Siiteri*, J. Amer. chem. Soc. *73*, 123 (1951).

[147] *H. Meerwein, B. v. Bock, B. Kirschnick, W. Lenz*, and *A. Migge*, J. prakt. Chem. [2] *147*, 211 (1937).

[148] *A. L. Wilds*, Org. Reactions, Vol. 2, p. 178 (1944); *C. Djerassi, ibid.* Vol. 6, p. 207 (1951); *D. C. Bradley*: Metal Alkoxides. Advances Chem. Ser. No. 23, Amer. chem. Soc., Washington, D.C. 1959, p. 10.

[149] *R. Hamelin*, Bull. Soc. chim. France *1961*, 915, 926.

[150] *R. B. Woodward, N. L. Wendler*, and *F. J. Brutschy*, J. Amer. chem. Soc. *67*, 1425 (1945).

[151] *V. J. Shiner Jr.* and *D. Whittacker*, J. Amer. chem. Soc. *85*, 2337 (1963).

[152] *V. J. Shiner Jr., D. Whittacker*, and *V. P. Fernandez*, J Amer. chem. Soc. *85*, 2318 (1963).

[153] *G. Wittig, H. J. Schmidt*, and *H. Renner*, Chem. Ber. *95*, 2377 (1962); *G. Wittig* and *H. D. Frommeld, ibid. 97*, 3541, 3548 (1964); *H. D. Frommeld*, Dissertation, Universität Heidelberg, 1964.

[154] *G. Wittig, H. D. Frommeld*, and *P. Suchanek*, Angew. Chem. *75*, 978 (1963), Angew. Chem. internat. Edit. *2*, 683 (1963).

[155] *G. Wittig* and *H. Wulff* (personal communication) have isolated a deep wine-red, diamagnetic complex from benzophenone and lithium diphenylamide.

[156a] *H. Gilman, N. N. Crounse, S. P. Massie Jr., R. A. Benkeser*, and *S. M. Spatz*, J. Amer. chem. Soc. *67*, 2106 (1945).

[156b] *R. A. Benkeser* and *C. E. DeBoer*, J. org. Chemistry *21*, 281 (1956).

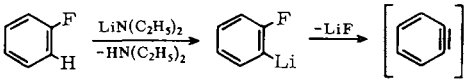
[157a] *H. S. Mosher* and *E. J. Blanz Jr.*, J. org. Chemistry *22*, 445 (1957).

[157b] *Th. Kauffmann*, Angew. Chem. *76*, 206 (1964), Angew. Chem. internat. Edit. *3*, 342 (1964).

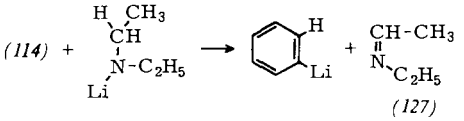
[158] *R. Huisgen* and *H. König*, Chem. Ber. *92*, 203 (1959).

[159] *W. Mack* and *R. Huisgen*, Chem. Ber. *93*, 608 (1960).

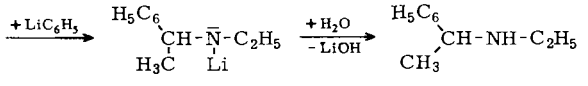
The hitherto unexplained discovery[160] that the principal product obtained from fluorobenzene, phenyllithium, and diethylamine (1:2:1) is 1-phenyldiethylamine *(130)* can also be explained in this way. Dehydrobenzene and lithium diethylamide react by a hydride



*(114)*



*(127)*



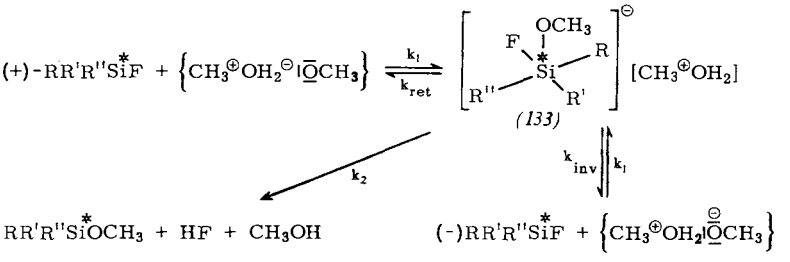
*(129)* *(130)*

shift to form phenyl-lithium and the Schiff base *(127)*, which is trapped by addition of phenyl-lithium to form *(129)*; this is converted on hydrolysis into the amine *(130)*.

in t-butanol or pentane, in which no other perceptible reaction occurs, can also be explained, according to *Sommer* and *Rodewald*[163], only by assuming a complex *(133)* containing 5-coordinate silicon, particularly since the methoxysilane $RR'R''SiOCH_3$ cannot occur as an intermediate. The addition of a methoxide anion to the silicon would lead to the adduct *(133)*, in which the fluorine and the three organic ligands form the base of a tetragonal pyramid with the methoxy group at the apex.

The intermediate *(133)* itself, which probably exists as a methanol-stabilized ion pair, would be optically active and could be re-converted into RR'R''SiF, either with retention or inversion of configuration, depending on which substituents (*e.g.* R and R'' or R' and F) move towards the methoxy group as the latter leaves; the silicon atom in *(133)* need not lie in the same plane as the substituents R,R',R'', and F. The observations can naturally also be explained in terms of a 6-coordinate silicon complex with two methoxy groups, although such an intermediate is less likely.

Salts of a complex silicate *(134)* in which the central atom is attached to three molecules of catechol were reported as early as 1931[164]. Compounds of this type can be readily prepared from tetraethyl orthosilicate, catechol, and amines[165]; this reaction can also be used

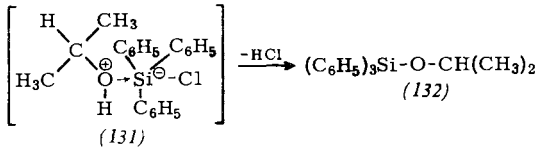


*(133)*

## G. Complexes with Group IV Elements

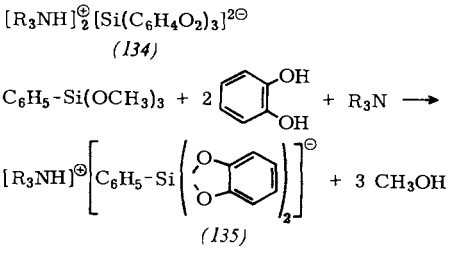
Using its d-orbitals silicon can expand its outer shell to accommodate more than eight electrons, so that substitutions on 4-coordinate silicon may proceed *via* 5-coordinate intermediates or by a type of $S_N2$ mechanism[161,167].

Kinetic studies[162] on the reaction of 2-propanol with triphenylchlorosilane in the presence of hydrochloric acid indicate, *e.g.*, an intermediate containing 5-coordinate silicon *(131)*, which decomposes to form triphenylisopropoxysilane *(132)*. The racemization of optically active α-naphthylphenylmethylfluorosilane with methanol



*(131)* *(132)*

for the synthesis of derivatives *(135)* which may contain 5-coordinate silicon. The method fails with coordination compounds containing more than one Si–C



*(134)*

*(135)*

bond. However, the structure of anions such as *(134)* has not yet been fully elucidated, since according to *Weiss*[166] they are dimeric, and can therefore be formulated with a coordination number of either 4 or 6 for the silicon. Attempts to resolve *(134)* into optical antipodes have so far been unsuccessful[166].

[160] *W. Merkle*, Dissertation, Universität Freiburg, 1942.

[161] For a discussion see *C. G. Swain, R. M. Esteve Jr.*, and *R. H. Jones*, J. Amer. chem. Soc. *71*, 965 (1949); *L. Kaplan* and *K. E. Wilzbach, ibid. 77*, 1297 (1955); *H. Gilman, A. G. Brook*, and *L. S. Miller, ibid. 75*, 4531 (1953); *C. R. Hauser* and *C. R. Hance, ibid. 73*, 5846 (1951); *E. D. Hughes*, Quart. Rev. (London) *5*, 245 (1951); *C. Eaborn*: Organosilicon Compounds. Butterworths, London 1960, pp. 177, 198; *U. Schöllkopf*, Angew. Chem. *72*, 159 (1960).

[162] *R. C. Petersen* and *S. D. Ross*, J. Amer. chem. Soc. *85*, 3164 (1963).

[163] *L. H. Sommer* and *P. G. Rodewald*, J. Amer. chem. Soc. *85*, 3898 (1963).

[164] *A. Rosenheim, B. Raibmann*, and *G. Schendel*, Z. anorg. allg. Chem. *196*, 160 (1931).

[165] *C. L. Frye*, J. Amer. chem. Soc. *86*, 3170 (1964).

[166] *A. Weiß, G. Reiff*, and *A. Weiß*, Z. anorg. allg. Chem. *311*, 151 (1961).

It is also likely that substitution in organotin compounds involves the formation of ate-complexes with more than eight electrons in the outermost shell of the tin atom. According to *Dessy* [167], nucleophilic assistance by anions is important in the acetolysis of tri-n-butyltin hydride in dimethyl sulfoxide (and in aprotic solvents in general), since lithium salts, which can be added to form *(136)*, cause a marked increase in the rate of the reaction. In the ate-complex *(136)* [168], the hydrogen is more mobile as hydride, and so becomes more accessible to attack by acetic acid.

$$(n\text{-}C_4H_9)_3SnH + LiX \xrightarrow[DMSO]{fast} \left[(n\text{-}C_4H_9)_3Sn\begin{matrix}X\\H\end{matrix}\right]^{\ominus} Li^{\oplus}$$

*(136)*

$$(136) \xrightarrow[CH_3COOH]{slow} (n\text{-}C_4H_9)_3SnOAc + H_2 + LiX$$

Nucleophilic assistance and acceleration probably occur in many nucleophilic substitutions involving elements with an incomplete octet or which can expand their outer shell.

The transmetalation reaction (q) [169], which is characteristic of organotin and organolead compounds, and which has recently been used for the preparation of vinyl-lithium and allyl-lithium compounds [170], could also involve ate-complexes such as *(137)*, with 5- or 6-coordinate metal, as intermediates. Reaction (q) in-

$$R_4M + R'Li \rightleftharpoons [R_4MR']Li \rightleftharpoons R_3MR' + RLi \qquad (q)$$

$M = Sn, Pb$ ? *(137)*

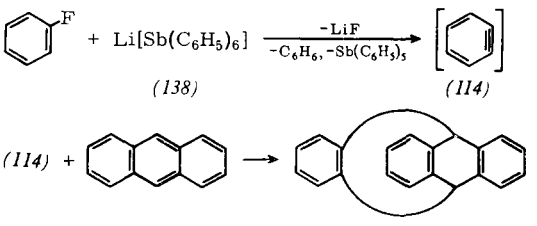
volves a series of equilibria and proceeds in the cases studied (R = propenyl) with retention of the geometrical configuration of the group R in $R_4Sn$ [170].

Salts containing complex organotin anions and large organic cations have been known for some time [171, 172].

## H. Complexes with Elements of Groups V and VI

Pentaphenylphosphorus, -arsenic, -antimony, and -bismuth [173] are covalent compounds with the unusual coordination number of 5, in which the outermost shell of the central atom contains ten electrons. Pentaphenylantimony, which reacts with phenyl-lithium to form the isolable lithium hexaphenylantimonate *(138)*, was the first of the pentacovalent compounds of the Group V elements to which an anion was added to give twelve electrons in the outer shell of the central atom [173].

In solution, *(138)* exists in equilibrium with $Sb(C_6H_5)_5$ and $LiC_6H_5$, as is shown by the fact that fluorene can be metalated by the solution. The slight dissociation corresponds to the use of phenyl-lithium at very low concentrations, and enabled *Wittig* and *Benz* [174] to develop a simple one-stage preparation of triptycene from *(138)*, fluorobenzene, and anthracene. "Free" phenyl-lithium would largely suppress the Diels-Alder reaction of dehydrobenzene with anthracene by addition to the former.



*(138)* *(114)*



*(114)*

Compound *(138)* can be used for the metalation of chloroform or benzyl chloride. In the presence of cyclohexene up to 60 % of dichloronorcarane and 15 % of phenylnorcarane are obtained [56]. The anionic ligand exchange between tetraphenylstibonium bromide and methyl-lithium, which ultimately leads to pentaphenylantimony, could also proceed *via* ate-complexes *(139)* [175, 176].

$$[(C_6H_5)_4Sb]Br \xrightarrow[-LiBr]{+2CH_3Li} [(C_6H_5)_4Sb(CH_3)_2]Li$$

*(139)*

$$\xrightleftharpoons[+C_6H_5Li]{-C_6H_5Li} [(C_6H_5)_3Sb(CH_3)_2]$$

$$[(C_6H_5)_4Sb]Br + C_6H_5Li \xrightarrow[-LiBr]{} (C_6H_5)_5Sb$$

Conversely, on reaction of pentaphenylantimony with butyl-lithium, 47 % of the pentabutylantimony was found, after hydrolysis, as tetrabutylstibonium tetraphenylborate, while methyl-lithium with pentaphenylantimony yields pentamethylantimony [177]. Since no ate-complex is formed by combination of phenyl-lithium with pentaphenylphosphorus [173, 178] or pentaphenylarsenic [173], an equilibrium similar to that of *(138)* appears to lie very much to the side of the dissociation products. Although the phosphorus [177, 178] and arsenic [179] compounds undergo ligand exchange with organolithium compounds without difficulty, it is not certain whether ate-complexes occur as intermediates (which seems likely), or whether the substitutions proceed by an $S_N2$-type mechanism.

[167] *R. E. Dessy, Th. Hieber,* and *F. Paulik,* J. Amer. chem. Soc. *86*, 28 (1964).

[168] Compounds containing 5-coordinate tin are discussed in: *O. Schmitz-DuMont* and *G. Bungard,* Chem. Ber. *92*, 2399 (1959); *I. R. Beattie, G. P. McQuillan,* and *R. Hulme,* Chem. and Ind. (London) *1962*, 1429; *R. C. Poller,* J. organomet. Chemistry *3*, 321 (1965).

[169] *H. Gilman* and *F. W. Moore,* J. Amer. chem. Soc. *62*, 3206 (1940); *H. Gilman, F. W. Moore,* and *R. G. Jones, ibid. 63*, 2482 (1941).

[170] *D. Seyferth et al.,* J. Amer. chem. Soc. *83*, 3583 (1961); *84*, 361, 4266 (1962); *86*, 883 (1964); J. org. Chemistry *26*, 563, 4797 (1961).

[171] *P. Pfeiffer,* Liebigs Ann. Chem. *376*, 310 (1910); *O. A. Reutov, O. A. Ptitsyna,* and *N. D. Patrina,* Zhur. Obshei Khim. *28*, 588 (1958); Chem. Abstr. *52*, 17151a (1958).

[172] *D. Seyferth* and *S. O. Grim,* J. Amer. chem. Soc. *83*, 1610 (1961).

[173] *G. Wittig* and *M. Rieber,* Liebigs Ann. Chem. *562*, 187 (1949); *G. Wittig* and *K. Clauss, ibid. 577*, 26 (1952), *578*, 136 (1952).

[174] *G. Wittig* and *E. Benz,* Tetrahedron *10*, 37 (1960).

[175] *G. Wittig* and *K. Torssell,* Acta chem. scand. *7*, 1296 (1953).

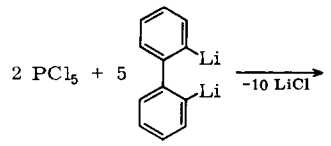
[176] The only pentaalkyl derivative obtained so far is pentamethylantimony.

[177] *G. Wittig* and *G. Steinhoff,* unpublished work.

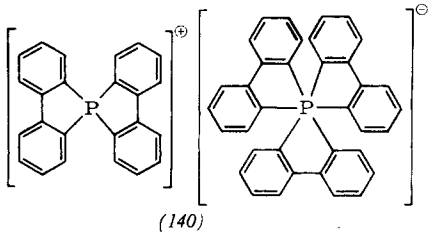
[178] *M. Schlosser* and *T. Kadibelban,* personal communication.

[179] *D. Hellwinkel,* personal communication.

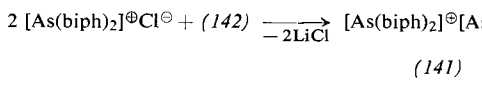
*Hellwinkel* [179,180] has found that phosphorus and arsenic can form stable complexes *(140)* and *(141)* in which they have the coordination number 6. These



*(142)*



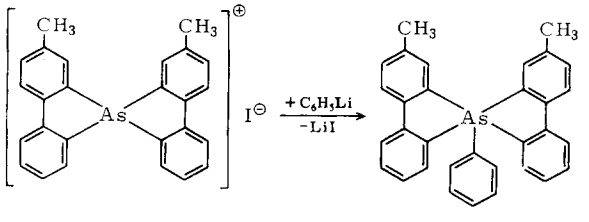
*(140)*



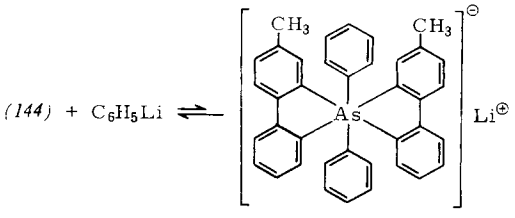
*(141)*

complexes can be cleaved by alkali metal halides; the product obtained from *(140)* + NaI is sodium tris(2,2'-biphenylylene)phosphate(V), which can be resolved into optical antipodes, so that the octahedral structure of this complex can be regarded as certain.

The loss of optical activity observed when the optically active arsonium iodide *(143)* is treated with phenyl-lithium may be due to reversible addition of further $LiC_6H_5$ to the active initial product *(144)* to form the ate-complex *(145)*, which would necessarily lead to the racemization of *(144)* [181].



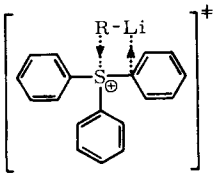
*(143)* *(144)*



*(145)*

[180] *D. Hellwinkel*, Angew. Chem. *76*, 756 (1964); *77*, 378 (1965); Angew. Chem. internat. Edit. *4*, 356 (1965); Chem. Ber. *98*, 576 (1965).

Attempts to prepare $Li[Te(C_6H_5)_5]$ have been unsuccessful [182]. *Franzen* and *Merz* [183] observed rapid ligand exchange between triarylsulfonium and triaryltelluronium salts and organolithium compounds. The authors favor the assumption that the exchange proceeds neither *via* an intermediate containing 4-coordinate sulfur or tellurium nor *via* a 5-coordinate ate-complex, but that it involves a cyclic transition state *(146)* of the sulfonium or telluronium stage, in which the aryl or alkyl group of the organolithium compound acts as the donor and the lithium cation as the acceptor.



*(146)*

However, other possible routes must also be considered in the case of tellurium, since *Hellwinkel* and *Fahrbach* [179] have shown that tetraaryltellurium derivatives undergo rapid substituent exchange with organolithium compounds [*].

## I. Conclusion

This review attempts to demonstrate that the basic concept of anionic activation of ligands in ate-complexes, as a counterpart to cationic activation in onium-complexes, is a useful one. Further investigations will have to show the extent to which these views can be generalized.

*I wish to thank Prof. Dr. Dr. h.c. G. Wittig for valuable discussions and for access to his unpublished results, as well as for critical examination of the manuscript, for which I am also grateful to Dr. H. F. Ebel, Dr. H. Küppers, and Dr. J. R. F. Fairbrother.*

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German version: Angew. Chem. *78*, 355 (1966)
Translated by Express Translation Service, London

[181] *G. Wittig* and *D. Hellwinkel*, Chem. Ber. *97*, 769 (1964).

[182] *G. Wittig* and *H. Fritz*, Liebigs Ann. Chem. *577*, 39 (1952).

[183] *V. Franzen* and *C. Merz*, Liebigs Ann. Chem. *643*, 24 (1961).

[*] On organometallic complexes with transition metals see, *e.g.*, *Fr. Hein* and *R. Weiss*, Z. anorg. allg. Chem. *295*, 145 (1958); *W. Herwig* and *H. H. Zeiss*, J. Amer. chem. Soc. *79*, 6561 (1957); *81*, 4798 (1959); *W. Herwig*, *W. Metlesics*, and *H. Zeiss*, *ibid. 81*, 6203 (1959); *M. Tsutsui* and *H. H. Zeiss*, *ibid. 81*, 6090 (1959); *Fr. Hein* and *R. Weiss*, Naturwissenschaften *46*, 321 (1959); *H. Funk* and *W. Hanke*, Z. anorg. allg. Chem. *307*, 157 (1961); *B. Sarry* and *M. Dettke*, Angew. Chem. *75*, 1022 (1963), Angew. Chem. internat. Edit. *2*, 690 (1963); *R. Nast*, Angew. Chem. *72*, 26 ((1960); *R. Nast* and *K. Kasperl*, Chem. Ber. *92*, 2135 (1959); *R. Nast* and *W. Hörl*, *ibid. 95*, 1470 (1962); *R. Nast* and *W. D. Heinz*, *ibid. 95*, 1478 (1962); *R. Nast*, *P.-G. Kirst*, *G. Beck*, and *J. Gremm*, *ibid. 96*, 3302 (1963); *C. Beermann* and *K. Clauss*, Angew. Chem. *71*, 627 (1959).

# The Chemistry of α-Carbonyl Azo Compounds

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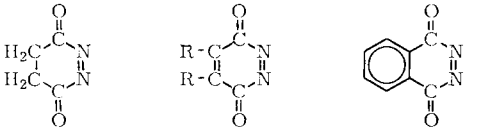
*α-Carbonyl azo compounds such as diesters of azodicarboxylic acids, diacylazo compounds, and esters of arylazocarboxylic acids are highly reactive. They add e.g. to amines, aromatic compounds, olefins, CH acids, Grignard and diazo compounds, aldehydes, ketones, and ketenes. These reactions can be used for the preparation of triazanes, hydrazones, oxadiazoline, azomethinimine, and diazetidine derivatives, etc. α,α'-Dicarbonyl azo compounds are among the strongest dienophiles known.*

## 1. Introduction

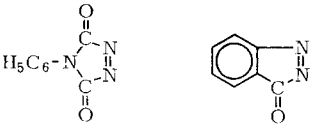
α-Carbonyl azo compounds contain one carbonyl function (R–N=N–CO–R', R–N=N–COOR') or two carbonyl functions (R–CO–N=N–CO–R', ROOC–N=N–COOR') adjacent to the azo group. These substances take part in a wide variety of reactions, and differ from the aliphatic and aromatic azo compounds in the pronounced reactivity of their N=N group. The present paper is concerned mainly with work published during the past two decades and with largely unpublished investigations carried out by the authors and their collaborators.

## 2. Preparation

α-Carbonyl azo compounds are generally prepared by oxidation of hydrazine derivatives. Methods that have proved particularly suitable include oxidation with halogens[1–4], concentrated nitric acid[5,6], and *N*-bromosuccinimide in pyridine[7,8], and (for aroylazo compounds) treatment of the hydrazine derivative with $HgCl_2$ or $AgNO_3$ to convert it into the metal derivative, which is then treated with iodine or bromine[9–15]. The extremely unstable α-carbonyl azo compounds *(1)* to *(5)* have been prepared by oxidation of the hydrazine compounds with lead(IV) acetate[16,17] or t-butyl hypochlorite[18,19,19a].



*(1)* *(2a)*: R = H, *(2b)*: R = F *(3)*



*(4)* *(5)*

The preparation[20] of bis(azodicarboxylic acid) derivatives such as

$ROOC–N=N–COO–(CH_2)_n–OOC–N=N–COOR$

and their possible technical applications[21] have been described.

Azodicarboxamides and phenylazocarboxamides are most easily obtained by reaction of the esters with ammonia. The same reaction with primary amines gives *N*-

[1] *M. C. Chaco* and *N. Rabjohn*, J. org. Chemistry *27*, 2765 (1962).

[2] *G. W. Kenner* and *R. J. Stedman*, J. chem. Soc. (London) *1952*, 2089.

[3] *N. Rabjohn*, Org. Syntheses, Coll. Vol. III, 375 (1955).

[4] *L. Horner* and *W. Naumann*, Liebigs Ann. Chem. *587*, 93 (1954).

[5] *S. G. Cohen*, *R. Zand*, and *C. Steel*, J. Amer. chem. Soc. *83*, 2895 (1961).

[6] *J. P. Picard* and *J. L. Boivin*, Canad. J. Chem. *29*, 223 (1951).

[7] *L. A. Carpino*, *P. H. Terry*, and *P. J. Crowley*, J. org. Chemistry *26*, 4336 (1961).

[8] *E. Baltin*, Dissertation, Universität München, 1963; *H. Bock* and *E. Baltin*, Chem. Ber. *98*, 2054 (1965).

[9] *R. Stollé*, Ber. dtsch. chem. Ges. *45*, 273 (1912).

[10] *R. Stollé* and *A. Benrath*, J. prakt. Chem. *70*, 263 (1904).

[11] *H. H. Inhoffen*, *H. Pommer*, and *F. Bohlmann*, Chem. Ber. *81*, 507 (1948).

[12] *J. E. Leffler* and *W. B. Bond*, J. Amer. chem. Soc. *78*, 335 (1956).

[13] *Y. S. Shabarov*, *N. I. Vasilev*, *I. S. Levina*, and *R. Y. Levina*, Zh. obshch. Khim. *32*, 2806 (1962), Chem. Abstr. *85*, 9063 (1963).

[14] *D. Y. Curtin* and *T. C. Miller*, J. org. Chemistry *25*, 885 (1960).

[15] Diesters and diamides of azodicarboxylic acid can also be prepared by oxidation of the hydrazo compounds with inorganic nitrates in glacial acetic acid in the presence of a little copper acetate. Brit. Pat. 873 597 (Jan. 1st, 1960), Wallace and Tiernan, Inc.

[16] *R. A. Clement*, J. org. Chemistry *27*, 1115 (1962); *25*, 1724 (1960).

[17] *E. F. Ullman* and *E. A. Bartkus*, Chem. and Ind. *1962*, 93.

[18] *R. C. Cookson*, *S. S. H. Gilani*, and *I. D. R. Stevens*, Tetrahedron Letters *1962*, 615.

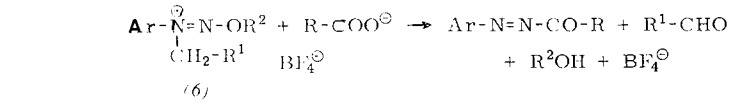
[19] *T. J. Kealy*, J. Amer. chem. Soc. *84*, 966 (1962).

[19a] *J. Sauer* and *B. Schröder*, Angew. Chem. *77*, 736 (1965); Angew. Chem. internat. Edit. *4*, 711 (1965).

[20] *E. Müller* and *S. Petersen*, Angew. Chem. *63*, 18 (1951).

[21] *S. S. Ivanov*, *N. A. Yuzefovich*, *A. V. Sidorovich*, and *E. F. Fedorova*, Kolloid Zhur. *18*, 285 (1956); Chem. Abstr. *51*, 1637 (1957); *P. J. Flory*, *N. Rabjohn*, and *M. C. Shaffer*, J. Polymer Sci. *4*, 225, 435 (1949); Ger. Pat. 930655 (July 21st, 1955) and 939536 (Feb. 23rd, 1956), Phönix Gummiwerke, inventors: *W. Stegemann* and *G. Reuter*; Ger. Pat. 919128 (Oct. 14th, 1954), Farbenfabriken Bayer, inventor: *H. Stephan*; US-Pat. 2507718 (May 16th, 1950), Du Pont, inventor: *R. M. Joyce*.

substituted amides (cf. Section 4.2.1 [22]). An interesting method for the preparation of α-carbonyl azo compounds having the structure Ar–N=N–CO–R (R = aryl or alkyl) was discovered by *Hünig* and *Eicher* [23], who obtained these compounds in yields between 75 and 100 % by the reaction of alkoxydiazenium salts *(6)* with carboxylate ions at room temperature (Ar = $C_6H_5$ and substituted phenyl; R = $C_6H_5$, substituted phenyl, and alkyl; $R^1$ = H, $C_6H_5$, and alkyl; $R^2$ = $CH_3$, $C_2H_5$).



*(6)*

the question of the geometrical structure of the α-carbonyl azo compounds remained unanswered for a long time. Most authors believed that the diesters of azodicarboxylic acids have the *trans* structure [25a–27]. *Schenck* and *Kopp* [28,29] recently converted diethyl azodicarboxylate into a photostationary system containing about 30 % of diethyl *cis*-azodicarboxylate by exposure to light of wavelength 300–370 mμ. This *cis* compound is much more reactive than the *trans* form (cf. Section 4.8), but can be stored for long periods in the dark (half-life at room temperature: $14 \times 10^3$ min), and is readily converted into the *trans* form by light or with the aid of a catalyst.

Table 1. α-Carbonyl azo compounds: position of the carbonyl stretching band; maxima and molar extinctions of the bands due to the n→π* and π→π* transitions.

| α-Carbonyl azo compound | Carbonyl stretching band ($cm^{-1}$) [35] | n→π* [34] | | π→π* [34] | |
|---|---|---|---|---|---|
| | | $\tilde{\nu}_{max}$ ($cm^{-1}$) | $\varepsilon_{mol}$ | $\tilde{\nu}_{max}$ ($cm^{-1}$) [38] | $\varepsilon_{mol}$ |
| $C_6H_5OOC-N=N-COOC_6H_5$ | 1789 [c] [37] | 24500 | 40 [37] | (40000) | (2000) |
| $CH_3OOC-N=N-COOCH_3$ | 1786 [a] [32] | 24690 | 56 [33] | | |
| $C_2H_5OOC-N=N-COOC_2H_5$ [36] | 1786 [a] [32], 1783 [e] [25b] | 24700 | 47 [8] | | |
| $(CH_3)_2CHOOC-N=N-COOCH(CH_3)_2$ | 1780 [e] [25b] | | | | |
| $NH_2-CO-N=N-CO-NH_2$ | 1721 [c] [37] | | | | |
| Pip.-CO–N=N–CO-Pip. [h] | 1704 [f] [37] | 23100 | 44 [37] | (37000) | (1500) |
| $(CH_3)_2N-CO-N=N-CO-N(CH_3)_2$ | 1701 [c] [37] | 23050 | 39 [37] | (38000) | (1600) |
| $C_6H_5-CO-N=N-COOC_2H_5$ | 1783/1733 [e] [37] | 23000 | 37 [37] | (41900) | (13700) |
| $C_2H_5OOC-N=N-CO-N(C_2H_5)_2$ | 1770/1707 [e] [37] | (23400) | (43) [37] | (35000) | (1000) |
| $C_6H_5-CO-N=N-CO-C_6H_5$ | 1740 [a] [32], 1730 [g] [14] | | | | |
| $C_6H_5-CO-N=N-CO-C_6H_4-p$-Cl | 1727 [c] [37] | 21000 | 49 [37] | (40800) | (24800) |
| $p$-Cl–$C_6H_4$–CO–N=N–CO–$C_6H_4$–$p$-Cl | 1709 [c] [37] | 20850 | 50 [37] | (39400) | (32800) |
| $p$-$CH_3$–$C_6H_4$–CO–N=N–CO–$C_6H_4$–$p$-$CH_3$ | 1718 [c] [37] | 21100 | 50 [37] | (39500) | (27700) |
| $C_6H_5-CO-N=N-CO-C_6H_4-p-NO_2$ | 1721 [c] [37] | 21000 | 50 [37] | (39050) | (25200) |
| $CH_3-CO-N=N-CO-CH_3$ | 1770 [a] [14] | | | | |
| $(C_6H_5)_3C-CH_2-CO-N=N-CO-CH_2-C(C_6H_5)_3$ | 1780 [g] [14] | | | | |
| $C_6H_5-N=N-COOCH_3$ | 1757 [e] [8] | 23800 | 131 [8] | 34850 | 10000 |
| $C_6H_5-N=N-COOC_2H_5$ | 1765 [a] [32] | 23900 | 146 [8] | 34800 | 10200 |
| $C_6H_5-N=N-COOC_6H_5$ | 1770 [c] [8] | 23700 | 133 [8] | 34350 | 12400 |
| $C_6H_5-N=N-CO-CH_3$ | 1742 [e] [8] | 22800 | 88 [8] | 34850 | 10800 |
| $C_6H_5-N=N-CO-C_6H_5$ | 1719 [c] [8] | 22500 | 121 [8] | 34700 | 13400 |
| $C_6H_5-N=N-CO-C_6H_4-p$-Cl | 1707 [c] [37] | 22300 | 126 [37] | 34600 | 19600 |
| $p$-Cl–$C_6H_4$–N=N–CO–$C_6H_5$ | 1712 [c] [37] | 22450 | 138 [37] | 33900 | 17900 |
| $p$-Cl–$C_6H_4$–N=N–CO–$C_6H_4$–$p$-Cl | 1701 [c] [37] | 22600 | 135 [37] | 33600 | 13700 |
| $p$-$NO_2$–$C_6H_4$–N=N–CO–$C_6H_5$ | 1704 [c] [37] | 21800 | 141 [37] | 35100 | 24300 |
| $C_6H_5-N=N-CO-NH_2$ | 1704 [c] [37] | 23500 | 124 [8] | 35530 | 10200 |
| $C_6H_5-N=N-CO-N(CH_3)_2$ | 1690 [c] [8] | 23100 | 129 [8] | 35250 | 10700 |
| $C_6H_5-N=N-COOK$ | 1664 [c] [8] | 23900 [b] | 98 [8] | 37700 | 10600 |
| *(4)* | 1780/1760 [c] [18] | | | | |
| *(5)* | 1792 [d] [17] | | | | |

[a] in $CCl_4$; [b] in ethanol; [c] in Nujol or Hostaflon oil (polytetrafluoroethylene); [d] in acetonitrile; [e] capillary; [f] KBr-method; [g] in $CHCl_3$; [h] Pip. = Piperidino.

## 3. Structure and Spectroscopic Behavior of α-Carbonyl Azo Compounds

Although *Hartley* [24] showed as early as 1937 that azobenzene exists in the *trans* form, and can be converted into the labile *cis* form by ultraviolet radiation, The infrared-spectroscopic data in Table 1 show that the carbonyl stretching frequency of α-carbonyl azo compounds is appreciably higher than the "normal" values of 1750–1735 and 1725–1705 $cm^{-1}$ found for saturated esters and ketones, owing to the influence of

[22] Phenylazocarboxamides are also formed on oxidation of phenylsemicarbazides with $NaNO_2$ in glacial acetic acid [141a, 141d], on hydrolysis of phenylazo cyanides [*A. Hantzsch* and *O. W. Schultze*, Ber. dtsch. chem. Ges. *28*, 2073 (1895)], on reaction of phenylhydrazinehydroxamic acids with acetic anhydride [141b], and from *N*-nitrosophenylhydrazinecarboxamides [*O. Widman*, Ber. dtsch. chem. Ges. *28*, 1925 (1895); cf. also *J. H. Boyer* and *J. A. Hernandez*, J. Amer. chem. Soc. *78*, 5124 (1956)].

[23] *S. Hünig* and *T. Eicher*, personal communication.

[24] *G. S. Hartley*, Nature (London) *140*, 281 (1937).

[25] a) *C. G. Le Fèvre, R. J. W. Le Fèvre*, and *W. T. Oh*, Austral. J. Chem. *10*, 218 (1957); b) *R. J. W. Le Fèvre, W. T. Oh, I. H. Reece, R. Roper*, and *R. L. Werner*, *ibid. 11*, 92 (1958); c) *R. S. Armstrong, M. J. Aroney*, and *R. J. W. Le Fèvre*, *ibid. 15*, 703 (1962).

[26] *A. Simon* and *H. Wagner*, Naturwissenschaften *47*, 540 (1960).

[27] See the dipole and parachor measurements reported by *P. R. Frey* and *E. C. Gilbert*, J. Amer. chem. Soc. *59*, 1344 (1937); *H. Lumbroso* and *J. Barassin*, Bull. Soc. chim. France *1964*, 3194; *A. I. Vogel, W. T. Cresswell, G. H. Jeffery*, and *J. Leicester*, J. chem. Soc. (London) *1952*, 514, and [25a] and [25c].

[28] *G. O. Schenck, H. R. Kopp, B. Kim*, and *E. Koerner von Gustorf*, Z. Naturforsch. *20b*, 637 (1965).

[29] *H.-R. Kopp*, Dissertation, Universität Göttingen, 1962.

the N=N group. Thus the effect of this group on the C=O frequency is similar to that of a halogen atom in the α-position. In azodibenzoyl (1740 $cm^{-1}$) and phenylazodibenzoyl (1719 $cm^{-1}$), the increase in the C=O frequency due to the presence of the azo group is partly cancelled by the mesomeric effect of the phenyl nucleus. As expected on theoretical grounds, the esters of phenylazocarboxylic acid fall between the diesters of azodicarboxylic acid and the azodiaroyl compounds, whereas *N,N*-dimethyl phenylazocarboxamide has a particularly low C=O frequency (1690 $cm^{-1}$) owing to the mesomeric influence of the amide nitrogen adjacent to the carbonyl group.

The position of the N=N stretching band of α-carbonyl azo compounds has not yet been determined. *Le Fèvre et al.*[25b] believe that the relatively wide band at about 1780 $cm^{-1}$ in the infrared spectra of the diesters of azodicarboxylic acid is due to superposition of the carbonyl and the azo stretching bands[30]. *Chaco* and *Rabjohn*[1], on the other hand, are of the opinion that the band which they found at 1610 $cm^{-1}$ for diethyl azodicarboxylate and at 1635 $cm^{-1}$ for ethyl t-butylazocarboxylate is due to the N=N stretching vibration. *Simon* and *Wagner*[26] and *Dubov* and *Ginsburg*[31] assigned the band at 1555 $cm^{-1}$ (diethyl azodicarboxylate[26]), 1562 $cm^{-1}$ (K salt of azodicarboxylic acid[26]), and 1553 $cm^{-1}$ (diisopropyl azodicarboxylate[31]) in the Raman spectrum to the N=N stretching vibration.

The absorption spectra of α,α′-dicarbonyl azo compounds (Table 1) contain the band due to the $n \rightarrow \pi^*$ transition between 20850 and 24700 $cm^{-1}$, with molar extinctions between 37 and 56, and (except in dimethyl, diethyl, and di-isopropyl azodicarboxylates[39]) the band due to the $\pi \rightarrow \pi^*$ transition, which is difficult to assign, between 35000 and 41900 $cm^{-1}$ ($\varepsilon_{mol}$ between 1000 and 32800). In the case of the phenylazocarbonyl compounds, the $n \rightarrow \pi^*$ band is situated between 21800 and 23900 $cm^{-1}$ ($\varepsilon_{mol}$ between 88 and 146), while the $\pi \rightarrow \pi^*$ band lies between 33600 and 37700 $cm^{-1}$ ($\varepsilon_{mol}$ between 10000 and 24300)[40]. The $n \rightarrow \pi^*$ band is very suitable in many cases for the quantitative determination of α-carbonyl azo compounds and for the spectrophotometric study of their reactions.

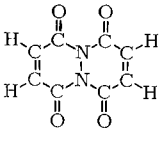
## 4. Reactions of α-Carbonyl Azo Compounds

Any classification of the reactions of α-carbonyl azo compounds can only be tentative, since it is necessary in many cases (particularly those of earlier work) to check not only the reaction course proposed by the authors, but also the structures of the products.

### 4.1. Thermal and Photochemical Decompositions

Diesters of azodicarboxylic acid have high thermal and photochemical stabilities. Thermal decomposition occurs only above 100 °C, sometimes explosively[41]. Irradiation for several hours at room temperature with a high-pressure mercury-vapor lamp causes only slight changes[29, 42].

On the other hand, diacylazo compounds and the cyclic α-carbonyl azo compounds *(1)* to *(5)* are much less stable. The latter decompose even below 0 °C[16–19], and some of them undergo polymerization. Compound *(2a)* loses $N_2$ to form *(7)* even at −30 °C.



*(7)*

The stability of the azodiaroyl compounds depends on the aroyl residue[43], being increased by electron-donating substituents and decreased by electron-withdrawing substituents on the aromatic nucleus[4]. When heated, azodiaroyl compounds decompose into nitrogen and aroyl radicals, which initiate secondary reactions[14, 44–47, 47a]. Thus azodibenzoyl in boiling xylene gives only 37 % of the maximum possible quantity of nitrogen, the other products including tribenzoylhydrazine, benzoic acid, 2,5-diphenyl-1,3,4-oxadiazole, and a little benzil[46]. The kinetics of the decomposition was studied by *Leffler* and *Bond*[12]. The decomposition of aliphatic diacylazo compounds over copper oxide can be used for the preparation of 1,2-diketones[11].

[30] With the aid of a grating spectrometer we resolved the band at 1786 $cm^{-1}$ in the spectrum of diethyl azodicarboxylate in carbon tetrachloride into the principal band at 1786 $cm^{-1}$ and a weak shoulder at 1779 $cm^{-1}$ [32].

[31] *S. S. Dubov* and *V. A. Ginsburg*, Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva *7*, 583 (1962), Chem. Abstr. *58*, 4041 (1963).

[32] *H. D. Rupp*, Diploma Thesis, Universität Würzburg, 1963.

[33] *A. Rodgman* and *G. F. Wright*, J. org. Chemistry *18*, 465 (1953).

[34] All measurements in dioxane, except for potassium phenylazocarboxylate (ethanol). Further values are given in *P. Grammaticakis*, Bull. Soc. chim. France *1953*, 86; *R. Andrisano*, *A. Bellotti*, and *T. Vitali*, Ricerca sci. *30*, 2142 (1961), Chem. Abstr. *55*, 19474 (1961).

[35] According to *L. A. Carpino*, *P. H. Terry*, and *P. J. Crowley* [7], the carbonyl stretching band in the spectra of di-t-butyl azodicarboxylate and t-butyl phenylazocarboxylate lies between 1748 and 1770 $cm^{-1}$.

[36] $\tilde{\nu}_{max}$ of diethyl *cis*-azodicarboxylate: 22990 $cm^{-1}$ [29].

[37] Unpublished results obtained by *H. Bock*, *G. Rudolph*, *E. Baltin*, and *J. Kroner*. We are grateful to Dr. *H. Bock*, Munich, for access to these results.

[38] The values in parentheses refer to poorly defined maxima or curves with inflections, which were calculated in some cases with the assumption of gaussian peaks.

[39] Diethyl azodicarboxylate has no other absorption maximum up to 42500 $cm^{-1}$ [8].

[40] Cf. the detailed discussion of the absorption spectra of azo compounds in *H. Bock*, Angew. Chem. *77*, 469 (1965); Angew. Chem. internat. Edit. *4*, 457 (1965); *E. Baltin* [8]; *E. Kinzel*, Dissertation, Universität München, 1964.

[41] The decomposition of methyl azodicarboxylate between 90 and 360 °C was studied by *E. I. Fedotova*, *R. Y. Khvilivitskii*, and *I. I. Zmachinskaya*, Uchenye Zapiski Gor'kovsk. Univ. *1953*, No. 24, 183; Chem. Abstr. *50*, 8461 (1956).

[42] *H. Lind*, Dissertation, Universität Würzburg, 1964.

[43] Azodibenzoyl is slowly converted into dibenzoylhydrazine when allowed to stand in air.

[44] *L. Horner* and *W. Naumann*, Liebigs Ann. Chem. *587*, 81 (1954).

[45] *R. Cramer*, J. Amer. chem. Soc. *79*, 6215 (1957).

[46] *R. Stollé* and *W. Reichert*, J. prakt. Chem. *123*, 82 (1929).

[47] *D. Mackay*, *U. F. Marx*, and *W. A. Waters*, J. chem. Soc. (London) *1964*, 4793.

[47a] *C. G. Pitt*, J. org. Chemistry *30*, 3242 (1965).

The products obtained on photochemical decomposition of azodibenzoyl in benzene are the same as those formed on thermal decomposition [4].

The salts of azodicarboxylic acid, which can be obtained by hydrolysis of the esters, decompose on acidification to give carbon dioxide and diimine [48]. Similarly, phenylazocarboxylic acid gives phenyldiimine, the intermediate formation of which was demonstrated by trapping with aldehydes to form hydrazides [49–50a]. The alkali metal salts of the arylazocarboxylic acids (prepared by hydrolysis of the amides or esters) can be used as arylating agents (preparation of organomercury, organoarsenic, and organoantimony compounds) [51].

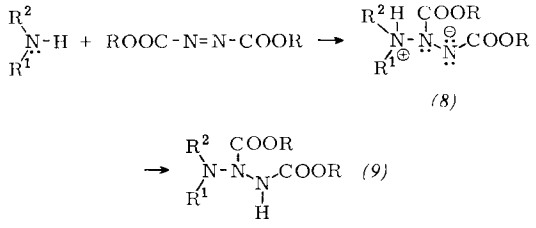
### 4.2. Electrophilic Addition

#### 4.2.1. Substitutive Electrophilic Addition to Amines

The reactions of the diesters of azodicarboxylic acid with amines are among the earliest known reactions of α-carbonyl azo compounds. Primary aliphatic amines lead to azodicarboxamides [52–54]. Piperidine and β-aminopyridine behave analogously [55].

$$ROOC{-}N{=}N{-}COOR \xrightarrow{+2R'NH_2} R'NH{-}OC{-}N{=}N{-}CO{-}NHR'$$

The reaction follows an entirely different course when secondary aliphatic amines are used. In this case, addition of the amine to a boiling solution of the ester in ether leads to an electrophilic attack of the ester (probably with initial formation of the betaine *(8)* [2]) and formation of a triazane *(9)*.

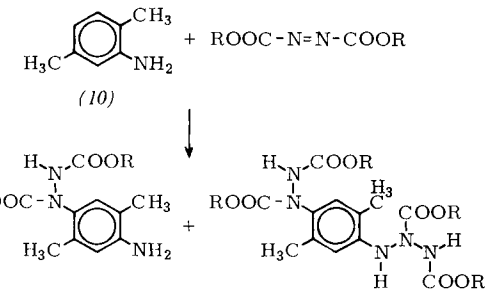


*(8)*



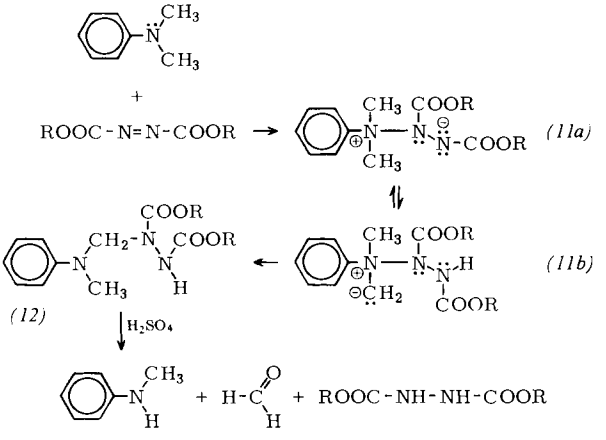
*(9)*

Aromatic amines represent a special case, since some of these (*e.g.* aniline, *o*-toluidine, and *p*-toluidine) yield the triazane derivative *(9)*, whereas others (*e.g.* α- and β-naphthylamine) undergo ring substitution [52,54,56,57]. Both modes of reaction are observed simultaneously with 2,5-dimethylaniline *(10)* [52].



*(10)*

Tertiary amines such as *N,N*-dimethylaniline add to diesters of azodicarboxylic acid under mild conditions. The products, presumably formed by ylide rearrangement of the intermediate *(11b)* [2,58], are the hydrazinedicarboxylic acid derivatives *(12)*, which decompose into secondary amines, aldehydes, and diesters of hydrazinedicarboxylic acid on treatment with boiling 2N sulfuric acid [2,59]. *Diels* suggested this reaction as a method of dealkylating tertiary amines [59,60].



*(11a)*

*(11b)*

*(12)*

*Huisgen* and *Jakob* [58] showed that the attack of the azodicarboxylate on the tertiary amine is electrophilic. They observed that the rate of this reaction increases with the basicity of the amine.

*N,N'*-Dimethyl and *N,N'*-diethylazodicarboxamide behave in the same way as the diesters of azodicarboxylic acid [52]. Azodibenzoyl undergoes a similar reaction with *N,N*-dimethylaniline at room temperature to form *N*-methylaniline, 1,2-dibenzoylhydrazine, formaldehyde, and *p*-(1,2-dibenzoylhydrazino)dimethylaniline [44,61,63].

[48] Cf. the survey of the reactions of diimine by *S. Hünig, H. R. Müller,* and *W. Thier,* Angew. Chem. *77,* 368 (1965); Angew. Chem. internat. Edit. *4,* 271 (1965).

[49] *A. Angeli,* Gazz. chim. ital. *47,* 220 (1917).

[50] *A. Pieroni* and *G. Giannini,* Gazz. chim. ital. *54,* 162 (1924).

[50a] Cf. *A. Nagasaka* and *R. Oda,* J. chem. Soc. Japan, Ind. Chem. Sect. *58,* 48 (1955); Chem. Abstr. *50,* 4903 (1956).

[51] *A. N. Nesmeyanov* and *O. A. Reutov,* Izvest. Akad. Nauk. SSSR, Otdel Khim. Nauk *1949,* 611, Chem. Abstr. *44,* 7791 (1950); *1948,* 316, Chem. Abstr. *43,* 171 (1949); *O. A. Reutov* and *Y. G. Bundel, ibid. 1952,* 1041, Chem. Abstr. *48,* 623 (1954); *O. A. Reutov* and *O. A. Ptitsyna, ibid. 1952,* 93, Chem. Abstr. *47,* 1631 (1953).

[52] *O. Diels,* Liebigs Ann. Chem. *429,* 1 (1922).

[53] *O. Diels* and *M. Paquin,* Ber. dtsch. chem. Ges. *46,* 2000 (1913).

[54] *O. Diels* and *P. Fritzsche,* Ber. dtsch. chem. Ges. *44,* 3018 (1911).

[55] *O. Diels* and *G. Behnen,* Ber. dtsch. chem. Ges. *56,* 561 (1923).

[56] *K. E. Cooper* and *E. H. Ingold,* J. chem. Soc. (London) *1926,* 1894.

[57] *G. S. Misra* and *S. B. Srivastava,* J. Indian chem. Soc. *37,* 177 (1960), Chem. Abstr. *55,* 22249 (1961).

[58] *R. Huisgen* and *F. Jakob,* Liebigs Ann. Chem. *590,* 37 (1954).

[59] *O. Diels,* Ber. dtsch. chem. Ges. *54,* 213 (1921); *O. Diels* and *H. Wackermann, ibid. 55,* 2443 (1922).

[60] *O. Diels* and *E. Fischer,* Ber. dtsch. chem. Ges. *47,* 2043 (1914).

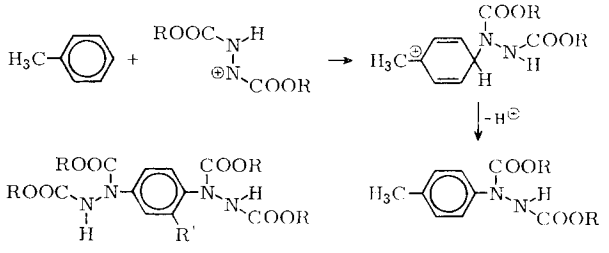
[61] Cf. the reaction of aniline and *N,N*-dimethylaniline with azodibenzoyl: *R. Stollé,* Ber. dtsch. chem. Ges. *45,* 2680 (1912).

[62] *R. Huisgen, F. Jakob, W. Siegel,* and *A. Cadus,* Liebigs Ann. Chem. *590,* 1 (1954); cf. also *R. Huisgen,* Österr. Chemiker-Ztg. *55,* 237 (1954).

[63] *R. Stollé* and *K. Leffler,* Ber. dtsch. chem. Ges. *57,* 1061 (1924).

### 4.2.2. Substitutive Electrophilic Addition to Aromatic Compounds

Another type of electrophilic addition is the reaction of α,α′-dicarbonyl azo compounds with aromatic compounds (*e.g.* hydrocarbons and ethers), which proceeds with ring substitution to yield the hydrazinedicarboxylic acid derivatives *(13)* [62–65]. Depending on the aromatic system, the reaction sometimes takes place when the reactants are simply warmed in an inert solvent, but it generally requires the addition of catalytic quantities of acid.



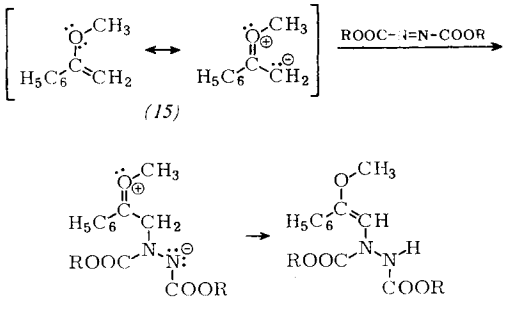
*(14a)*: R′ = $CH_3$, *(14b)*: R′ = H  *(13)*

On addition of a little concentrated sulfuric acid, diethyl azodicarboxylate reacts exothermically with toluene to give a mixture of the 1:1 and 1:2 adducts *(13)* and *(14a)*. Under the same conditions, benzene gives the 1:2 adduct *(14b)*, even when present in excess with respect to the diethyl azodicarboxylate [62].

The reaction of mesitylene with diesters of azodicarboxylic acid in the presence of $BF_3$ has been described by *Carlin* and *Moores* [66].

### 4.2.3. Substitutive Electrophilic Addition to Olefins

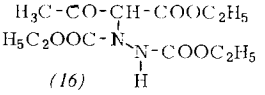
Esters of azodicarboxylic acid add electrophilically to vinyl ethers such as *(15)* to form hydrazine derivatives [67, 68].



*(15)*

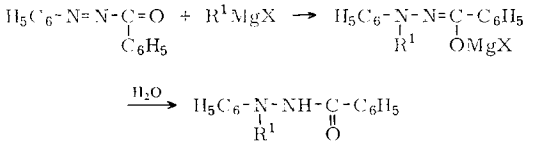
### 4.2.4. Electrophilic Addition to CH Acids and Grignard Compounds

Diethyl azodicarboxylate and esters of phenylazocarboxylic acid react with sodium salts of CH acids such as acetoacetic ester, cyanoacetic ester, and acetylacetone to form substituted hydrazines [69, 70]; for example, diethyl azodicarboxylate and sodium acetoacetate give the compound *(16)*.



*(16)*

α-Carbonyl azo compounds such as benzoylazobenzene, azodibenzoyl, and diesters of azodicarboxylic acid undergo 1,4-additions with Grignard reagents to form substituted hydrazides, *e.g. (17)* [7, 71].



*(17)*

### 4.2.5. Electrophilic Addition to Diazo Compounds

α,α′-Dicarbonyl azo compounds such as esters of azodicarboxylic acid, azodibenzoyl, and azodiacetyl react readily with diazoalkanes and diazoacetic esters to liberate nitrogen. However, the products are not, as had been assumed [72–75], derivatives of the diaziridine system *(18)* [76], but either hydrazones *(23)* or oxadiazolines *(19)* [77–81, 81a–81c], depending on the reaction conditions. The diazo compound first undergoes

[64] *R. Stollé* and *G. Adam*, J. prakt. Chem. *111*, 167 (1925); *R. Stollé* and *W. Reichert*, *ibid. 123*, 74 (1929).

[65] *O. Diels*, *S. Schmidt*, and *W. Witte*, Ber. dtsch. chem. Ges. *71*, 1186 (1938).

[66] *R. B. Carlin* and *W. S. Moores*, J. Amer. chem. Soc. *84*, 4107 (1962).

[67] *R. Huisgen* and *H. Pohl*, Chem. Ber. *93*, 527 (1960).

[68] *K. Alder* and *H. Niklas*, Liebigs Ann. Chem. *585*, 97 (1954).

[69] *T. N. Ghosh* and *P. C. Guha*, J. Indian Inst. Sci. *16*, 103 (1933), Chem. Abstr. *28*, 2691 (1934).

[70] Vgl. *O. Diels* and *H. Behncke*, Ber. dtsch. chem. Ges. *57*, 653 (1924).

[71] *R. Stollé* and *W. Reichert*, J. prakt. Chem. *122*, 344 (1929).

[72] *E. Müller*, Ber. dtsch. chem. Ges. *47*, 3001 (1914).

[73] *H. Staudinger* and *A. Gaule*, Ber. dtsch. chem. Ges. *49*, 1961 (1916).

[74] *O. Diels* and *H. König*, Ber. dtsch. chem. Ges. *71*, 1179 (1938).

[75] *L. Horner* and *E. Lingnau*, Liebigs Ann. Chem. *591*, 21 (1955).

[76] Diaziridine and diazetidine structures have also been proposed for the products of the reaction of azopyridine and azoquinoline derivatives and of esters of quinolylazocarboxylic acid with diazomethane and diphenyldiazomethane; *M. Colonna* and *A. Risaliti* [158], and Gazz. chim. ital. *87*, 923 (1957), *89*, 2493 (1959); *M. Colonna*, Atti Accad. naz. Lincei, Rend., Cl. Sci. fisice, mat. natur. *26*, 248 (1959), Chem. Abstr. *54*, 3420 (1960); *A. Risaliti* and *A. Monti*, Gazz. chim. ital. *90*, 397 (1960); cf. *E. Jolles*, *M. Ridi*, and *G. Long*, *ibid. 68*, 496 (1938).

[77] *F. Scheckenbach*, Dissertation, Universität Würzburg, 1961.

[78] *K. Döppert*, Dissertation, Universität Würzburg, 1965.

[79] *K. Königsdorfer*, Dissertation, Universität Würzburg, 1965.

[80] *E. Fahr*, *K. Döppert*, and *F. Scheckenbach*, Angew. Chem. *75*, 670 (1963); Angew. Chem. internat. Edit. *2*, 480 (1963).

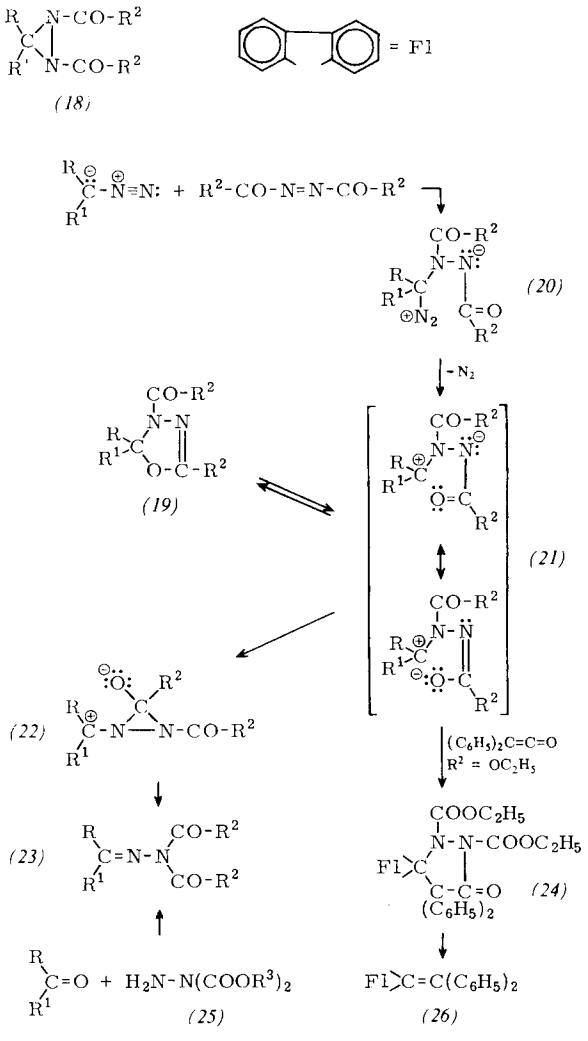
[81] *R. Breslow*, *C. Yaroslavsky*, and *S. Yaroslavsky*, Chem. and Ind. *1961*, 1961.

[81a] *G. F. Bettinetti* and *L. Capretti*, Gazz. chim. ital. *95*, 33 (1965).

[81b] *G. F. Bettinetti* and *P. Grünanger*, Tetrahedron Letters *1965*, 2553.

[81c] *Bettinetti* and *Capretti* [81a] discuss an oxadiazoline structure for the product of the reaction of diphenyldiazomethane with azodibenzoyl. We have however shown that it has the dibenzoylhydrazone structure *(23e)* [79].

electrophilic attack by the α,α′-dicarbonyl azo compound, probably with formation of the diazonium compound *(20)*, which then decomposes into *(21)* with liberation of nitrogen.



*(19a)*: R/R¹ = Fl; R² = OR³
*(19b)*: R/R¹ = Fl; R² = $OC_2H_5$
*(19c)*: R = H; R¹ = COOR⁴; R² = OR³
*(19d)*: R/R¹ = Fl; R² = $CH_3$
*(19e)*: R = H; R¹ = COOR³; R² = $C_6H_5$
*(19f)*: R = R¹ = H; R² = $C_6H_5$
*(23a)*: R/R¹ = Fl; R² = OR³
*(23b)*: R = H; R¹ = COOR⁴; R² = OR³
*(23c)*: R = H; R¹ = CO–R⁴; R² = OR³
*(23d)*: R/R¹ = Fl; R² = $C_6H_5$
*(23e)*: R = R¹ = R² = $C_6H_5$
*(23f)*: R = H; R¹ = CO–R⁴; R² = $C_6H_5$
*(23g)*: R/R¹ = Fl; R² = $CH_3$

The subsequent reaction of *(21)* depends on the groups R, R¹, and R², and on the reaction conditions. In the products obtained from diazofluorene and diesters of azodicarboxylic acid, a new form of ring/chain isomerism is observed. The products exist in the solid state as oxadiazolines *(19a)*; in solution, on the other hand, an equilibrium [80] is established between *(19a)* and the isomeric form *(21)* [82]. Thus the oxadiazoline *(19b)* in mixed solvents has isosbestic points at 242 and 263 mμ (measured in dichloromethane/n-heptane).

[82] For nomenclature see *R. Huisgen* and *A. Eckell*, Tetrahedron Letters *1960*, 5; *R. Huisgen, R. Grashey, P. Laur*, and *H. Leitermann*, Angew. Chem. *72*, 416 (1960).

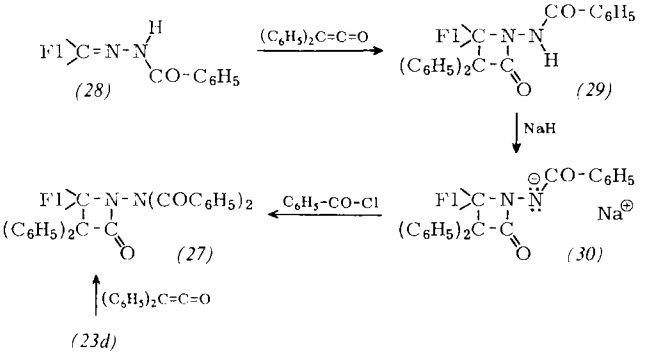
The azomethinimine *(21b)* [R/R¹=biphenylylene ("Fl"), R² = $OC_2H_5$] can also be trapped by 1,3-dipolar addition with diphenylketene to form *(24)*, the structure of which has been proved, *inter alia*, by degradation to the olefin *(26)*. As the dielectric constant of the solvent and the temperature increase, the equilibrium *(19)* ⇌ *(21)* is displaced to the right. Above 50 °C, *(21)* starts to undergo irreversible isomerization to the ester *(23a)* of the hydrazonedicarboxylic acid (where R² = $OC_2H_5$), probably *via* the azomethinimine *(22)*. The structure *(23)* can be proved by comparison with the products obtained when fluorenone reacts with asymmetric diesters of hydrazinedicarboxylic acid.

The reaction of diphenyldiazomethane with diethyl azodicarboxylate also leads to the intermediate *(21)* (where R = R¹ = $C_6H_5$, R² = $OC_2H_5$), which undergoes 1,3-dipolar reactions with dimethyl acetylenedicarboxylate and phenylisocyanate [81a, 81b].

The reaction of diazoacetic esters with diesters of azodicarboxylic acid below 80–100 °C leads to the oxadiazolines *(19c)*, which do not isomerize either in solution or when heated alone [83]. The same reactants above 80–100 °C give the isomeric ester *(23b)* of hydrazonedicarboxylic acid.

Even diazoketones are sufficiently nucleophilic to react with diesters of azodicarboxylic acid; however, a reaction temperature of over 100 °C is necessary. The raction yields esters *(23c)* of hydrazonedicarboxylic acids, which can very readily be broken down into the α-oxoaldehydes (yields between 75 and 93 %, determined as the osazones). The reaction can also be carried out in the sugar series [84].

The reaction of diazofluorene, diphenyldiazomethane, or diazoketones with azodibenzoyl yields the dibenzoylhydrazones *(23d)*, *(23e)* [81c], and *(23f)*. Compound *(23d)* reacts with diphenylketene to give the azetidinone *(27)*, the structure of which was proved by synthesis from the monobenzoylhydrazone *(28)* [79].

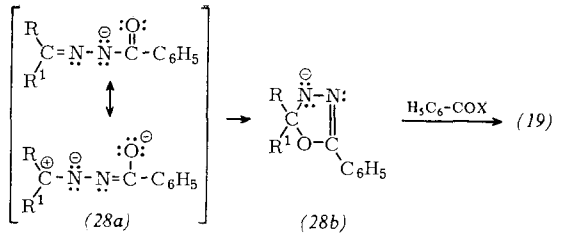


Compound *(28)* reacts with diphenylketene to give the azetidinone *(29)*, which reacts in turn with sodium hydride to form the anion *(30)*. Benzoylation of *(30)* leads to *(27)*.

The obvious "proof" of the dibenzoylhydrazone structure [*(23d)*, *(23e)*, *(23f)*] by reaction of the monobenzoylhydrazone with metallic sodium or potassium, or with sodium hydride to the anion *(28a)*, is not reliable, since the oxadiazoline *(19)* can also be formed in this case *via* *(28b)*. In the method used, this possibility is ruled out by the fact that the C=N bond is fixed in *(29)* by diphenylketene.

[83] An exception is the oxadiazoline obtained from ethyl diazoacetate and dibenzyl azodicarboxylate, which isomerizes to the ester of the hydrazonedicarboxylic acid when heated [77].

[84] *E. Fahr* and *F. Scheckenbach*, Liebigs Ann. Chem. *655*, 86 (1962).

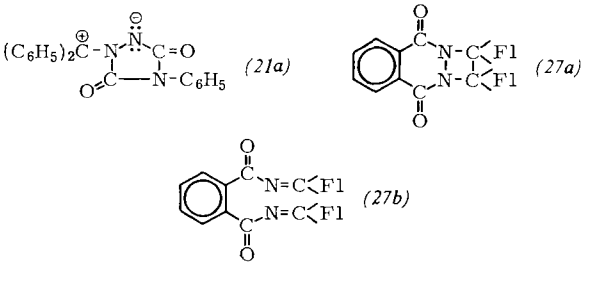


(28a) (28b) (19)

The proof of the structure of the dibenzoylhydrazone *(23d)* by synthesis from *(28)* [85] made possible the use of infrared spectra to verify the dibenzoylhydrazone structure of the products obtained by the reaction of diazoketones with azodibenzoyl.

The reaction of diazofluorene with azodiacetyl, on the other hand, leads to the oxadiazoline *(19)*. Diazofluorene and azodicarboxamide react to form fluorenone semicarbazone [77]. When *(19d)* is heated, it rearranges to give the diacetylhydrazone *(23g)*. The action of diazoacetic esters or diazomethane [79,81] on azodibenzoyl leads to the oxadiazolines *(19e)* or *(19f)*. α,α'-Dicarbonyl diazo compounds having the structure R–CO–$CN_2$–CO–R', such as methyl benzoyldiazoacetate, benzoyldiazoacetone, dibenzoyldiazomethane, and diazodimedone, as well as azibenzil (1-diazo-2-oxo-1,2-diphenylethane) are not sufficiently nucleophilic for reaction with α,α'-dicarbonyl azo compounds. Attempts to force the reaction by heating lead to decomposition of the diazo compounds into nitrogen and a carbene; the carbene rearranges to the ketene, which either adds to the azo compound or dimerizes and resinifies (cf. Section 4.8).

Cyclic α,α'-dicarbonyl azo compounds react in different ways with diazo compounds. Thus *(4)* reacts with diphenyldiazomethane to form the cyclic azomethinimine *(21a)* [81a, 81b], whereas the reaction of *(3)* with diazofluorene leads to the unstable tricyclic diazetidine derivative *(27a)*, which isomerizes when heated to yield *(27b)* [79].



(21a) (27a) (27b)

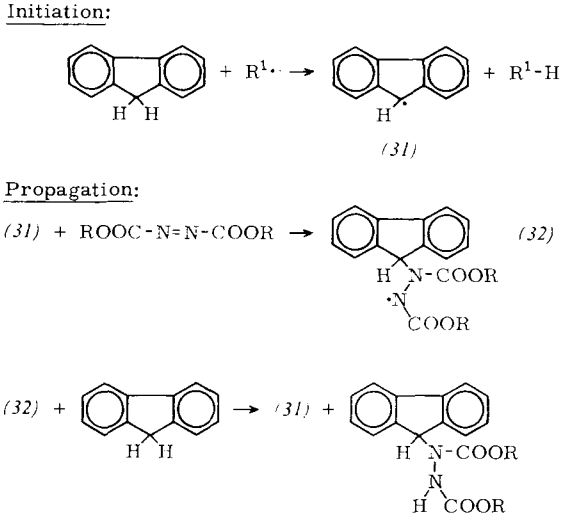
## 4.3. Substitutive Addition by a Free-Radical Chain Mechanism

### 4.3.1. Addition to Aromatic Side Chains and Olefins

*Huisgen, Jakob, Siegel,* and *Cadus* [62] carried out an extensive study in which they found that the reaction of aromatic compounds with diesters of azodicarboxylic acid formally follows the same pattern as the halogenation of aromatic compounds. In polar media, electrophilic ring substitution takes place, whereas in the presence of free-radical initiators this reaction is replaced by free-radical addition to side chains [86].

To induce such a free-radical reaction, it is not essential to add free-radical initiators; if the reaction mixture is heated to a sufficiently high temperature, the dissociation of the azodicarboxylate in accordance with ROOC–N=N–COOR → 2 ROOC· + $N_2$ yields free radicals which can initiate the reaction.

The reaction conditions can therefore be chosen in such a way as to direct the addition either into the ring or into the side chain [62].

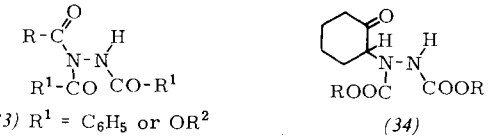


(31) (32)

Similar behavior is observed in the substitution of the allyl position in some cyclic mono-olefins with diesters of azodicarboxylic acid [58, 67]. In this case, however, the free radical substitution may compete with substitution *via* a cyclic transition state (cf. Section 4.4).

### 4.3.2. Addition to Aldehydes and Ketones

Aldehydes react readily with diesters of azodicarboxylic acid and with azodibenzoyl to give the hydrazine derivative *(33)*. The reaction proceeds by a free-radical chain mechanism [58, 44, 87]. As was shown by *Huisgen* and *Jakob* [58], free-radical and ionic mechanisms compete in the reaction of cyclohexanone with diesters of azodicarboxylic acid; however, both mechanisms lead to the same product *(34)*.



(33) $R^1$ = $C_6H_5$ or $OR^2$ (34)

## 4.4. Substitutive Addition to Olefins via a Cyclic Transition State

Olefins behave in various ways towards diesters of azodicarboxylic acid. The latter add by an ionic mechanism

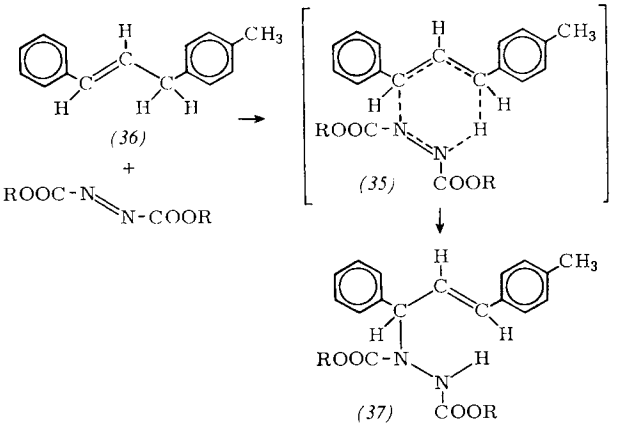
[85] The rather laborious proof of the structures of *(23d)* and *(27)* was necessary because, according to [81], the reaction of esters of diazoacetic acid and diazomethane with azodibenzoyl leads to oxadiazoline derivatives, so that we originally also assigned an oxadiazoline structure to the product obtained from diazofluorene and azodibenzoyl; cf. [80].

[86] *Horner* and *Naumann* [44] also proposed a free-radical mechanism for the addition of esters of azodicarboxylic acid to tetralin.

[87] *K. Alder* and *T. Noble*, Ber. dtsch. chem. Ges. *76*, 54 (1943).

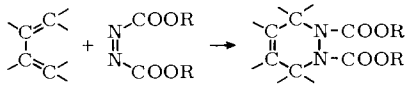
to the β-C atom of vinyl ethers, whereas the reaction with cyclic mono-olefins leads to substitutive addition by a free-radical chain mechanism. Sterically unhindered 1,3-dienes and styrene give diene reactions. Diesters of azodicarboxylic acid can also add to olefins in the allyl position with shift of the double bond [88]; this reaction in many cases proceeds by a mechanism [67] that cannot be influenced either by free-radical initiators or inhibitors or by polar catalysts. The reaction proceeds in a one-step process *via* the cyclic transition state *(35)* (formulated for the reaction of the olefin *(36)* with diesters of azodicarboxylic acid to form *(37)* [67]). A similar transition state [89] has been proposed for the reaction of acyclic aliphatic olefins and 1,3- and 1,4-cyclohexadiene [90–94].

The reaction of 1,2- or 1,4-dihydronaphthalene proceeds not only *via* the cyclic transition state, but also to a small extent by a free-radical mechanism [67]. The reaction of cycloheptatriene with azodicarboxylates probably also involves a cyclic transition state [95,96].



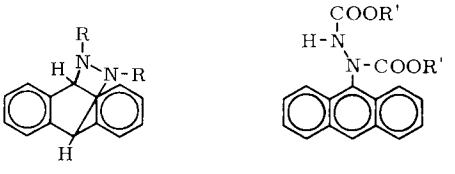

Some reactions of olefins with α-carbonyl azo compounds cannot be unambiguously assigned a mechanism (see [97]).

α,α′-Dicarbonyl azo compounds are among the strongest dienophiles known. The reaction with dienes was first observed by *Diels*, *Blom* and *Koll* [98] for diethyl azodicarboxylate and cyclopentadiene.



Other suitable diene components, apart from cyclopentadiene [5,98,99,105], include butadiene, isoprene, substituted butadienes, and cylic dienes [100–109,93,94]. Whereas 2,3-dimethylbutadiene gives the diene adduct, the addition does not take place with 2,5-dimethylhexa-2,4-diene and 2,4-dimethylpenta-1,3-diene because of steric hindrance [93,13,94], and substitutive addition occurs instead. Anthracene also gives an unstable adduct *(38)* [65,101,103,110], which is converted into the ring-substituted derivative *(39)* on treatment with acid [101,111].

The behavior of 1,3-cyclohexadiene as the diene component depends on the conditions. *Cohen* and *Zand* [104, 104a] obtained a diene adduct, whereas *Gillis* and *Beck* [93] observed substitutive addition to form the hydrazinedicarboxylic acid derivative. *Franzus* [91,92]



*(38)*: R = COOR′ *(39)*

*(40)*: R = H

[88] *K. Alder, F. Pascher*, and *A. Schmitz*, Ber. dtsch. chem. Ges. *76*, 27 (1943).

[89] Cf. *H. P. Koch*, J. chem. Soc. (London) *1948*, 1111.

[90] *W. A. Thaler* and *B. Franzus*, J. org. Chemistry *29*, 2226 (1964).

[91] *B. Franzus* and *J. H. Surridge*, J. org. Chemistry *27*, 1951 (1962).

[92] *B. Franzus*, J. org. Chemistry *28*, 2954 (1963).

[93] *B. T. Gillis* and *P. E. Beck*, J. org. Chemistry *27*, 1947 (1962).

[94] *B. T. Gillis* and *P. E. Beck*, J. org. Chemistry *28*, 3177 (1963).

[95] *G. O. Schenck, E. Koerner v. Gustorf, B. Kim, G. v. Bünau*, and *G. Pfundt*, Angew. Chem. *74*, 510 (1962), Angew. Chem. internat. Edit. *1*, 516 (1962).

[96] *J. M. Cinnamon* and *K. Weiss*, J. org. Chemistry *26*, 2644 (1961).

[97] *O. Diels*, Ber. dtsch. chem. Ges. *55*, 1524 (1922) (cf. also [52]); *A. Risaliti*, Boll. sci. Fac. Chim. ind. Bologna *20*, 75 (1962), Chem. Abstr. *58*, 4519 (1963); *A. Risaliti* and *P. Bruni*, Ann. Chimica *53*, 595 (1963), Chem. Abstr. *59*, 9865 (1963); *O. Achmatowicz* and *O. Achmatowicz Jr.*, Roczniki Chem. *37*, 317 (1963), Chem. Abstr. *59*, 12655 (1963); *T. Suzuki* and *R. Oda*, Bull. Inst. chem. Res., Kyoto Univ. *30*, 48 (1952), Chem. Abstr. *47*, 5357 (1953); *R. Y. Levina, Y. S. Shabarov*, and *M. G. Kuzmin*, Doklady Akad. Nauk SSSR *131*, 1080 (1960), Chem. Abstr. *54*, 20838 (1960); *V. R. Skvarchenko, M. G. Kuzmin*, and *R. Y. Levina*, Vestnik Moskov. Univ. *12* Ser. Mat., Mekh. Astronom. Fiz., Khim. No. *3*, 169 (1957), Chem. Abstr. *52*, 6358 (1958); cf. also [20, 68, 88].

[98] *O. Diels, J. H. Blom*, and *W. Koll*, Liebigs Ann. Chem. *443*, 242 (1925).

[99] *J. G. Kuderna, J. W. Sims, J. F. Wikstrom*, and *S. B. Soloway*, J. Amer. chem. Soc. *81*, 382 (1959).

[100] *O. Diels* and *K. Alder*, Liebigs Ann. Chem. *450*, 237 (1926).

[101] *K. Alder, H. Niklas, R. Aumüller*, and *B. Olsen*, Liebigs Ann. Chem. *585*, 81 (1953).

[102] *L. E. Gast, E. W. Bell*, and *H. M. Teeter*, J. Amer. Oil Chemists' Soc. *33*, 278 (1956), Chem. Abstr. *50*, 10426 (1956).

[103] *J. Harley-Mason* and *J. C. W. Tims*, Proc. chem. Soc. (London) *1963*, 335.

[104] *S. G. Cohen* and *R. Zand*, J. Amer. chem. Soc. *84*, 586 (1962).

[104a] See also *R. Askani*, Chem. Ber. *98*, 2551 (1965).

[105] *N. I. Vasilev, I. S. Levina, Y. S. Shabarov*, and *R. Y. Levina*, Zh. obshch. Khim. *33*, 734 (1963), Chem. Abstr. *59*, 8165 (1963).

[106] *P. Baranger, J. Levisalles*, and *M. Viudart*, C. R. hebd. Séances Acad. Sci. *236*, 1365 (1953), Chem. Abstr. *48*, 2715 (1954).

[107] *P. Baranger* and *J. Levisalles*, Bull. Soc. chim. France *1957*, 704.

[108] *S. G. Cohen, S. Hsiao, E. Saklad*, and *C. H. Wang*, J. Amer. chem. Soc. *79*, 4400 (1957).

[109] *Y. K. Yurev* and *N. S. Zefirov*, Zhur. obshch. Khim. *29*, 2954 (1959), Chem. Abstr. *54*, 12093 (1960).

[110] See *C. W. Huffman*, Canad. J. Chem. *41*, 1018 (1963), Chem. Abstr. *59*, 3847 (1963).

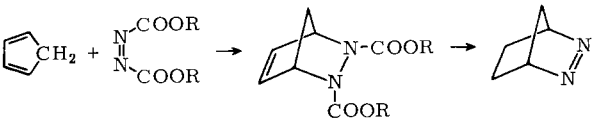
[111] The acid cleavage of the diene adduct obtained from diesters of azodicarboxylic acid and cyclopentadiene was studied by *J. K. Stille* and *T. Anyos*, J. org. Chemistry *27*, 3352 (1962).

showed that the diene reaction and the substitutive addition occur simultaneously. Diaroylazo compounds also take part in diene reactions [105, 13, 106, 112], and the reaction of styrene with azodicarboxylates can be interpreted as a diene reaction [100, 68, 113, 119].

Detailed kinetic studies have shown that the diene reaction of the azodicarboxylates is faster in polar than in non-polar solvents, and that the reaction in non-polar solvents is accelerated by the addition of acid. Moreover, the reactivities of the azodicarboxylates decrease with increasing size of the alkoxycarbonyl group. Thus the dimethyl ester reacts 5 to 6 times as rapidly as the diethyl ester [33], while the di-t-butyl ester reacts only with the more active diene components [7]. The reaction of cyclopentadiene with substituted azodibenzoyl derivatives is accelerated by electron-attracting substituents on the aromatic ring [105].

Particularly marked dienophilic activity is shown by *cis*-α,α′-dicarbonyl azo compounds; for example, diethyl *cis*-azodicarboxylate reacts about 30 times as rapidly as the "normal" diethyl azodicarboxylate [28, 29, 104a]. The cyclic azo compounds *(1)* to *(4)* react even at temperatures far below 0 °C [16, 18, 19, 19a].

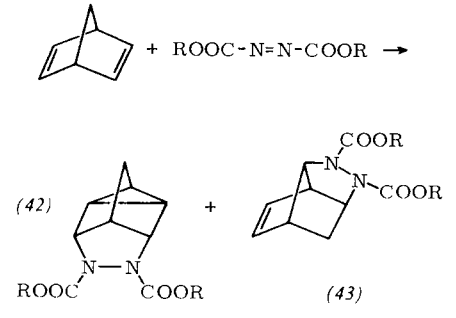
Diene reactions with diesters of azodicarboxylic acid, followed by hydrolysis, decarboxylation, and oxidation of the diene adduct, provide an excellent method for the preparation of cyclic azo compounds [98, 5, 108, 104, 94, 114, 115]. *Diels et al.* [98] used this method to prepare the bicyclic azo compound *(41a)*, which they converted into *(41b)* by hydrogenation, hydrolysis, decarboxylation, and oxidation.



*(41a)* *(41b)*

According to *Corey* and *Mock* [116], hydrolysis and decarboxylation of the adduct *(38)*, which is obtained from anthracene and diethyl azodicarboxylate, leads to the product *(40)*, which decomposes when heated to anthracene and diimine.

Monocarbonyl azo compounds do not give diene reactions, with the exceptions of the cyclic compound *(5)* and ethyl cyanoazocarboxylate [103].



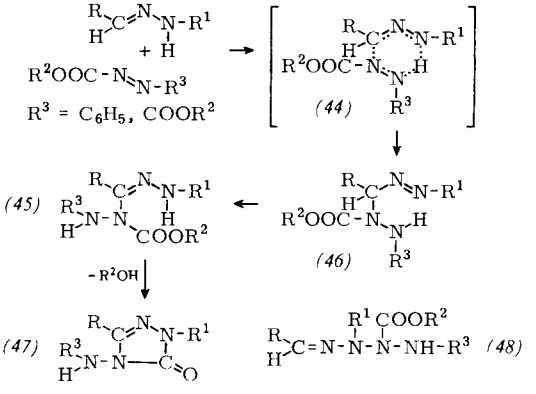
*(42)* *(43)*

Norbornadiene reacts with diesters of azodicarboxylic acid in a reaction known as a "homoconjugated Diels-Alder addition" to give a mixture of *(42)* and *(43)* [117, 118].

### 4.6. Addition to Aldehyde Phenylhydrazones

The reaction of aldehyde phenylhydrazones with diesters of azodicarboxylic acid or esters of phenylazocarboxylic acid leads to 1:1 adducts, for which *Busch, Müller,* and *Schwarz* [120] proposed the tetrazane structure *(48)*, whereas *Gillis* and *Daniher* [121] proposed the isomeric hydrazidine structure *(45)*. The adducts are readily converted into the triazoline derivatives *(47)* by heat or by treatment with acid or alkali.

However, ultraviolet, NMR, and infrared spectroscopic studies by the present authors showed that the adducts possess the azohydrazino structure *(46)* [122, 123]. On careful dissolution in pyridine, they isomerize to the very unstable hydrazidines *(45)*, which lose alcohol to form *(47)*. We believe that this reaction also involves a cyclic transition state *(44)*.



*(44)* *(45)* *(46)* *(47)* *(48)*

### 4.7. Reactions of Diesters of Azodicarboxylic Acid with Hydrazines, Hydrazides, and Hydrazones

Phenylhydrazine and *o*-tolylhydrazine react very vigorously, even at room temperature, with diethyl azodicarboxylate. In addition to diethyl hydrazinedicarboxylate, we obtained benzene (43 % yield) or toluene (63 % yield). Benzoylhydrazine or acetylhydrazine reacts with diethyl azodicarboxylate to give 1,2-dibenzoylhydrazine (73 % yield) or 1,2-diacetylhydrazine (41 % yield), with vigorous evolution of nitrogen [123].

The reactions of the aryl- and acylhydrazines with diesters of azodicarboxylic acid can be explained either

[112] *Y. S. Shabarov, N. I. Vasilev,* and *R. Y. Levina,* Doklady Akad. Nauk SSSR *129*, 600 (1959), Chem. Abstr. *54*, 14259 (1960).

[113] *N. Rabjohn* and *H. M. Molotsky,* J. Amer. chem. Soc. *77*, 2907 (1955).

[114] *R. Criegee* and *A. Rimmelin,* Chem. Ber. *90*, 414 (1957).

[115] *J. Pirsch* and *J. Jörgl,* Ber. dtsch. chem.Ges. *68*, 1324 (1935).

[116] *E. J. Corey* and *W. L. Mock,* J. Amer. chem. Soc. *84*, 685 (1962).

[117] *S. J. Cristol, E. L. Allred,* and *D. L. Wetzel,* J. org. Chemistry *27*, 4058 (1962).

[118] *R. M. Moriarty,* J. org. Chemistry *28*, 2385 (1963).

[119] *C. K. Ingold* and *S. D. Weaver,* J. chem. Soc. (London) *127*, 378 (1925).

[120] *M. Busch, H. Müller,* and *E. Schwarz,* Ber. dtsch. chem. Ges. *56*, 1600 (1923).

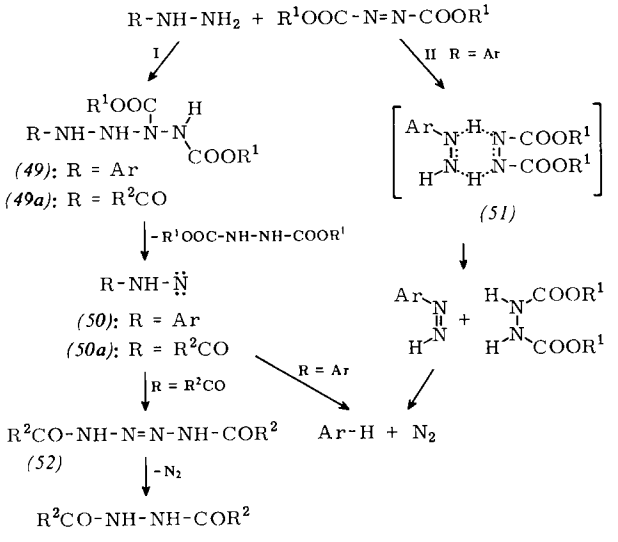
[121] *B. T. Gillis* and *F. A. Daniher,* J. org. Chemistry *27*, 4001 (1962).

[122] *E. Fahr* and *H. D. Rupp,* Angew. Chem. *76*, 684 (1964), Angew. Chem. internat. Edit. *3*, 693 (1964).

[123] *H. D. Rupp,* Dissertation, Universität Würzburg, 1964.

(as in the case of the amines) as an electrophilic addition (route I) of the ester to form the tetrazane *(49)* or *(49a)*, which then decomposes into the diester of hydrazinedicarboxylic acid and the fragment *(50)* or *(50a)*, or as a direct dehydrogenation (route II), possibly *via* the transition state *(51)* for the arylhydrazines [124]. *(50)* then loses nitrogen to form the hydrocarbon, whereas *(50a)* is converted into the diacylhydrazine *via* the intermediate tetrazene *(52)* [125].

Attempts to isolate the tetrazane derivatives *(49)* and *(49a)* and the tetrazenes *(52)* or to intercept the fragments *(50)* and *(50a)* were unsuccessful [123].



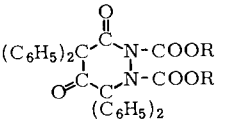

Asymmetric dialkyl- and diarylhydrazines react with azodicarboxylates to form tetrazenes [126]. The reaction is probably similar to that of acylhydrazines.

The action of diethyl azodicarboxylate on hydrazones (the hydrazones of benzaldehyde, benzophenone, and fluorenone were studied) leads to azines (yields: 30, 41, and 33 %, respectively), probably *via* the diazo compound [123]. This reaction can again be interpreted as involving a tetrazane similar to *(49)*, which decomposes into the diazo compound and the diesters of hydrazinedicarboxylic acid.

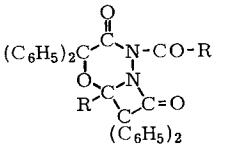
### 4.8. Cycloadditions of α-Carbonyl Azo Compounds to Ketenes and Olefins

The reaction of a ketene with an α-carbonyl azo compound was first studied by *Ingold* and *Weaver* [119]. On mixing diethyl azodicarboxylates with diphenylketene, these authors obtained a 1:2 adduct, for which they proposed the structure *(53)*. We have found that this adduct has the structure *(54)* [127–129].

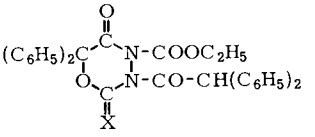
When heated with ethanol, *(54)* is converted into *(55)*; this reacts with alkali to form diphenylacetic acid and *(56)*, while with dilute acid it gives *(57)*. Moreover, when *(54)* is boiled in water, or better, with dilute acid, it forms *(57)*, which is converted into benzilic diphenylacetic hydrazide *(59)* on treatment with alkali. Compound *(56)* reacts with dilute acid to give *(58)*, which can be converted into *(57)* by reaction with diphenylacetyl chloride. When heated, *(54)* is



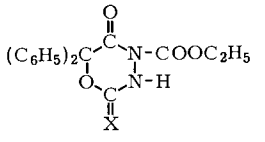

*(53)*



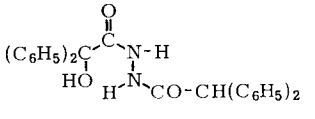

*(54)*: R = $OC_2H_5$



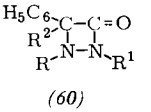

*(55)*: X = $(OC_2H_5)_2$
*(57)*: X = O




*(56)*: X = $(OC_2H_5)_2$
*(58)*: X = O




*(59)*




*(60)*

*(60a)*: $R = R^1 = COOC_2H_5$; $R^2 = C_6H_5$
*(60b)*: $R = R^1 = CO{-}C_6H_5$; $R^2 = C_6H_5$
*(60c)*: $R = R^1 = COOC_2H_5$; $R^2 = COOCH_3$
*(60d)*: $R = R^2 = C_6H_5$; $R^1 = COOC_2H_5$
*(60e)*: $R^1 = R^2 = C_6H_5$; $R = COOC_2H_5$

converted into a 1:1 adduct by irreversible elimination of diphenylketene [130]; this 1:1 adduct is also obtained, together with *(54)*, by the reaction of diphenylketene with diethyl azodicarboxylate. Its structure is not yet certain [131].

The first step in the formation of the bicyclic substance *(54)* is probably the formation of the $-CO-N(COOC_2H_5)$ linkage *(61)*, which is favored by the amide resonance. This is followed by ring closure to give either diazetidinone *(60a)* or the unstable 1,3,4-oxadiazine derivative *(62)*, which is stabilized by addition of diphenylketene to form *(54)*.

Azodibenzoyl also forms a 1:2 and a 1:1 adduct with diphenylketene [132]. Infrared-spectroscopic comparison with *(54)* and alkaline degradation to *(59)* show that the 1:2 adduct has the bicyclic structure *(54)* with R = $C_6H_5$ [133]. The 1:1 adduct is the diazetidinone *(60b)* [132].

[124] For the formulation of the transition state, see *S. Hünig, H. R. Müller,* and *W. Thier,* Tetrahedron Letters *1961*, 353; *S. Hünig* and *H. R. Müller,* Angew. Chem. *74*, 215 (1962); Angew. Chem. internat. Edit. *1*, 213 (1962).

[125] For the tetrazene formation, see *O. Diels* [126]; *W. R. McBride* and *H. W. Kruse,* J. Amer. chem. Soc. *79*, 572 (1957); *E. Kinzel,* Dissertation, Universität München, 1964. The oxidation of hydrazides to 1,2-diacylhydrazines with various oxidizing agents has been described by *Y. Wolman, P. M. Gallop, A. Patchornik,* and *A. Berger,* J. Amer. chem. Soc. *84*, 1889 (1962).

[126] *O. Diels,* Ber. dtsch. chem. Ges. *56*, 1933 (1923).

[127] *K. H. Keil,* Dissertation, Universität Würzburg, 1963.

[128] *E. Fahr, K. H. Keil, F. Scheckenbach,* and *A. Jung,* Angew. Chem. *76*, 579 (1964); Angew. Chem. internat. Edit. *3*, 646 (1964).

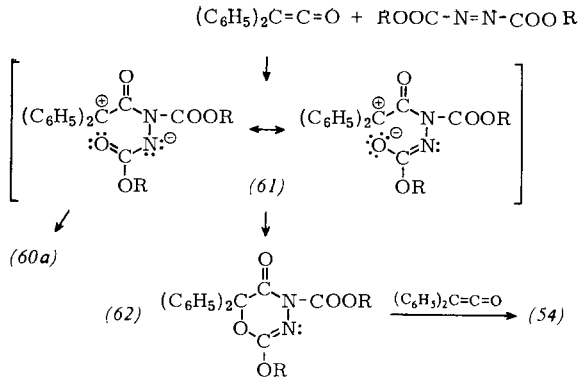
[129] *E. Fahr,* Angew. Chem. *76*, 505 (1964).

[130] In some cases, in addition to the 1:1 adduct (m.p. 233 to 234 °C) obtained in this way, we also isolated very small quantities of another 1:1 adduct (m.p. 162–164 °C) in the reaction of azibenzil with diethyl azodicarboxylate.

[131] This is probably the diazetidinone *(60a)*. When heated with acids it is converted into *(58)*.

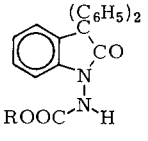
[132] *L. Horner* and *E. Spietschka,* Chem. Ber. *89*, 2765 (1956).

[133] *A. Jung.* Diploma Thesis, Universität Würzburg, 1963.



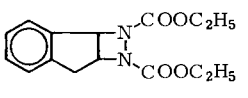
As pointed out in Section 4.2.5., α,α'-dicarbonyl diazo compounds do not react with α,α'-dicarbonyl azo compounds, but decompose at sufficiently high temperatures to give an α-ketocarbene, which rearranges to a ketene. However, in the thermal and photochemical decomposition of the esters of acetyl-, propionyl-, and benzoyldiazoacetic acids and of benzoyldiazoacetone, dibenzoyldiazomethane, diazodimedone, and esters of 3-diazo-2-oxosuccinic acid in the presence of diethyl azodicarboxylate, we observed addition of the azo compound to the resulting ketene only with the benzoyl- and propionyldiazoacetic esters. Methyl benzoyldiazoacetate gives the diazetidinone *(60c)*, while ethyl propionyldiazoacetate gives a viscous oil which cannot be purified [42,133].

The structure of the 1:1 adduct obtained in the reaction of phenylazocarboxylates with diphenylketene was established by *Bird* [134]. It is not the diazetidinone *(60d)* [119], but the diazetidinone *(60e)*. The latter isomerizes in the presence of hydrochloric acid/ethanol to *(63)*.

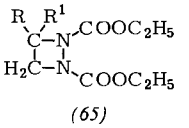


*(63)*

Diesters of azodicarboxylic acid also have been observed to add across olefinic double bonds to form diazetidine derivatives. Thus diethyl azodicarboxylate reacts with indene to form the compound *(64)* [135]; vinyl ethers and vinyl esters give the diazetidines *(65)*. The diethyl *cis*-azodicarboxylate reacts much more rapidly than the *trans* isomer [136].



*(64)*



*(65)*

R = H; $R^1 = OC_2H_5$
R = H; $R^1 = COOCH_3$
$R = CH_3$; $R^1 = COOCH_3$

[134] *C. W. Bird*, J. chem. Soc. (London) *1963*, 674.

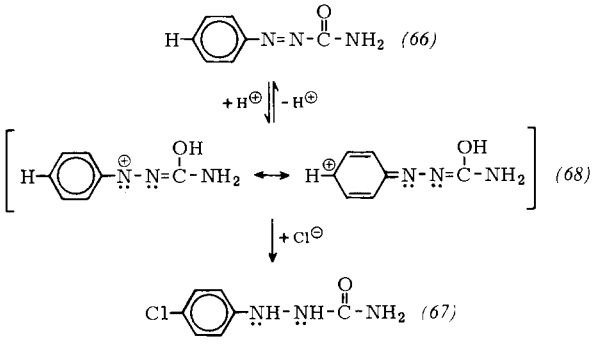
[135] The diazetidine *(64)* has already been described by *Alder* and *Niklas* [68], but it was then assigned another structure.

[136] *E. Koerner v. Gustorf* and *B. Kim*, Angew. Chem. *76*, 592 (1964).

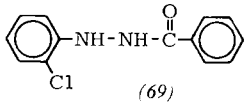
Diethyl azodicarboxylate adds analogously to tetramethoxy- and tetrafluoroethylenes [137,138] and to difluoroallene [139].

### 4.9. The Reaction of Arylazocarbonyl Compounds with Concentrated Hydrochloric or Hydrobromic Acid

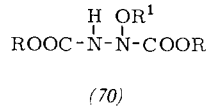
Arylazocarboxamides [140] react with concentrated hydrochloric acid, even at room temperature, to form arylhydrazocarboxamides with halogen substituents at the ring [141b–141d]. Thus phenylazocarboxamide *(66)* gives the compound *(67)*. If position 4 is occupied, the chlorine atom enters position 2 or 6. A β-naphthyl group α to the azo group is substituted first in position 1, then in position 6 [141a]. A similar reaction was observed with hydrobromic acid [141a]. On the basis of investigations by *Kniese* [142], we believe that this reaction does not proceed by initial addition of hydrogen halide to the azo bond followed by rearrangement to give the hydrazo derivative (as was supposed by *Quilico* and *Justoni* [141c]), but that it involves nucleophilic substitution by chloride ions *via* the mesomeric ion *(68)*.



Surprisingly, the reaction of phenylazobenzoyl with concentrated hydrochloric acid leads to the *o*-substituted product *(69)* [143]. The first step in this reaction could be the addition of HCl to the N=N bond.



*(69)*



*(70)*

[137] *R. W. Hoffmann* and *H. Häuser*, Angew. Chem. *76*, 346 (1964), Angew. Chem. internat. Edit. *3*, 380 (1964).

[138] US-Pat. 2456176 (Dec. 14th, 1948), Du Pont, inventor: *R. D. Cramer*; US-Pat. 2860154 (Nov. 11th, 1958), Du Pont, inventor: *J. C. Kauer*.

[139] *W. H. Knoth* and *D. D. Coffman*, J. Amer. chem. Soc. *82*, 3873 (1960).

[140] Arylazoformamide oximes, arylazohydroxamic acids, arylazoaldoximes, and arylazoamidines also undergo this reaction: *E. Bamberger*, Ber. dtsch. chem. Ges. *35*, 54 (1902); *M. Busch* and *H. Brandt*, *ibid. 39*, 1395 (1906); *A. Quilico*, Atti Congr. naz. Chim. pura appl. V. Congr., Roma, *1935*, 514 (1936), Chem. Abstr. *31*, 3886 (1937).

[141] a) *R. Justoni*, Gazz. chim. ital. *66*, 375 (1936); b) *A. Quilico* and *R. Justoni*, *ibid. 65*, 201 (1935); c) *A. Quilico* and *R. Justoni*, *ibid. 66*, 19 (1936); d) *R. Justoni*, Atti Congr. naz. Chim. pura appl., V. Congr., Roma *1935*, 370 (1936), Chem. Abstr. *31*, 3887 (1937).

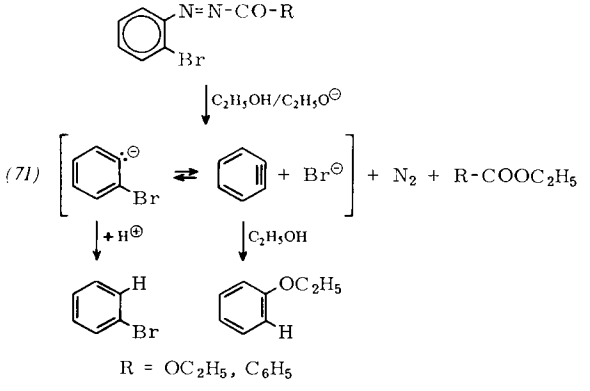
[142] *W. Kniese*, Dissertation, Universität Marburg, 1963, studied the reaction of heterocyclic phenylazo quaternary salts with hydrogen halides; see *S. Hünig*, Chimia *18*, 399 (1964).

[143] *A. Hantzsch* and *M. Singer*, Ber. dtsch. chem. Ges. *30*, 319 (1897).

### 4.10. Decompositions with Bases

α-Carbonyl azo compounds decompose in alcoholic solution, sometimes very vigorously, on addition of bases. The addition of potassium acetate or alkoxide to diethyl azodicarboxylate in ethanol, even in the cold, leads to the vigorous formation of nitrogen, diethyl carbonate, and diethyl hydrazinedicarboxylate [144, 123]. When diethyl dicarboxylate is decomposed in methanol, ethyl methyl carbonate is formed. Similar decomposition products are obtained from the extremely unstable 1:1 adducts of alcohols with esters of azodicarboxylic acid, which are formed when the alcoholic solutions are allowed to stand. The adducts are thought to have the structure *(70)* [123].

*Hoffmann* [145] studied the decomposition of ethyl 2-bromophenylazocarboxylate and 2-bromophenylazobenzoyl in ethanol under the action of ethoxide. The products obtained led him to assume that the reaction proceeds by fragmentation *via* phenyl anions *(71)* and dehydrobenzene. *Cohen* and *Nicholson* [145a], however, showed that the decomposition of phenylazobenzoyl with methanol in acidic or alkaline solutions leads to the formation of phenyl radicals.




Oxidative cleavage of phenylhydrazide protecting groups from peptides probably also proceeds by fragmentation of the phenylazocarbonyl intermediate [146a]. The reaction of phenylazocarbonyl compounds having the structure

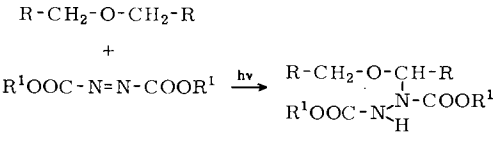
$$H_5C_6CH_2-O-CO-NH-CHR-CO-N=N-C_6H_5$$

with esters of amino acids in the presence of triethylamine can be used for the synthesis of peptides [146b]. The phenylazocarbonyl compounds are obtained by oxidation of the hydrazo compounds with *N*-bromosuccinimide.

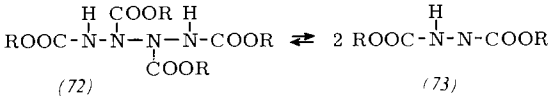
When phenylazobenzoyl in methanol is decomposed with acid or alkali, it forms nitrogen, methyl benzoate, benzene, 2-benzoyl-1,1-diphenylhydrazine, and 1-benzoyl-1,2-diphenylhydrazine. A free-radical mechanism with initial formation of phenyldiimine was proposed [147].

### 4.11. Photochemical Reactions

It was mentioned in Section 3 that "normal" diethyl azodicarboxylate is converted by radiation into the very reactive *cis* form. When the ester is irradiated in the presence of ethers, substitutive addition takes place in the α-position [104a, 148, 148a].




Irradiation in isopropanol yields hydrazinedicarboxylates and acetone together with the tetrazane *(72)*, which dissociates when heated at 80 °C into the radicals *(73)* [148, 29].




Irradiation of a mixture of diesters of azodicarboxylic acid with acetaldehyde yields diacetyl and diesters of hydrazinedicarboxylic acid [148]. Attempts to make nitrenes react with azodicarboxylates in the presence of ultraviolet radiation have been described by *Lwowski et al.* [149], *Hancock* [150], *Jung* [133], and *Königsdorfer* [79].

### 4.12. Miscellaneous Reactions

Diesters of azodicarboxylic acid are good hydrogen acceptors [9]. They can be titrated with sodium iodide in acetic acid [9, 58]. Azodibenzoyl reacts with isopropanol to give acetone and dibenzoylhydrazine [47].

The reaction of diethyl azodicarboxylate with trifluoronitrosomethane leads to the oxatriazetidine derivative *(74)* [151]. With benzonitrile oxide *(75)*, the oxatriazoline derivative *(76a)* is formed, which rearranges to *(76c)* *via* *(76b)* [152a, 152b]. Diethyl phosphite gives *(77)* [153]. The reaction of diethyl azodicarb-

[144] *O. Diels* and *C. Wulff*, Liebigs Ann. Chem. *437*, 309 (1924).

[145] *R. W. Hoffmann*, Chem. Ber. *97*, 2763, 2772 (1964); *98*, 222 (1965); Angew. Chem. *75*, 168, 677 (1963), Angew. Chem. internat. Edit. *2*, 153, 553 (1963).

[145a] *S. G. Cohen* and *J. Nicholsen*, J. org. Chemistry *30*, 1162 (1965).

[146] a) *R. B. Kelly*, J. org. Chemistry *28*, 453 (1963); b) *H. B. Milne* and *W. D. Kilday*, J. org. Chemistry *30*, 64, 67 (1965).

[147] *S. G. Cohen* and *J. Nicholson*, J. Amer. chem. Soc. *86*, 3892 (1964).

[148] *G. O. Schenck* and *H. Formanek*, Angew. Chem. *70*, 505 (1958).

[148a] *R. C. Cookson*, *I. D. R. Stevens*, and *C. T. Watts*, Chem. Commun. *1965*, 259.

[149] *W. Lwowski*, *T. W. Mattingly Jr.*, and *T. J. Maricich*, Tetrahedron Letters *1964*, 1591.

[150] *J. Hancock*, Tetrahedron Letters *1964*, 1585.

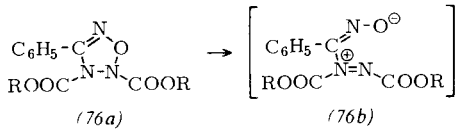
[151] *S. P. Makarov*, *V. A. Shpanskij*, *V. A. Ginsburg*, *A. I. Shchekotikhin*, *A. S. Filatov*, *L. L. Martynova*, *I. V. Pavlovskaya*, *A. F. Golovaneva*, and *A. Y. Yakubovich*, Dokl. Akad. Nauk SSSR *142*, 596 (1962), Chem. Abstr. *57*, 4527 (1962).

[152a] *R. Huisgen*, *H. Blaschke*, and *E. Brunn*, Tetrahedron Letters *1966*, 405.

[152b] *P. Rajagopolan*, Tetrahedron Letters *1964*, 887.

[153] *D. C. Morrison*, J. org. Chemistry *23*, 1072 (1958).

oxylate with metallic potassium leads to the salt *(78)*, which reacts with halogenoalkanes to form the esters *(79)*, and with 1,4-dibromobutane to form the diesters

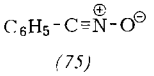


*(76a)*

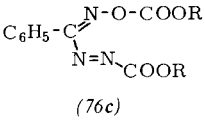
R = $CH_3$, $C_2H_5$



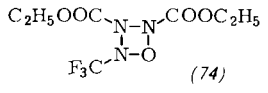
*(76b)*



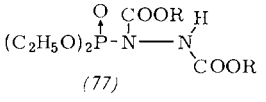
*(75)*



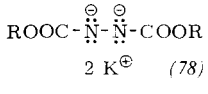
*(76c)*



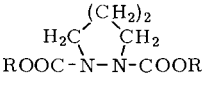
*(74)*



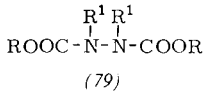
*(77)*



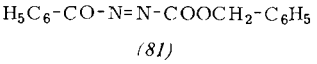
*(78)*



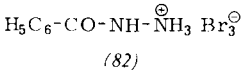
*(80)*



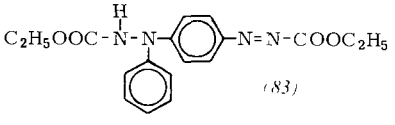
*(79)*



*(81)*



*(82)*



*(83)*

*(80)* of pyrazolidinedicarboxylic acid[154]. Benzyl benzoylazocarboxylate *(81)* reacts with HBr to form the salt *(82)*[155].

The reaction of α-carbonyl azo compounds with hydrazoic acid or with azides has been studied by a number of authors[156–158]. In our opinion, further investigation is required with regard to both the course of the reaction and the structure of the products.

α-Carbonyl azo compounds give very unstable adducts with boron trifluoride. The ethyl phenylazocarboxylate/boron trifluoride adduct decomposes to form the dimer *(83)*, which is also formed when the ester is dissolved in concentrated sulfuric acid at −5 °C[159].

*We are grateful to Dr. K. Döppert, W. Fischer, Dr. A. Jung, Dr. K. H. Keil, Dr. K. Königsdorfer, Dr. H. D. Rupp, and Dr. F. Scheckenbach for their participation in our investigations, to Prof. Dr. S. Hünig for his kind assistance in the discussion of problems that arose during the work, and to the Fonds der Chemischen Industrie for financial support.*

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German version: Angew. Chem. *78*, 376 (1966)
Translated by Express Translation Service, London

[154] *A. Zweig* and *A. K. Hoffmann*, J. Amer. chem. Soc. *85*, 2736 (1963).

[155] *L. A. Carpino*, J. Amer. chem. Soc. *79*, 96 (1957).

[156] *R. Stollé* and *G. Adam*, Ber. dtsch. chem. Ges. *57*, 1656 (1924).

[157] *T. Curtius* and *W. Sieber*, J. prakt. Chem. *125*, 444 (1930).

[158] *M. Colonna* and *A. Risaliti*, Gazz. chim. ital. *91*, 204 (1961).

[159] *W. Fischer*, Diploma Thesis, Universität Würzburg, 1965.

# Specification of Molecular Chirality

BY R. S. CAHN [1], SIR CHRISTOPHER INGOLD [2], AND V. PRELOG [3]

*The topological analysis of chiral molecular models has provided the framework of a general system for the specification of their chirality. The application, made in and before 1956, of this system to organic-chemical configurations is generally retained, but is re-defined with respect to certain types of structure, largely in the light of experience gained since 1956 in the Beilstein Institute and elsewhere. The system is now extended to deal, on the one hand, with organic-chemical conformations, and, on the other, with inorganic-chemical configurations to ligancy six. Matters arising in connexion with the transference of chiral specifications from model to name are considered, notably that of the symbiosis in nomenclature of expressions of the general system and of systems of confined scope.*

1. Scope, divisions, and definitions
   1.1. Scope of this paper
   1.2. Asymmetry and chirality
   1.3. Centre, axis, and plane of chirality
   1.4. Configuration and conformation
   1.5. Conformation and axial chirality
   1.6. Conformation and planar chirality
   1.7. Chirality and the helical model: helicity
2. Chirality to ligancy four: modifications and additions
   2.1. The sequence rule procedure to ligancy four: Ligancy complementation; Factorisation rule; Sequence rule; Standard sub-rules; Chirality rule; Helicity rule
   2.2. Valence-bond conventions: multiple-bond unsaturation and aromaticity; Convention for π-complexes
   2.3. Precedence of sub-rules: ordering by mass-number
   2.4. Ordering by stereochemical differences; *seqcis* and *seqtrans*
   2.5. Central chirality: symmetry and its procedural consequences; Rule for equivalent centres
   2.6. Axial chirality: scope, procedure, and symmetry; Selection rule
   2.7. Planar chirality: procedure and symmetry; Selection rule
   2.8. Secondary structures
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## 1. Scope, Divisions, and Definitions

### 1.1. Scope of this Paper

Two papers, published in 1951 and 1956, hereinafter called Papers I [4] and II [5], describe a method, the sequence-rule method, for specifying the absolute configuration of enantiomers on the self-contained basis of a few general rules. This condition precludes dependence on genetic assumptions, and on conventions of nomenclature and formulation, all matters that cannot be comprised within a few rules. The method achieves its independence, and hence its relative simplicity, by working directly with the space model. The model is built only from atoms and bonds. However, the specifying labels, which the sequence-rule method attaches primarily to the model, are made succinct enough to be taken therefrom into the name of the substance.

An important general aspect of Papers I and II is that they, along with the present continuation paper, represent a contribution to the still unformed subject of chemical topology. That is why, although the applications are chemical, the basic concepts are topological. It is, of course, because they are topological that they can be defined sharply, and also permanently, despite the ever-changing face of chemistry.

Paper I was limited to optical isomers dependent on asymmetric carbon atoms or other octet-forming asymmetric atoms. Paper II took as its more extended scope optical isomers, whether involving asymmetric atoms or not, but still limited to structures of atoms with no more than four directed bonds.

The present paper has two purposes. The first is to consolidate the method throughout the field covered in Paper II, in the light of the experience which has been accumulated

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[4] *R. S. Cahn* and *C. K. Ingold*, J. chem. Soc. (London) *1951*, 612.

[5] *R. S. Cahn*, *C. K. Ingold*, and *V. Prelog*, Experientia *12*, 81 (1956).

since that paper appeared. A number of investigators [6] have called our attention to special difficulties, which they have most helpfully discussed with us. By far the most searching of all the tests to which the method has been subjected is that which has arisen in the Beilstein Institute from its adoption for the description of configuration in the 4th Edition of Beilstein's "Handbuch der organischen Chemie". The letters of the late Prof. *F. Richter*, and, since his death on 22nd November 1961, of Dr. *O. Weissbach*, analysing the results of their joint study of the method, have been an important source of inspiration to us in the writing of the relevant sections of the present paper.

There are two sections concerned essentially with consolidating the already occupied area. In Section 2, we deal with the analysis of configuration in structures of atoms with up to four directed bonds, and with its specification on the space model. A few applications of the procedure are modified, and some others are more closely prescribed than before, with improvement, as we think, both to the conceptual unity of the method, and to the ease of its use in some of the more difficult types of application. A number of examples are given, including some due to Prof. *Richter* and Dr. *Weissbach*, most of which have been constructed *ad hoc* in order to illustrate difficulties of various kinds. In Section 3, we take up certain special, essentially practical, problems concerned with the transfer of stereochemical specifications from the molecular model to within the framework of nomenclature.

The second purpose of this paper is to extend, as was foreshadowed in Paper II, the application of the sequence rule, beyond the basal area covered in Paper II and Sections 2 and 3 of this paper. We move out from it in two directions, which were, in fact, considered for exploration at the time of writing Paper II, though the final conclusion then was that Chemistry was not experimentally advanced enough to require either development. But since then, the situation has changed sufficiently, we think, to justify reversing that conclusion.

In the first of the extensions now proposed, which is described in Section 4, a starting-point, already given by *Klyne* and one of us [7], is made the basis of a use of the sequence rule to specify enantiomeric conformations in structures of atoms having up to four directed bonds, chiefly, of course, carbon conformations. In the second extension, described in Section 5, we take the first step in raising the covalency limit, or, more properly expressed, the ligancy limit above four, by proposing an application of the sequence rule in the specification of group-arrangements about an atom of maximum ligancy six. We prefer the terms "ligancy", "quadriligant", *etc.*, because they refer to the number of bonds formed but are non-committal as to bond-type, whereas the terms "covalency", "quadricovalent", *etc.*, imply theories as to the type of bond. Moreover the term "ligating" atom carries no implication as to how the atom becomes bound, whether by co-ordinating as an electron donor or acceptor, or by colligating [*] as a radical; and this, as a genetic implication, is of a type that we like to avoid.

This is as far as we go. But one can foresee that in the future these extensions themselves will require filling-out, and that further extensions, for example, to higher than primary protein structures, to ligancies higher than six, and to polyatomic elemental clusters, will be wanted. However, it would seem premature to map these areas before they are better explored.

[6] Professors *S. J. Angyal*, *H. Dahn*, *E. L. Eliel*, *K. Mislow*, and *O. Th. Schmidt* and Drs. *K. R. Hanson*, *S. J. Tauber*, and *R. S. Tipson*, as well as (the late) Professor *F. Richter* and Dr. *O. Weissbach*, to all of whom we are deeply grateful.

[7] *W. Klyne* and *V. Prelog*, Experientia *16*, 521 (1960).

[*] This term (cf. *C. K. Ingold*: Structure and Mechanism in Organic Chemistry. Cornell University Press, Ithaca, New York, 1953, pp. 5, 205) suits our general preference for "ligating" and its congeners. The syllable "co" signifies like participation by the involved atoms, as in "covalency".



Chemists habitually use the word "asymmetry" (and its grammatical congeners) in two different senses, sometimes without appreciating the difference. One sense is correct, and the other is so loose that it must be considered incorrect. Yet many authors must have felt, as we have, the embarrassment of having, either to avoid the word, or to complicate statements containing it with some periphrase contrived to indicate in which of its two senses it is to be understood. It will be convenient now to end this difficulty.

The symmetry of any molecular model consists in the totality of independent symmetry operations of (a) rotation (by sub-multiples of $2\pi$) round the axes of symmetry, (b) reflexion in planes of symmetry, and (c) combinations of such a rotation and a reflexion, which will bring the molecule into coincidence with itself. Only when no symmetry operation can so convert the molecule, has the molecule no symmetry. Only then may it be called "asymmetric" in the correct usage of that term.

Thus Cabcd has no symmetry whatever, and therefore the term "asymmetric carbon atom" is entirely correct, if the atom's surroundings are taken into account, as is always intended.

Asymmetry is a sufficient condition for the existence of optical enantiomers. But it is not, though it is sometimes referred to as if it were, the necessary and sufficient condition. We need a separate word for that.

The necessary and sufficient condition is that reflexion in a plane converts the model into a non-identical one, that is, one which cannot be superposed on the original by translations and rotations only. The model then has two non-identical forms, inter-related by a reflexion, that is, two enantiomeric forms: it has the topological property of handedness. Its possibilities of symmetry are much restricted; but they are not eliminated. Obviously, it cannot have any symmetry of types (b) and (c) above, which require superposability after a reflexion. But there is no such ban on symmetry of type (a). A model which has no element of symmetry except at most axes of rotation may be called *chiral*. Thus *chirality* expresses the necessary and sufficient condition for the existence of enantiomers. Chirality means handedness, and, in our context, topological handedness [*].

[*] This useful word was brought to our attention by Professor *K. Mislow*, who referred us to Webster's Dictionary (2nd Edition), where "chiral" is defined as "Of, or pertaining to the hand, specifically turning the plane of polarisation of light to either hand", and to two articles by *Whyte* [8] on the history of the word. It has occurred in the literature of physics since 1904, when it appeared in a publication [9] by *Lord Kelvin* of lectures delivered at earlier dates, in particular one of 1884 rewritten in 1903, and one of 1893 in which it is defined to mean topological handedness. Today its meaning is broadened to include the spin-handedness of elementary particles. However, we shall be concerned only with its original meaning of space-handedness.

[8] *L. L. Whyte*, Nature (London) *180*, 513 (1957); *182*, 198 (1958).

[9] *Lord Kelvin*: Baltimore Lectures. C. J. Clay and Sons, London 1904, pp. 436, 619.

An unambiguous division of the overall field of topological chirality must itself be topological. For the problem is to describe a space relation, and the primary classification should therefore be concerned with the types of geometrical relation requiring to be described, not with where the forces come from which make them what they are. Thus, the main framework for the classification of chirality has to be geometrical. To introduce theories of chemical bonding, or structural energetics, at this fundamental level would create great difficulties.

It was in this understanding that, in Paper II, we introduced a primary division of chirality (there called "asymmetry", or sometimes, "dissymmetry") into central, axial, and planar chirality, a classification which is based only on the three-dimensional nature of space. The chiral centre is an abstraction of the asymmetric atom: the space about it, when unoccupied, is undifferentiated in its three dimensions, and certain differences in its occupation have to be established in order to produce chirality. A chiral centre that is not the seat of an atom can be contemplated (Sub-section 2.8). A chiral axis does distinguish one dimension from the other two, and hence lesser differences in the occupation of the surrounding space are sufficient for the development of chirality. A chiral plane distinguishes two dimensions from the remaining one, and again reduced differences in the occupation of the ambient space suffice to create chirality.

A given chiral structure may contain one or more of some or all of these elements of chirality. The first step in the procedure for specifying chirality is to factorise the overall chirality into as many chiral centres as are present, and, if their specification leaves that of the overall chirality incomplete, into chiral axes, or chiral planes, or both, as far as necessary. This procedure of factorisation was implied in Paper II, but was not formally stated as a rule.

It is well known that, whilst the chiral sense of different elements of chirality can commonly be varied independently, some elements in some structures may be so stereospecifically linked that that cannot be done. However, this does not interfere with the assigning of specific designations of chirality to such elements.

The above broad geometrical lay-out is unequivocal and universal, as long as it is not upset by non-geometrical considerations, for example, by theories of bonding, or of structural energetics, or by chemical classifications. Nevertheless, the practical problem does sometimes arise of arranging a convenient symbiosis between these geometrical concepts, which are sharply definable, and chemical concepts, which it may be impossible satisfactorily to define, but which do convey distinctive general ideas. The difficulty is not so much that the geometrical and chemical concepts are not co-extensive, but that the margins of the latter carry a penumbra.

We meet this type of problem unavoidably, as a result of our decision to apply the sequence rule to conformations.



These terms have come down, the one through a long history, and the other through a short one, each carrying a generally distinctive set of ideas. Yet history has never produced satisfactorily distinguishing definitions. It results from this that the newer concept of conformation has an agreed area of application, an agreed area of non-application, and a penumbra.

We shall take it that conformations arise from pure rotations around the internuclear lines of formally single bonds. However, the concept of conformation became important as a result of the discovery that rotation around the C–C bond of ethane is resisted, and that therefore some of the arising conformations are stable with respect to all small relative displacements of the atoms, and thus are molecular states, now commonly called conformational isomers, rotational isomers, conformers, or rotamers. Such molecular states will have a first claim on our attention in applying the sequence rule, but conformations which are not molecular states will have a claim, because their relation to conformers has to be considered in many connexions.

We now ask what types of resistance to rotation are qualified to produce a conformer. The type present in ethane would universally be considered to be so qualified. However, the restriction on rotation round a single bond, caused by its inclusion in a small ring, might not be considered as so qualified: it could be argued that the incapacity of the bond for rotation is not a situation for which the bond is primarily responsible. But what is to be said, if the inhibition arises because some attached groups are too large to pass one another? Neither is that the primary responsibility of the bond. A range of such intermediate situations can be found which constitute the penumbra.

Let us examine another approach. As is emphasised in the different histories of the concepts of configuration and conformation, the energy barriers that protect configurations are usually much larger than those which separate conformers. Thus stable optical activity is widespread throughout the realm of configuration, having created the multitude of practical problems of specifying chirality, to deal with which the sequence-rule system was devised. On the other hand, in the domain of conformation, stable optical activity is much less common, and, indeed, is largely associated with the area of the penumbra. For several reasons, no sharp distinction between configurational and conformational molecular states can be based on barrier heights. No delimiting energy figure could be exclusively justified. Most actual barrier heights are unknown.

We must explain our concern with this matter of the penumbra. We wish to specify, in particular, the chirality of conformations about the C–C bond. This amounts to specifying the space relations of the maximum of six atoms bound to the $C_2$-unit, given that the configurations of the two sets of three, of which the set of six is composed, are pre-determined. By introducing unsaturation at either end, or at both ends, of the $C_2$-unit,

specialisations can be created, in which the six atoms become reduced to five, composed of sets of three and two, and to four, composed of two pairs. However, in spite of this last specialisation, the problem of conformational specification as a whole is different enough from that of the configurational specification of four groups about an asymmetric atom, or about any of the general elements of chirality, the centre, axis, or plane, to determine that we must in general apply the sequence rule to configuration and to conformation in different ways. We need not now go into the difference; the present point is simply that its existence requires us carefully to examine the margins between configuration and conformation.

Conformations which are not molecular states present no procedural dubiety. The penumbra has to do with molecular states. We might try to draw a sharp boundary between the alternative procedures by inventing some particular definition of a conformer, which either includes the penumbral area, or takes some other prescribed course through or around it. Whatever definition we set down, we cannot expect its universal acceptance, either in general or for our particular purpose.

Let us consider, for example, the following classification of molecular states, which gives to conformers a scope embracing the whole penumbral area. By configuration is meant the space-arrangement of a model representing a molecular state with neglect of the distinctions between varieties of that state which differ only as after relative rotations of groups directly bonded together, about the internuclear lines of their intervening, formally single bonds; and by a conformational molecular state (conformational isomer, rotational isomer, conformer, rotamer) is meant a space-arrangement which signalises such a distinction, and identifies such a variety-state.

This definition includes not only examples of the general nature of those which formed the historic foundations of the subject of conformation. It includes also cases in which rotation round a single bond is prevented by interactions of groups possibly some bonds away from the single bond in question, as in biaryls; or by the locking of the single bonds in rings which in turn create non-bonded group-interactions, as in *para*-cyclophanes. These situations are today accepted by many as configurational, as, indeed, those of stereoisomerism in the biaryl series were for a decade before the fundamental discovery of 1936 by *Kemp* and *Pitzer* concerning ethane. For these reasons among others, we do not expect our wide-limit definition of conformations to be unanimously acceptable, and so we have to devise a means by which the necessary definiteness of the sequence-rule system can co-exist with such a penumbral area of allowably diverse opinions.

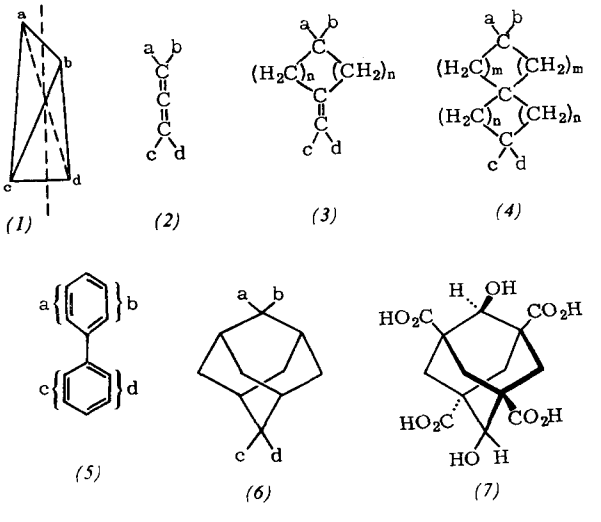
The whole penumbral area falls into two parts, one contained within the broader field of axial chirality, and the other within that of planar chirality. These primary geometrical divisions of chirality refer only to the topological relations requiring to be described, and do not ask the question of whether their chemical origins are configurational or conformational. Thus, the dubieties which arise are concerned, not with whether some case or class of cases should be treated as configurational or conformational, but with whether it should be treated on a basis indifferent to that question, or by a specifically conformational method, when allowed by the wide-limit definition given above. We discuss the two parts of the penumbral area in the next two sub-sections.

### 1.5. Conformation and Axial Chirality

The chirality of four groups arranged out-of-plane in pairs about an axis, as diagrammatically illustrated by the elongated tetrahedron *(1)*, was discussed in Paper II. With no distinction at all between its four groups, a, b, c, d, the tetrahedron has a four-fold alternating axis of symmetry, which becomes the chiral axis when differences of any kind between the groups import chirality. It was noted in Paper II that fewer differences in groups are required to produce chirality about an axis than are necessary for chirality about a centre. Thus the four groups, shown as abcd in *(1)*, need not all be different: so long as a and b are different, and c and d are different, *(1)* will be chiral, even if identities arise between the pairs, as in ab, ac, or ab, ab.

This form of chirality was illustrated in Paper II with examples of four kinds typified by allenes*(2)*,alkylidenecycloalkanes *(3)*, spirans *(4)*, and biaryls *(5)*. To these, we must now add a fifth type, the adamantoids *(6)*, one of which *(7)* has already been optically resolved [10]. All these illustrations may be taken to represent more general classes, in which some carbon atoms may be replaced by stereochemically similar hetero-atoms, such as nitrogen. The classes typified by *(2)*, *(3)*, *(4)* and *(6)* are clearly configurational. The class typified by *(5)* is conformational by our wide-limit definition. All five classes display stable optical activity.

Evidently two views are possible as to how chirality of type *(5)* should be specified. One is that, because, by the definition given above, the enantiomers are conformational isomers, they should be specified by the method




[10] *H. Stetter* and *O. E. Bänder*, Chem. Ber. *88*, 1535 (1955).

devised to cope with conformations. The other is that, because, in all the five types *(2)–(6)*, all that is being specified is the similar space-relations of the four groups abcd, and not the forces that hold them where they are, it would be suitable, and perhaps convenient, to specify all in the same way, and hence as forms of axial chirality.

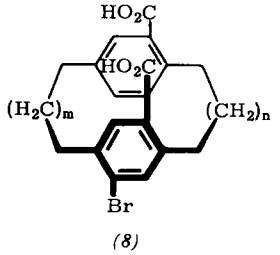
We think that both points of view must be considered tenable; and rather than presuming exclusively to decide between them, we should prefer that both methods of specifying the chirality of biaryls would be regarded as available. That is to say, biaryls would be treated, either as examples of axial chirality, as illustrated in Paper II and additionally in Sub-section 2.6 below, or by the appropriate specialisation of the treatment of conformational chirality, as discussed in Section 4 below. Of course, if the method is to be left to choice, the results must be expressed in forms which disclose the choice. We do that in the sequel by using contrasting symbolisms in the two methods.

### 1.6. Conformation and Planar Chirality

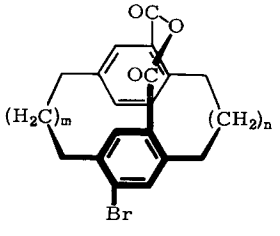
As explained in Paper II, a plane of chirality is derived by desymmetrisation of a plane of symmetry in such a way that chirality depends on a distinction between one side of the plane and the other, and on a pattern of three groups (of which two or even all three may be equivalent). These are basic conditions, not changed at all by the fact that planar chirality is discussed again in Sub-section 2.7 below, where some modifications of procedure are introduced. Most, though not all, of the examples available at present belong to the chemical class of bridged rings with bridge-heads in aromatic rings.

Once again, alternative approaches to the specification of chirality arise in a part of the general field of planar chirality. For some examples fall within the wide-limit definition of conformations given above, and some do not. Yet those which do and those which do not may be geometrically very similar. In order to bring out the distinction, two *para*-cyclophanes, closely resembling two illustrated in Paper II, are represented at *(8)* and *(9)*.

The dicarboxylic acid *(8)* is a conformational isomer by the definition. For its enantiomer differs from it as would the result of a conceptual rotation of both benzene rings through 180° about their *para*-situated arylmethylene bonds. We may note in passing that the acid which differs from *(8)* as after a conceptual rotation of one benzene ring only, an acid which would normally




*(8)*




*(9)*

be regarded as a position isomer of *(8)*, is by the same definition a conformational isomer.

On the other hand, the anhydride *(9)* is not a conformational isomer, even by the definition. For the rings cannot now be rotated, not even in imagination, without the introduction of deformations other than rotational. The enantiomeric product of such rotation bears a permanent bending deformation, inasmuch as the valency angle of the single-bonded oxygen atom has been widened from $\Theta$ to $2\pi-\Theta$. If this is not immediately obvious, it can be made so by imagining the oxygen atom to be replaced by Cab, an ordinary asymmetric carbon atom, in *R*-form say, which will clearly have to go into *S*-form in the enantiomer, a conversion which, at best, involves bending the pair of bonds to the carbonyl groups past the pair to the atoms a and b, and reciprocally.

Here we have two examples, which are broadly similar geometrically, and closely related chemically, both belonging to the domain of planar chirality. Yet one falls within the scope of the definition of conformers given above, whilst the other does not, and is thus inevitably configurational. The chirality of the anhydride *(9)* can be specified by only one sequence-rule method, namely, that applicable to planar chirality. However, alternative procedures are possible for specifying the chirality of the dicarboxylic acid *(8)*. Either it can be treated, like its anhydride, as an example of planar chirality; or it can be specified by an application of the procedure devised for conformations (Section 4).

Again our view is that both methods should be considered available, and that the one used should be left to choice, which the resulting specification would disclose.

### 1.7. Chirality and the Helical Model: Helicity

A helix is characterised by a helical sense, a helical axis, and a pitch (ratio of axially linear to angular properties). Thus, helicity is a special case of chirality, because it implies two additional properties. When a natural object or process has all the three properties, the helical model, just because it provides so well-filled-in a portrait, may be the easiest abstract model to recognise and use, even though it summarises more properties than may be relevant to the matter under discussion. Of course, when a chiral object has not all the helical properties, nor by a simple adaptation can be given them, the specialised helical model is inapplicable, and the object belongs to the general case of chirality.

A familiar example of the use of the specialised helical model, when valid, for less specialised purposes, is that of the spinning elementary particle in free space. It has helicity; and, in reference to it, the term "helicity", is frequently used in discussions to which only part of its full meaning, only helical sense (*i.e.* chirality), is relevant.

Our concern is with molecular structures. In some, for example, some secondary protein structures, a well-developed helical arrangement contributes to chirality. The chirality of conformations is most conveniently referred to the helical model, so we have reason enough

to follow precedent in using the helical model, when applicable and particularly convenient, even though the only one of its several properties which is relevant to our considerations is its sense.

As to this, right- or left-handed helicity associates a right- or left-handed turn, as the case may be, with axial translation away from the observer; and to reverse the helix with respect to the observer makes no difference. We shall propose designations for right- and left-handed helicity in Sub-section 2.1.

## 2. Chirality to Ligancy Four: Modifications and Additions

### 2.1. The Sequence-Rule Procedure to Ligancy Four

This method of specifying chirality works directly with the space-model. The models treated are of conventionally approximated valence-bond structures. We defer to Sub-section 2.2 the stating of the conventions, because we want to change one of them. As allowed by the ligancy limit, electron-octet valence-bond structures are employed.

Conceptually, all atoms other than hydrogen are complemented to quadriligancy by providing them, as far as necessary, with imaginary bonds and atoms to bind, as follows. First, they are provided, respectively, with one or two duplicate representations of any ligands to which they are doubly or triply bonded; and then their unsaturation, if any, of unshared valency electrons or incomplete valency electron shells is satisfied with phantom atoms of atomic number zero.

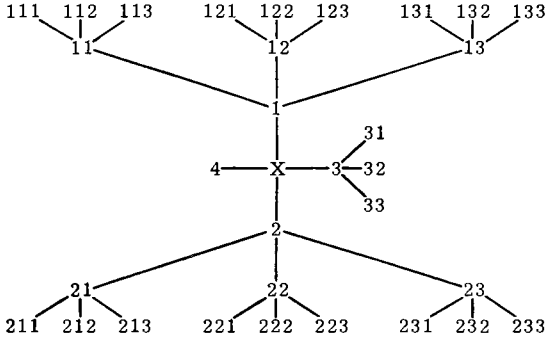
The chirality of such a formalised valence-bond structure is now factorised into chirality in the occupation of space about the identifiable chiral elements, first the centres, and then, as far as necessary, the axes and planes of chirality. The elements are then stereochemically characterised by the following procedure applied to each in any applicable order.

For the purpose of characterising an element of chirality, for example, an asymmetric atom, the ligands associated with it are put into a priority sequence, and the most important of the characters used for this purpose is atomic number. Thus, the ligands about an asymmetric atom are arranged in order of decreasing atomic number of the atoms by which they are bound to it; or, if the relative order of two ligands cannot thus be decided, it is determined by a similar comparison of atomic numbers of the next atoms in the ligands, or, if this fails, of the next: so one works outward, always first towards atoms of higher atomic number, where there is any choice, until a decision is obtained.

In this outward exploration along the bonds, we thus follow paths of highest precedence. It is so important to be clear as to what this means that we here repeat the detailed prescription, illustrated by formula *(10)* and given in Paper I, for the ordering by atomic number of the ligands about an asymmetric atom. The ligands are placed in order of decreasing atomic numbers of selected sets of their atoms, the sets being selected, and so used, successively, as fas as necessary, as follows.

First set: To an asymmetric atom let four atoms, 1, 2, 3, and 4 be directly bound. Then the atoms 1, 2, 3, 4 constitute the first set.

Second Set: Let 1 and 2 be any two atoms of identical atomic number in the first set. To 1 let there be directly bound atoms 11, 12, 13, ...., here arranged as far as possible in order of decreasing atomic number. To 2 let there be directly bound atoms 21, 22, 23, ...., similarly here arranged. Then the second set contains 11 and 21, unless these have the same atomic number, when it contains instead 12 and 22, unless these also have the same atomic number, when it contains instead 13 and 23. The complete second set is to be composed by applying this procedure to every pair of ligands whose atoms of the first set have the same atomic number.




*(10)*

Third Set: Let the atoms 1 and 2 have identical atomic number, and let the atoms 11, 12, ...., and 21, 22, ..., be identical in atomic number in pairs, 11 with 21, 12 with 22, and so on throughout. Then the atoms of the third set are selected from the atoms 111, 112, ...., directly bound to atom 11 and here arranged in order of decreasing atomic number as far as possible, and from the atoms 211, 212, ...., directly bound to atom 21, and similarly here arranged, as were the atoms of the second set from the atoms, 11 12, ...., directly bound to atom 1, and the atoms 21, 22, ..., directly bound to atom 2; unless all the atoms from which the atoms of the third set might thus have been selected are identical in atomic number in pairs, each of the series 111, 112, ...., with one of the series 211, 212, ..., when the atoms of the third set are similarly selected from the similarly arranged atoms 121, 122, ...., directly bound to atom 12, and likewise the atoms 221, 222, ...., bound to atom 22; and so on. The complete third set of atoms is to be composed by applying this procedure to every pair of ligands having relationships of identity similarly to those assumed for the ligands to which the atoms 1 and 2 belong.

Higher Sets: The method for selection of the $(n + 1)$th set of atoms is to be developed from that of the $n$th set as was that of the third set from that of the second set.

In case outward exploration by this method does not order the ligands completely, because of the absence of a distinction of atomic number between certain of the ligands, the exploration is repeated with respect to such ligands using characters other than atomic number as basis for comparisons made at each step of exploration.

In Paper I, it was proposed to order ligands having only isotopic differences by reference to atomic mass-numbers, higher mass-numbers taking precedence over lower. In Paper II, it was proposed to order ligands which had only stereochemical differences by reference to these differences, with a prescribed order for *cis* and *trans* differences, and also for enantiomeric features.

In Paper II, the further generalisation was made of using this procedure not only for centres of chirality, but also, with suitable adaptations, for axes and for planes of chirality.

The object of the procedure, however applied, is to arrange the ligands associated with an element of chirality in a sequence. The succeeding processes are simple. The sequence is allowed to trace a path on the space-model, and the chiral sense of the path, designated in a prescribed way, then classifies the element of chirality.

The procedure was summarised in Paper II in a schedule of consecutively applicable rules, the various characters, used for the comparisons made during exploration of the ligands, being covered in a series of consecutively applicable sub-rules. This schedule is reproduced in a revised form below. Two changes of substance are made, which set up a new sub-rule, and renumber and rearrange some of the older sub-rules. The reasons for these changes are explained in Sub-sections 2.3 and 2.4. The special nomenclature used in Sub-rule (3) is explained in Sub-section 2.4, and the symbols *M* and *P*, which appear in Sub-rules (4) and (5) are defined later in the present Sub-section.

Ligancy Complementation. *All atoms other than hydrogen are complemented to quadriligancy by providing respectively one or two duplicate representations of any ligands to which are doubly or triply bonded, and then any necessary number of phantom atoms of atomic number zero.*

Factorisation Rule. *Overall chirality is factorised into elements, which are treated in the order, centres first, and then axes, and finally planes, as far as necessary.*

Sequence Rule. *The ligands associated with an element of chirality are ordered by comparing them at each step in bond-by-bond explorations of them, from the element, along the successive bonds of each ligand, and, where the ligands branch, first along branch-paths providing highest precedence to their respective ligands, the explorations being continued to total ordering by use of the following* Standard Sub-rules, *each to exhaustion in turn, namely*:

(0) *Nearer end of axis or side of plane precedes further.*

(1) *Higher atomic number precedes lower.*

(2) *Higher atomic mass-number precedes lower.*

(3) *Seqcis precedes seqtrans.*

(4) *Like pair R,R or S,S precedes unlike R,S or S,R; and M,M or P,P precedes M,P or P,M; and R,M or S,P precedes R,P or S,M; and M,R or P,S precedes M,S or P,R; also p precedes s.*

(5) *R precedes S; and M precedes P.*

Chirality Rule. *Among ligands of highest precedence the path of their sequence is followed from the preferred side of the model, that is, the side remote from the group of lowest precedence, and, according as the path turns to right or left, the element is assigned the chiral label R or S, or, if pseudo-asymmetric, r or s.*

In planar chirality, the preferred side of the model may be said to be on that side of the chiral plane which contains an atom, called the "pilot atom", which we shall define, and show how to identify, in Sub-section 2.7.

When the specialised helical model is applicable, and is to be used, a different rule of assignment will be required. The helix may immediately identify itself in the molecular model, as do the helices of secondary structures (Sub-section 2.8). In the area of conformations (Section 4), a limited use of the Sequence Rule is made in order to identify the helix. Supposing the helix to have been identified, it is necessary only to specify its sense. For this purpose, we propose the following rule of assignment:

Helicity Rule. *According as the identified helix is left- or right-handed, it is designated "minus" and denoted by M, or designated "plus" and denoted by P.*

There are some areas, notably, as explained in Sub-sections 1.4–1.6, around the margins of the field of conformations, and also, as will be observed in Sub-section 2.8, in the field of secondary structures, where two methods of specifying chirality are left open, one of which would use the Chirality Rule, whilst the other would employ the Helicity Rule. In the most important of these areas, notably in the biaryl series, *R* and *S* by the former correspond respectively to *M* and *P* by the latter. One result of the choice of symbols for designating helicity is the mnemonic that, in alphabetical order, *R* and *S* correspond to *M* and *P*, respectively, in the field mentioned.

### 2.2. Valence-Bond Conventions: Multiple-Bond Unsaturation and Aromaticity

The sequence rule has to be applied to valence-bond structures, though structural valency is an approximation concept, indeed, one which seriously loses precision in the presence of any form of unsaturation.

For this reason, four conventions, defining the valence-bond approximation by which an unsaturated molecule was to be represented for the purpose of applying the sequence rule, were proposed in Paper I [4]. They were as follows:

(a) *Hyperconjugation is neglected.*

(b) *Contributions by d orbitals to bonds of quadriligant atoms are neglected.*

(c) *A mesomeric system is represented by its usual valence-bond structure or structures. By "usual" is meant selected, first, to have fewest formal charges and radical centres, and then, given this, with preference for multiple bonds and conjugated systems of them, and chief preference for closed-conjugated systems.*

(d) (Now discarded). A mesomeric system with several usual valence-bond structures is represented by one of them, selected by a special rule, which was enunciated.

Convention (b) excludes double-bonded structures of, *e.g.*, sulphoxides and sulphinates. Under convention (c), charges are minimised and double bonds introduced subject to convention (b), and hence subject to such exclusions. We do not restate the rule contained in convention (d), because the present proposal is to discard it, and, indeed, to change the whole direction of convention (d). We must first explain the need for a change.

By far the most important area to which convention (d) applies is that of the six-membered aromatic rings. These always have several Kekulé-type structures,which can all be taken as usual valence-bond structures. Some subsidiary areas are covered by the convention, but they present only minor variations of the same problem of ambiguity in double-bond arrangement. The special rule in the old convention (d) for the selection of a particular arrangement was unequivocal, but it was excrescent to the logic of the sequence rule; and (as Prof. *Richter* and Dr. *Weissbach* convinced us) experience has proved that it is undesirably intricate in some of its applications.

Now the treatment of systems to which convention (d) applies is a last step, and so is dependent on earlier steps, in the treatment of multiple-bond unsaturation as a whole. Even though it is only in the last step that the difficulties mentioned have arisen, we cannot appropriately change that step in isolation, but must revise the treatment of unsaturation more generally.

We have had three aims in mind in designing the revision now to be proposed. One was to retain a maximum of orthodoxy in assignments of configuration to the traditional and didactically basic cases of molecular chirality, such as tartaric and lactic acids, glyceraldehyde, and serine. Another was to improve the logical unity of the sequence-rule procedure. The third aim was the practically important one of simplifying the more involved applications of the sequence rule in the field of polyunsaturated systems.

The treatment of unsaturation now proposed, and its relation to the former treatment, may be explained with the aid of a simple example. Let us consider a molecule containing one asymmetric carbon atom, and, as a feature of unsaturation, one carbonyl group. We shall assume that the ordering of ligands about the asymmetric atom is being accomplished on the basis of atomic number, that is, by Sub-rule (1). Following the fundamental sequence-rule method, we conceptually travel from the asymmetric atom along each of its bonds, recording their characters by the atoms found at their further ends, in numerically coded form for ordering, as the atomic numbers of these atoms. Then, having arrived by way of a bond at an atom, we explore similarly all its other bonds. And we repeat this procedural step as far as it is material. When we arrive at carbonyl-carbon, we record its double bond as two single bonds both ending on oxygen: for purposes of accountancy, we refer to one as terminating on the real oxygen atom, and the other on its duplicate representation. The old procedure stopped there; but it is an illogical place to stop; and the new proposal is that the procedure should be continued through one further and complementary step. This step is that, having arrived by way of a bond at carbonyl-oxygen, we explore its (only) other bond, which ends on carbon. Thus, for numerical coding with a view to ordering, we represent C=O, not, as before by C–O , but by C—O ,
(O) (O) (C)
where (O) and (C) are duplicate representations of the double-bonded atoms.

Generalising from this illustration, we see that the amended formulation of multiple bonds for application of the sequence rule involves adding, not merely at the first-encountered end, but at *each* end of each double or triple bond, one or two duplicate representations, as the case may be, of the atom at its other end.

This method has the simplifying effect, particularly helpful in the field of unsaturated ring compounds, that one has not necessarily to keep a strict account of which is the end of a multiple bond that is first encountered in the exploratory process. The same answers would follow if the multiple bonds were conceptually supplied with the duplicate representations of atoms before the exploration was begun. This simplification in turn opens the way to a simpler convention (d), one not involving an excrescent special rule.

It may be noted in passing that we could have achieved a similar though not identical result by an instruction to treat double and triple bonds as rings, in particular, as two-membered rings and bridged rings, respectively. This would obviate reference to duplicate representations of atoms; but we find duplicate representations, like phantom atoms, an aid to accounting, and hence prefer to retain them. As before, all real atoms other than hydrogen, and all duplicate representations, are made up to ligancy four with phantom atoms. The full representation of carbonyl thus becomes C———Ooo ,
(O)ooo (C)ooo
where o denotes a phantom atom.

This amended formulation of multiple bonds is immediately applicable to non-mesomeric unsaturated systems. They are subject only to the structure-defining conventions (a) and (b).

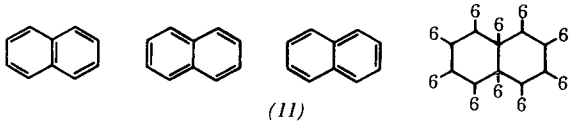
It is immediately applicable also to mesomeric systems with a uniquely usual valence-bond structure. They are governed by conventions (a), (b), and (c), the last being an instruction to employ the unique structure. It was noted in Paper I that a large number of types of mesomeric system fall into this general case, and that one important type which does so is that of the hererocyclic five-membered-ring aromatic molecules. Quite generally, the unique structure is a least polar one; and this is true for the five-ring aromatics, the unique structures of which have two-double-bonded non-dipolar rings, with no uncertainty as to double-bond positions. This applies even to sydnones, for which the overall structure is dipolar, but the ring is not. In some five-ring aromatics, the complication of prototropy arises: this is discussed in Sub-section 3.5.

It is in the field of mesomeric systems with several usual valence-bond structures that the amended formulation of multiple bonds is most helpful. The primary

area here is that of those even-membered rings whose unsaturation is expressible in fully-closed conjugated systems of double bonds. The field embraces the six-membered aromatic rings, and some even-rings in molecules not typically aromatic, for instance, that in cyclo-octatetraene, and the ten-membered ring (but not the component rings) of azulene. In all these rings, the closed-conjugated double bonds can be inserted in two ways, and our concern is to prevent this Kekulé-type ambiguity from producing an ambiguity of sequence-rule result.

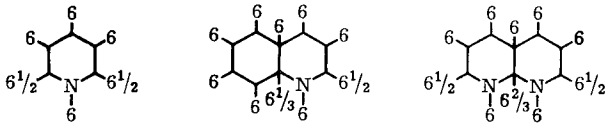
We may interpolate here, as a comment on the two immediately preceding paragraphs, that the application of common treatment to aromatic and non-aromatic systems should occasion no surprise. For we are dealing with valence-bond structures, and have no concern with molecular energetics, and hence none with aromaticity as such. Aromaticity is another chemical concept which conveys a distinctive set of ideas, but is incapable of satisfactory definition, and hence has an area of application, one of non-application, and a penumbra.

With the revised formulation of multiple bonds, it is easy to arrange that the ambiguity of double-bond distribution in closed-conjugated even-rings shall lead to no ambiguity of sequence-rule result. Actually, this consequence follows inevitably and without more ado, provided that the rings are homocyclic: if they were the only problem, no convention (d) at all would be required. For in them, the delocalised valency of each ring-carbon binds only carbon, and hence can be supplied with a duplicate representation of carbon. Thus the various usual valence-bond structures give the same representation to which to apply the sequence rule, as illustrated for naphthalene, and thus for a naphthyl residue in a chiral molecule, in *(11)*. The duplicate representation is here denoted by its atomic number 6, instead of by (C), for comparison with the group of cases next to be considered.



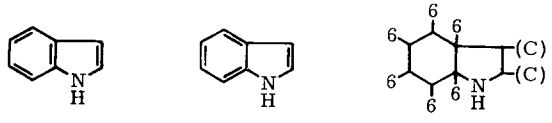
*(11)*

In the homocyclic series, the representation is so automatic that it is immaterial whether we regard it as derived from one selected valence-bond structure, or from a blend. Actually the latter idea is the better for adaptation to closed-conjugated even-rings containing one or more hetero-atoms. In such systems, a ring atom may be concurrently part-binding atoms of more than one kind, and hence, in the blend, may be binding an average atom of fractional atomic number. As any ring-atom must have either two or three next-neighbour ring-atoms, we conventionalise the possible proper fractions to $^1/_3$, $^1/_2$, or $^2/_3$, by assuming for simplicity equal partitioning of the delocalised valency among the next-neighbour atoms, as illustrated at *(12)–(14)*, where the figures denote the atomic numbers of the blended duplicate representations.



*(12)* *(13)* *(14)*

The importance of distinguishing between systems with unique, and with several, usual valence-bond structures, and, in particular, between odd-rings and closed-conjugated even-rings in aromatic molecules containing both, should be emphasized. Only in the even-ring of a residue of indole, for example, are the usual structures different, and therefore to be blended. To mark the distinction, the duplicate representations of carbon, blended or otherwise, are denoted by two kinds of symbols in formula *(15)*, which, it will be noted, contains no fractional atomic numbers, because the hetero-atom belongs to the unique odd-ring part of the structure.

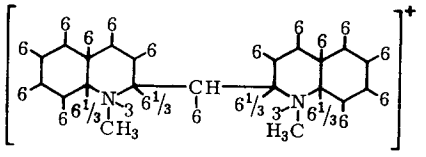


*(15)*

The "primary" field of mesomeric systems with several usual valence-bond structures to be blended is that just considered, the field of *closed-conjugated even-atomic rings*. But a "secondary" field of such exists, *viz.* that of the *mesomeric odd-atomic ion and radical systems*, as we illustrate below. The two types of system may be present together, and may be overlapped. Two odd-atomic systems may be overlapped in a bivalent ion or di-radical, which may thus be even-atomic overall.

An odd-atomic mesomeric system of the "secondary" field may be endless or ended. In either case, we shall express the unsaturation with a maximum of formal double-bond conjugation; and we shall have a plurality of usual valence-bond structures. The system will possess a phantom atom. Typically, this will occupy different positions in those valence-bond structures which have to be blended. Thus it will be present, though delocalised, in the blend. As examples, we may consider the cyclopentadienylide ion, the tropylium ion, the phenalenylide ion, the acetylacetonate ion, and the cyanine dyes. In some of these, blending does not fractionate atomic numbers only into halves and thirds. In the cyclopentadienylide ion, each of the five delocalised carbon valences is taken to contribute to the extent of one-fifth to the binding of the phantom atom, and hence to the extent of four-fifths to the binding of carbon, wherefore it is associated with the atomic number $(4/5)\times 6$. In the tropylium ion, and likewise in the phenalenylide ion, the phantom atom can have any of seven positions, and thus the delocalised valency at each such position is taken to contribute to the extent of one-seventh to the binding of the phantom atom, and is accordingly associated with the atomic number $(6/7)\times 6$. In the acetylacetonate ion, each oxygen atom has a delocalised valency, which in one of our valence-bond structures binds carbon and in the other a phantom atom, and hence is associated with the atomic number $(1/2)\times 6$. The nitrogen atoms of the cyanine dyes are in the same situation, as is illustrated in formula *(16)*. All these conventionalised structures, here de-

scribed as for parent ions, hold for residues of the ions, as they might be encountered in chiral ions requiring to be treated by the sequence rule.



*(16)*

Just as, when blending in the "primary" field of closed-conjugated even rings, we divide a delocalised bond equally (into halves or thirds), irrespective of the symmetry of the model, so in the "secondary" field, we blend structures of a mesomeric odd-atomic ion system with an equal division of the delocalised bond to the phantom atom, irrespective of the symmetry of the model. Thus the phantom atom representing the ionic charge in the pyrrolylide ion, the pyrazolylide ion, or the imidazolylide ion, is taken as bound equally by each of the five ring atoms, so that only four-fifths of the delocalised bond of each ring atom is available for equal division between nearest-neighbour atoms in the ring. Again what is here said of the simple ions will apply when they are substituted to give chiral ions.

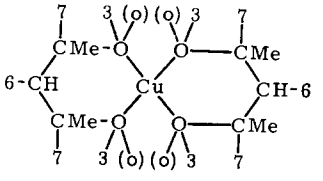
When one or more systems of the "primary" field in which we blend usual valence-bond structures, and one or more systems of the "secondary" field, are overlapped, blending is effected with structures which maximally retain "primary" systems, in accordance with convention (c). The phantom atom in the indenylide ion, or in the indolylide ion, is thus delocalised only between positions 1 and 3; and in the fluorenylide ion or in the carbazolylide ion, it is localised on position 9. Chiral or other substituents in the benzo-rings make no difference to these locations. Triarylmethyl cations, anions, and radicals, are taken with a maximum of "primary" systems, that is, in fully benzenoid form, with the phantom atom therefore localised on the central atom. Accordingly, a conventionalised structure, thus prepared for application of the sequence rule, is in no way dependent on the actual (not exactly known) electron distribution, and substituents, chiral or otherwise, though they might make a great difference to the actual electron distribution, make no difference to the conventionalised structure.

When two ionic systems of the "secondary" field are overlapped, as in the pentalene-di-ide ion, we distribute the bonds to their respective phantom atoms additively and independently. In this example, two-fifths of the delocalised bond of each ring-junction atom, and one-fifth of that of each other ring atom, that is, ten-fifths altogether, are concerned with binding the two phantom atoms.

Having explained the reasons for, and the scope, substance, and method of application, of the new convention (d), we may now formally enunciate it:

(d) *(New) A mesomeric system with several "usual" valence-bond structures is represented by their blend, in which each delocalised bond is assumed equally to bind the next-neighbour atoms of the system, the atomic number characterising the bond being the arithmetic mean of those of these atoms. Delocalised bonds to phantom atoms are taken as equally divided between their several positions.*

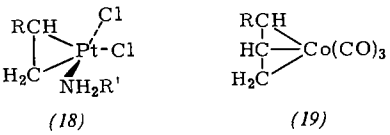
In the treatment of σ-bonded metal derivatives of mesomeric ions, the metal atom is given a bond to each ligating atom of each ligand. In σ-chelated derivatives, the model may contain one or more systems belonging to the "secondary" field of blending, wherein, typically, phantom atoms are delocalised. In cupric acetylacetonate *(17)*, each chelate ligand thus has mono-oxonium character, and carries three phantom atoms, one of which is delocalised. Metal porphyrins are chelated σ-complexes, and an example of this class is given in Section 5.4.



*(17)*

When a metal is π-bonded to a non-conjugated double or triple bond, then, in the valence-bond structure prepared for application of the sequence rule, the multiplicity of the bond is reduced by unity, and the atoms of the bond are made to bind the metal by single bonds, as illustrated for an olefin-platinum complex in *(18)*. When a metal is π-bonded to a conjugated unsaturated system, whether radical, ion, or molecule, for example, an allyl radical, a cyclopentadienylide ion, a cyclohexadienylium ion, a 1,3-diene, or benzene or a derivative, all the unsaturated atoms concerned in the binding of the metal are similarly made to bind it with single bonds, with a corresponding reduction in the formal unsaturation of the ligand, as illustrated for an allyl-cobalt complex in *(19)*. The resulting formulae are limiting with respect to the (not exactly known) degree to which the unsaturation electrons are binding the metal, and thus substituents, although they might alter the actual electron distribution, make no difference to the conventionalised π-bonded structures. The need for blending does not now arise. The convention covering this type of situation is therefore as follows:

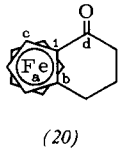
Convention for π-Complexes. *Those ligating atoms of an unsaturated ligand which are π-bonded to a metal atom are taken each to bind that atom with a single bond, their quadriligancy being preserved by reducing by unity the multiplicity of the multiple bonds in which they participate within the ligand.*



*(18)*



*(19)*



*(20)*

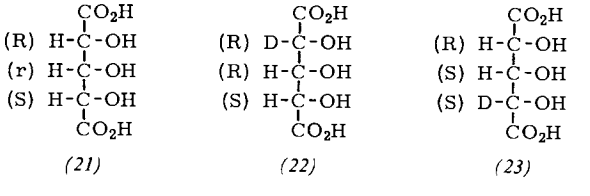
The use of such structures in the assignment of chiral symbols may be illustrated by reference to the optically resolved ferrocene ketone *(20)*, the represented configuration having been determined by *Schlögl* and *Falk*[11] for the enantiomer having $[\alpha]_D = +580°$ in

ethanol. Each of the five carbon atoms of the substituted cyclopentadienyl ring is an asymmetric atom, but the chirality of the whole molecule will be specified if we designate the chirality of any one of these atoms, conveniently C-1, the one most preferred by the Standard Sub-rules. In the sequence required for its designation, the first member, a, which is the iron atom, lies below the plane of the other three members, b, c, and d, as marked on *(20)*. Hence C-1 is *S*, and the ferrocene might be designated [*] as 1*S*.

### 2.3. Precedence of Sub-Rules: Ordering by Mass-Number

The rules scheduled in Sub-section 2.1, the Factorisation Rule, the Sequence Rule, with its Standard Sub-rules, and the Chirality Rule, are the fundamentals of sequence-rule procedure. Furthermore, the order of the rules and sub-rules is an essential part of the procedure, because stated specifications of chirality would be meaningless unless the order of use of the rules were known. We have to have a firm order, one in which opportunistic variations are not allowed. Therefore an order may not be prescribed which renders the sequence-rule system inoperable in some part of its legitimate field.

When Paper II was written, it was felt that, as ordering by isotopic differences would seldom be required, the mass-number sub-rule might conveniently be made the last sub-rule. It has, however, been pointed out to us by Prof. *Richter* and Dr. *Weissbach* that this prevents the sequence rule from specifying correctly chiral forms that can be derived by asymmetric isotopic substitution in a parent compound such as *(21)* or *(24)*. Compounds *(22)* and *(23)* are derived thus from the parent compound*(21)*. Had the mass-number sub-rule been allowed to remain last, they could not have been assigned the correct specifications shown: in both, the central atom would have been specified as *R* by the same earlier sub-rule that specified the central atom of *(21)* as *r*; and this would have been a *reductio ad absurdum*, inasmuch as *(22)* and *(23)* are enantiomers.




*(21)* *(22)* *(23)*

In order to avoid this difficulty, and reach the correct assignments shown, we prescribe that all ordering by material differences should be done before any ordering by stereochemical distinctions. Therefore, in the schedule of rules in Sub-section 2.1, the mass-number sub-rule has been re-numbered (2), and brought to a position immediately following the atomic-number sub-rule (1).

Similar arguments can be developed with respect to the internal order of the two former stereochemical sub-rules, now expanded to three, and numbered (3), (4), and (5). But in this case, the same principles of decision require that, as before, differences of geometrical isomerism be treated before chiral differences. The chief reason is that the sub-rules employing the latter are "parasitic" on the other sub-rules, requiring as intake-material, not merely the model itself, but also the answers that the other sub-rules give: wherefore, unless Sub-rules (4) and (5) were last, specifications in structures with many chiral centres could depend on the indeterminate order [*] in which the various chiral centres were specified.

The finally obtained order of the sub-rules, though reached essentially on pragmatical grounds, has a certain logical tidiness. Material differences are dealt with in sub-rules (1) and (2) before stereochemical in sub-rules (3) to (5); and, within each class, the grosser distinction is used before the finer, elemental before isotopic material differences, and differences involving scalar magnitude before those of vector-sense alone among stereochemical distinctions.

### 2.4. Ordering by Stereochemical Differences

The ordering of two groups, A and A′, which are identical except for a stereochemical difference, is based on Sub-rules (3) to (5).

We must first explain the special nomenclature that has been introduced into Sub-rule (3). This sub-rule was formerly written "*cis* precedes *trans*", and an explanation was added, of which it is easy to lose sight, unless signalised, as now, in the notation.

Applications of the terms *cis* and *trans* to group arrangements about an atom-pair XY in a double bond or ring have developed traditionally but irregularly, inasmuch as it has never been generally prescribed which substituent of a pair ab in Xab, and which of a pair cd in Ycd, are fiducial for the assignment of *cis* and *trans* labels to the whole arrangement abX=:::=Ycd. It is not our business to revise the nomenclature of geometrical isomerism; but we have to have a regulated method of supplying the geometrical labels that we require in the course of assigning chirality by the sequence rule. Our labels, now distinguished as *seqcis* and *seqtrans*, will not always correspond to the traditional ones *cis* and *trans*. But ours are mere scaffolding: they disappear in the final assignments of chirality; and hence they do not get embodied in chemical nomenclature. As a definition we may write:

> Seqcis and seqtrans. *An atom-pair is called seqcis or seqtrans according as the sequence-rule-preferred ligand bound to each atom of the pair is cis or trans with respect to the other such ligand.*

We assign our labels, *seqcis* and *seqtrans*, to the atom-pair XY, with respect to a double bond or ring to which it belongs, by taking as fiducial the sequence-rule-preferred substituent of the pair ab, and the preferred

[11] *K. Schlögl* and *H. Falk*, Angew. Chem. *76*, 570 (1964); Angew. Chem. internat. Edit. *3*, 512 (1964); *H. Falk* and *K. Schlögl*, Mh. Chem. *96*, 266 (1965).

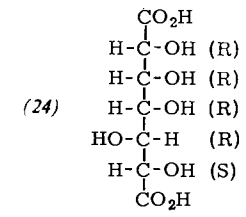
[*] In Professor *Schlögl*'s papers it is called *R*, and for this we are to blame, having expressed to him our agreement with that designation before our generalised treatment of metal π-complexes had been developed.

[*] We have no rules, and could not have any general rules, prescribing the order in which different chiral centres are to be assigned: feasibility is the sole condition (cf. Sub-section 2.1).

one of the pair cd. If atoms of the pair XY belong simultaneously to several rings, so that some of its substituents with respect to one ring are parts of other rings, the pair XY should first be assigned by this method a geometrical label with respect to each ring; and then, in case these labels are different, we accept as effective that which depends on the most preferred substituent of all, or the more preferred pair of fiducial substituents. The atoms of the pair XY might belong each to one of two co-planar double bonds in a series of cumulated double bonds, as in a cumulene; but, provided that a conventional label, *cis* or *trans*, could describe, the stereochemical relation of the fiducial substituents at X and Y, we shall apply a label *seqcis* or *seqtrans* to the atom-pair XY. And we shall use a similar method when double-bonds in such as cumulated system are replaced by rings, as in alkylidenecycloalkanes or spirans.

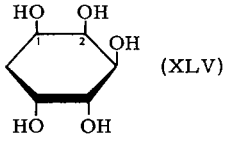
Having thus recognised the *seqcis* or *seqtrans* geometrical character of all relevant atom-pairs, we order the groups A and A′, as far as Sub-rule (3) allows, by exploring them for geometrical character, comparatively and in steps, from the chiral element outwards. If we number the atoms in A and in A′ independently from the chiral element, our first comparison is of the 1,2-atom-pair in A with the 1,2- in A′, the second is of the 1,3-pair in A with the 1,3-in A′, and so on, the general order being 1,2 > 1,3 > 2,3 > 1,4 > 2,4 > 3,4 > ..., where > means "precedes". Sub-rule (3) is applied to the first distinction encountered.

The previous sub-rule that *R* precedes *S* is replaced by Sub-rules (4) and (5), of which Sub-rule (4) is new. These sub-rules employ chirality specifications assigned to other elements of chirality. Such chirality specifications, when spread over two groups A and A′ that are not differentiated by the previous sub-rules, generate a true element of chirality, if at least one pair of specified elements of chirality in the group A is diastereoisomeric with the corresponding pair in the group A′. The new Sub-rule (4), which prescribes that *R,R* or *S,S* precedes *R,S* or *S,R*, and generally that a pair of specifications of like individual priority (see Sub-rule 5) precedes a pair of unlike, deals with this situation. The groups A and A′ are explored for already assigned pairs of specifications, comparatively, and in outward steps, the order of the comparisons, with the previous numbering, being 1,2 > 1,3 > 2,3 > ..., as above. Sub-rule (4) is applied to the first difference encountered. Formula *(24)* is a simple example of its application. Sub-rule (4) also prescribes that *r* precedes *s*. These symbols can by themselves distinguish such diastereoisomeric differences as are the subject of this sub-rule. The specification of chirality of an atom X in a structure of the type {*(RSr)*, *(RSs)*, a,b}X would exemplify this application. The earlier sub-rule that *R* precedes *S*, now generalised in Sub-rule (5), is used to assign chirality symbols to an atom X in combinations such as $(R_1,S_1,R_2,S_2)$X. This sub-rule is also used to specify diastereoisomerism characterised by pseudo-asymmetry of the type (*R*,*S*,a,b)Y. We specify pseudo-asymmetry, as before, by the symbols *r* and *s*, noting that they are unchanged on reflexion of the model.



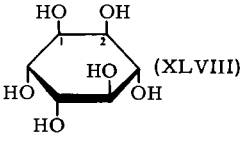

*(24)* - according to Sub-rule (4)

Turning to illustrations, we must first correct a mistake in Paper II, pointed out to us by the friends already mentioned [6]. This is that, in some of our assignments to cyclitols, we forgot, despite having stated it, that the geometrical characters, now denoted by *seqcis* and *seqtrans*, are internal to either group A or A′, and do not describe a relation of such a group to some other group of the complete set AA′bc. The formulae which were mis-labelled on this account, with their original numbers from Paper II, are reproduced below, but in association with the correct chiral assignments [*]:



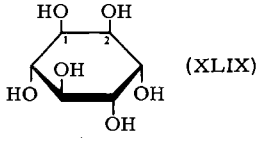

(XLV)

(1R, 2R, 4R, 5R)



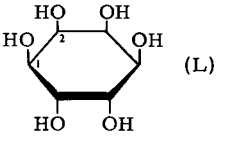

(XLVIII)

(1S, 2R, 3R, 4R, 5R, 6S)



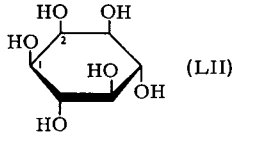

(XLIX)

(1S, 2R, 3R, 4S, 5S, 6S)



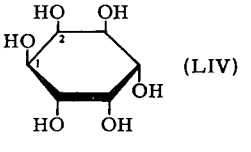

(L)

(1R, 2R, 3S, 4S, 5R, 6S)




(LII)

(1R, 2s, 3S, 4R, 5s, 6S)




(LIV)

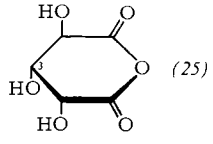
(1S, 2r, 3R, 4R, 5r, 6S)

We refer finally to some of the further examples that have come under discussion [6]. In the anhydride *(25)*, C-3 is symmetric, as in the free acid, and hence receives no label. In hydroshikimic acid *(26)*, and its diastereoisomer *(27)*, C-1 and C-4 are asymmetric, and are labelled by Sub-rule (3). In the myoinositol ether,

[*] The convenient "local" system of cyclitol notation, the so-called "fractional" system, illustrated in Paper II, automatically specifies absolute configuration, even within the type $(Xab)_n$, if the numbering system, applied within that type, and illustrated in the inositol series $(CH{-}OH)_6$ is employed. This system is applicable when no unambiguous starting-point for numbering is given by the constitution, apart from any stereospecificity, as, for example, in cyclic systems of the series $(Xab)_n$, $(Xab{-}Ycd)_n$, $(Xab{-}Ycd{-}Ycd)_n$, $(Xab{-}Ycd{-}Zef{-}Ycd)_n$, ... The numbering system involves so placing the ring horizontally that at least as many fiducial groups (OH in the examples) point upward as downward, and that lowest numbers may mark the former when the ring is numbered clockwise from above. Thus the (−)- and (+)-inositols, (XLVIII) and (XLIX), are specified as to absolute configuration by their local-system prefixes (1,2,4/3,5,6)- and (1,2,5/3,4,6)-, respectively. Although no additional symbols are required, one could signalise each enantiomer with an additional configurational symbol, such as 4*R* or 4*S*: one need not fall back on symbols that signify optical rotation only. It will be clear that the numbers used in this system satisfy our requirement of suggesting no genetic relations between the atoms of (XLVIII) and those of (XLIX).

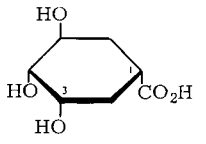
bornesitol *(28)*, and its diasteroisomer *(29)*, C-1 and C-4 are labelled by Sub-rule (3), and the difference at C-1 shows in the symbols for its chirality.

Example *(30)* has been contrived as a case of special complexity, inasmuch as the specification of chirality of C-7 depends on a stereochemical difference between the 1,2- and 4,5-atom-pairs, each belonging to two rings with respect to which it has opposite geometrical descriptions. However, the specification is not difficult to follow. With respect to its five-membered ring, the



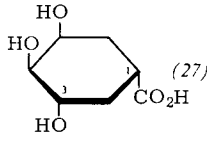
*(25)*

(2R, 4R)



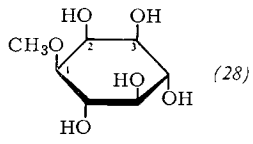
*(26)*

(1S, 3S, 4R, 5S)



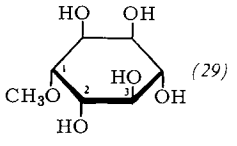
*(27)*

(1R, 3S, 4S, 5S)



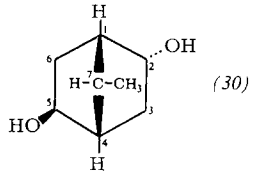
*(28)*

(1R, 2S, 3S, 4R, 5R, 6S)



*(29)*

(1S, 2S, 3R, 4R, 5S, 6S)

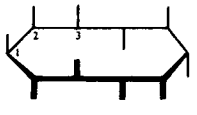


*(30)*

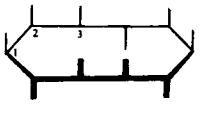
1,2-atom-pair carries the fiducial substituents 6-$CH_2$ and 2-OH, which are *cis*. With respect to the six-membered ring, the fiducial substituents carried by the same atom-pair are 7-CHMe and 2-OH, which are *trans*. The latter fiducial pair is the more preferred, and hence the 1,2-atom-pair is *seqtrans*. Similarly, the 4,5-atom-pair is *seqcis*. Hence the chirality of C-7 is described as *S*, and the specifying prefix for compound *(30)* is (2*R*, 5*S*, 7*S*) [*].

[*] In applying the stereochemical Sub-rules as prescribed in the text, we do not reflect, in the final description, *R* or *S*, of the asymmetric atom under specification, *all* the details of the stereochemistry on which that description depends. Thus, when a specification depends on ordering groups by Sub-rule (3) or (4), we do not show in the final symbol by which of their atom-pairs they were ordered, whether by the 1,2-pairs, or 1,3-, or other pairs; and when ordering by Sub-rule (5), we do not finally show by which atoms the groups were ordered.

This failure to express part of the provided data must in principle open the possibility of lost distinctions in the resulting descriptions, so that two stereochemically different models would receive the same description. Actually, such cases seem so rare that we think that it would be a mistake to to elaborate descriptions as a routine, though they can easily be elaborated in order to separate them when required. No case has yet been realised experimentally, and the only ones yet thought of, as far as we know, both by Dr. *Weissbach*, are two pairs among the 44 diastereoisomers of $X(ab)_{10}$, *e.g.*, of cyclodecanedecaols.



*(30a)*



*(30b)*

*(30a)* $1R^{\alpha\beta}$, 2s, $3S^{\alpha\beta}$, $4R^{\alpha\gamma}$, $5R^{\alpha\gamma}$, $6S^{\alpha\gamma}$, 7s, $8R^{\alpha\gamma}$, $9S^{\alpha\gamma}$, $10S^{\alpha\gamma}$

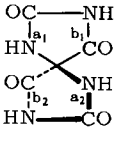
*(30b)* $1R^{\alpha\beta}$, 2s, $3S^{\alpha\beta}$, $4R^{\alpha\beta}$, $5R^{\alpha\beta}$, $6S^{\alpha\beta}$, 7s, $8R^{\alpha\beta}$, $9S^{\alpha\beta}$, $10S^{\alpha\beta}$

## 2.5. Central Chirality: Symmetry and its Procedural Consequences

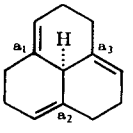
We have not previously considered what types of symmetry can be accepted by a quadriligant chiral centre. Such a centre can fall into any of the following four symmetry classes. The most familiar and by far the most extensive class is that of no symmetry ($C_1$ in Schoenflies symbols), as in Cabcd, the asymmetric carbon atom.

The next higher symmetry class, among those to which chiral centres can belong, contains one two-fold axis (class $C_2$). An illustration can be derived from achiral Caabb by making each ligand b related differently to the a's, and each ligand a differently to the b's, as can be done by connecting each ligand a with a separate b in equivalent rings. This proceeding destroys the two previously present planes of symmetry, but it retains the two-fold rotational axis. The resulting spiro-compound, (ab)C(ab), is chiral. Its two-fold axis passes through the mid-point between the a's, the atom C, and the mid-point between the b's.

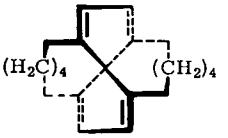
As an example, we may take the spiro-hydantoin *(31)*, treated in Paper II, as we now know, incorrectly, on the basis of axial chirality. Its chiral centre, the spiro-atom, has, as its next neighbours, two equivalent nitrogen atoms, and two equivalent carbon atoms; and the specification of its chirality provides a further application of the general principle, illustrated in Paper II, that when a choice has to be made between equivalents for the leading place in a sequence, the choice is immaterial, provided that, once made, its consequences are followed through. Here we may take, as first member of the sequence, either of the next-neighbour nitrogen atoms, say, $a_1$. The first consequence of this choice is that the other next-neighbour nitrogen atom, $a_2$, must constitute the second member of the sequence. Of the next-neighbour carbon atoms, that which occupies the same ring as the most preferred nitrogen atom will take the third place. It will be $b_1$. The reason is that exploration from it, outwards and round the ring, will lead to the more preferred nitrogen atom, $a_1$, whereas the comparison exploration from the other next-neighbour carbon atom, $b_2$, round the other ring will similarly lead to the less preferred atom, $a_2$, of the next-neighbour



*(31)*



*(32)*



*(33)*

The elaboration would consist simply in showing the atom-pairs used in applying Sub-rule (3) or (4), or the atoms used in applying Sub-rule (5), by means of a superscript associated with the final symbol of chirality; but we suggest using Greek letters, rather than numbers, for outward-enumeration of the stereochemically compared groups, in order to avoid confusion with nomenclatural enumeration in the model as a whole. In one of the pairs mentioned above, of cyclodecanedecaols *(30a)* and *(30b)*, the symbols for the asymmetric atoms, based on Sub-rule (3), are elaborated as described, whilst the symbols for the pseudo-asymmetric atoms, based on Sub-rule (5), require no elaboration.

nitrogen atoms. The sequence is thus completed, and it shows that the model represented at *(31)* is an *S*-enantiomer.

The third of the symmetry classes into which a chiral centre may fall contains one three-fold axis as its only symmetry (class $C_3$). An illustration can be derived from achiral Caaab by connecting the a's in cyclic sequence with three like bridges that have no transverse symmetry-plane. This gives, to each ligand a, identical differences of relationship with other a's. It destroys the previous three planes of symmetry, but retains the three-fold axis. The hexahydrophenalene *(32)* will serve as an example. Its chiral centre, the carbon atom common to its three rings, may be assigned its symbol of chirality by the method just illustrated. Any of its three, equivalent, next-neighbours, say, $a_1$, may be placed first in sequence. The second will be that other one, $a_2$, from which outward exploration, along the route of highest precedence, that is, starting with a double bond, leads the more directly to it. The model shown is an *S*-enantiomer.

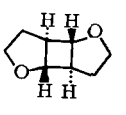
The fourth symmetry class available to a chiral centre has three two-fold axes of symmetry (class V). The case can be derived from tetrahedral Caaaa be connecting the a's cyclicly as in *(33)*, with four bridges of two kinds introduced alternately, each bridge having a transverse plane of symmetry. In the resulting double spiran, the original six planes of symmetry, and the four three-fold axes of symmetry, are destroyed, and only the three two-fold axes remain. The chirality of the central atom is specified as in the preceding examples. Any of its four, equivalent, next-neighbour atoms may be placed first in sequence, and then that which shares the five-ring with it will come second, and that which does not share a ring with it will come third. The model represented is in the *R*-configuration.

We may consider the relation of a tetrahedral atom to higher symmetry classes, in particular, to the class of highest chiral symmetry within the scope of quadriligancy, *viz.* the class T, which is characterised by four three-fold and three two-fold rotational axes of symmetry. It is possible to build a molecule of symmetry T round a tetrahedral atom by bridging in pairs with six like bridges four like tetrahedral atoms directly bound to it, each bridge containing a plane of chirality which destroys planes of symmetry, but preserves a two-fold rotational axis between the atoms bridged. The bridges might, for example, be *trans*-olefinic, of the form $-(CH_2)_n-CR=CR-(CH_2)_n-$. The chiralities of the chiral planes being alike, the four three-fold axes of rotation will be preserved, and hence the overall symmetry will be T. But no symbol of chirality can be assigned to the central atom, and the chirality of the structure derives from its outer planes of chirality. We have here described a chiral envelope, and we shall describe and illustrate the simpler case of a chiral girdle in Sub-section 2.7.

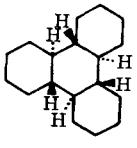
A further problem in the detailed method of designating the chirality of chiral centres in the presence of rotational axes of symmetry arises when such axes inter-relate *equivalent chiral centres*[*]. It may then happen that outward exploration of two ligands belonging to one centre, along routes of highest precedence, will lead, without producing on the way any distinction useful for ordering, for one ligand, back to the original chiral centre, and, for the other, to its symmetry-equivalent. When that happens, we give precedence to the ligand which has not led back to the original chiral centre. The situation is highly specialised, but it needs, in extension of the Sequence Rule, a Rule for Equivalent Centres, as follows:

Rule for Equivalent Centres. *Of two ligands at a chiral centre, whose only distinction is that, on exploration under the Sequence Rule, one leads to the original centre whilst the other leads to an equivalent centre, the latter takes precedence in the sequence of ligands.*

An example, belonging to the $C_2$ symmetry class, is furnished by structure *(34)*. The stereochemistry of these compounds has been discussed[12]. The inner ring consists of two pairs of equivalent chiral centres, and in formula *(34)* all are in *R*-form. Specifying the chirality of any of them involves giving that one of its ligands, which starts with CH in the same hetero-ring, lower precedence than that which starts with the other CH. This order follows from our preference, when a distinction depends on it, for a route which, in the comparative exploration, does not return to the original chiral centre.



*(34)*



*(35)*

An example of higher symmetry is provided by the *trans*-perhydrotriphenylene *(35)*. It belongs to the class $D_3$, having one three-fold and three two-fold rotational axes of symmetry. The central ring consists of six equivalent chiral centres, which, as here illustrated, are all in *R*-form. The process of specifying any of them is as in the previous example. It may be worth noting that, in both examples, exploratory routes of highest precedence (leading round the central ring in opposite ways) yield no distinction, wherefore, at the first branching point, exploration is continued along the routes next in precedence (which lead round the separate lateral rings).

### 2.6. Axial Chirality: Scope, Procedure, and Symmetry

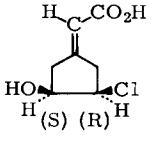
We mentioned in Sub-section 1.5 the derivation of axial chirality by the giving of one dimension to an original chiral centre. We referred also to the five main areas of application of the concept of axial chirality, namely, to allenes, alkylidenecycloalkanes, spirans, biaryls, and

[*] A similar problem arises in infinite regular polymers, when such equivalence is produced by a translation, without or with rotation.

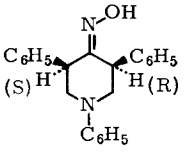
[12] *M. Farina* and *G. Bressan*, Makromolekulare Chem. *61*, 79 (1963); *G. Natta* and *M. Farina*, Tetrahedron Letters *1963*, 703; *M. Farina*, *ibid.* *1963*, 2097.

adamantoids, along with their respective isomorphs. In these areas, the axis of chirality is derived by desymmetrization from a four-fold alternating axis of symmetry: that is its fundamental property. To mention the chemical classes which provide examples of axial chirality is not, of course, to suggest laying aside the Factorisation Rule, in accordance with which the chirality of many alkylidenecycloalkanes and spirans, for example, will be fully specified in terms of chiral atoms, without requiring recourse to an axis of chirality.

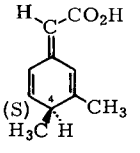
Discussion has shown [6] that our original statement in Paper II on the *scope of axial chirality* needs amplification with respect to certain special types of case. Thus, the alkylidenecycloalkane and piperidone oxime, shown at *(36)* and *(37)*, do not fall within the scope of axial chirality, though they might, perhaps, have been thought to do so. The reason that they do not is that, when the chiral centres in the rings have been assigned, the remaining matter is purely one of geometrical isomerism, outside the province of the sequence rule. Once the rules for assigning the *cis* and *trans* labels have been determined, the stereochemical specifications can be finished. (In the meantime, the exocyclic double bonds might provisionally be labelled *seqcis* in the forms here represented.) Example *(38)* also has nothing to do with axial chirality; for C-4 is an asymmetric carbon atom, and the description of the exocyclic double bond, as *cis* or *trans*, is out of our hands.



*(36)*



*(37)*



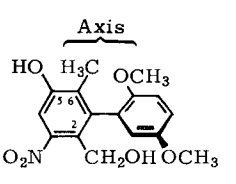
*(38)*

The other matter of scope concerns the chiral spirans. It is understood that spirans are a chemical class, and not a chirality class, and that therefore they can extend into more than one chirality class (Sub-section 1.3). They may exhibit either central or axial chirality, and in either case may either be asymmetric or possess rotational axes of symmetry. Examples *(31)* and *(33)* illustrate centrally chiral spirans with symmetry $C_2$ and V, respectively. Formula *(4)* on p. 388 represents an axially chiral spiran without symmetry. But by replacing the end-groups cd by ab, it could be given symmetry $C_2$, without losing its axially chiral character.

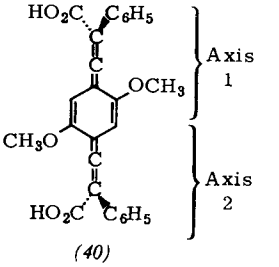
A *change of procedure* is now proposed in the choice for ordering of groups about an axis, when more groups are present than are needed for the specification of chirality. The first atom of each such group must be an atom bound directly to the chiral axis; but there are, for instance, four such atoms (the carbon atoms 2,3,5, and 6) in each ring of a biphenyl compound, whereas we need no more than two in each ring.

Sub-rule (0) has to be taken into account. It prescribes that groups about the near end of an axis take precedence over groups about the far end. It never matters which end is taken as the near end, provided that the choice, once made, is adhered to. In Paper II, we had this sub-rule in mind when proposing that the nearest and furthest pairs of groups should be chosen. It now would seem more convenient if, on the contrary, we take the extended tetrahedron *(1)* (p. 388) as defined by the pairs nearest together of groups that lie one pair on each of the planes that intersect along the axis.

The arguments for doing this, due entirely to Prof. *Richter* and Dr. *Weissbach*, are (a) that the fiducial groups are then more often those most intimately concerned in producing the chirality, especially in the biaryl series where choice is most often necessary; and (b) that by giving chiral axes a minimum effective range, we can deal more easily with molecules containing several. These points are shown in the examples *(39)–(42)*, in each of which the chiral descriptions would be changed by allowing the axis or axes more than minimal effective lengths, whilst in two cases an overlapping of axes would result. In example *(42)*, we have, beyond the effective axis, a geometrical configuration requiring to be specified as *cis* or *trans*, when the methods for doing so are provided.



*(39)*



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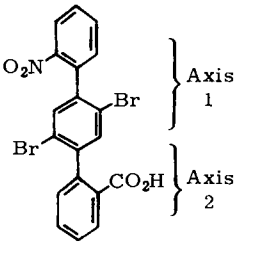
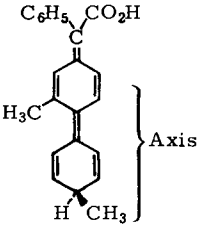


*(41)*



*(42)*

It should be noted that, when ordering groups, which necessarily start with first off-axis atoms, for instance, with the 2- and 6-carbon atoms of one ring in a biphenyl, we allow exploration over the whole molecule. It follows that the order of the 2- and 6-atoms is not always determined solely by the 2- and 6-side-chains. Example *(39)* has been chosen to illustrate the point. Here, the methyl-bearing carbon atom derives precedence over the methylol-bearing one by virtue of an exploration from the former through the carbon atom which bears the phenolic hydroxyl group.

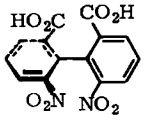
The Selection Rule for Axial Chirality, which defines the groups that are to be taken as fiducial, is as follows:

> **Selection Rule for Axial Chirality.** *The fiducial groups shall be the pairs nearest together of groups, directly bonded to atoms on the axis, that lie one pair in each of the planes of atoms that intersect along the axis.*

This revised procedure changes one of the axial assignments in Paper II, that of the formula there numbered (LXXIV), which would now be described as an

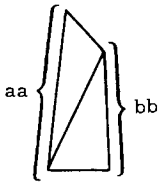
*S*-enantiomer. The new procedure does not change any of the designations tabulated by *Mislow*[13] of known absolute configurations in the biaryl series.

The illustrations of axial chirality given in Paper II, and here up to this point, have been random as to *symmetry classification*, with the result that one symmetry class is not yet illustrated. Within the limit of atomic quadriligancy, axial chirality can be found in three symmetry classes. The first ($C_1$ in Schoenflies symbols), represented in a general form by *(1)* on p. 388, and illustrated by *(39)*, has no symmetry. The second (class $C_2$), represented by *(44)*, and exemplified by *(43)*, has one two-fold axis. The third (class V), which we now want to consider, has three two-fold axes.

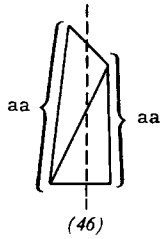



*(43)*

*(44)*




*(45)*



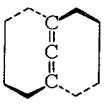

*(46)*

Starting from *(44)*, we can develop the more highly symmetrical form of axial chirality, by connecting like groups with bridges having transverse planes of symmetry as in *(45)*. This only adds a stereochemical distinction to the constitutional one between the members of either a,b-pair, and hence it does not change the symmetry ($C_2$). We can now abolish the constitutional distinction, as in *(46)*, and, because the stereochemical distinction is here preserved, chirality is retained. But the new structure contains three two-fold rotational axes (symmetry V). Naturally, one of these, the axis of chirality (marked), remains unique, as the only four-fold alternating axis when the stereochemical distinction, on which chirality depends, is destroyed by opening the aa-rings into four independent a-groups. The other axes become indistinguishable, as they should, as completely equivalent two-fold rotational axes.

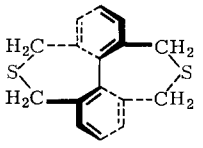
It is easy to allot a symbol of chirality to *(46)*, as follows. The ends of the chiral axis are alike, but we know (Paper II) that it is immaterial which end we select as the "near" end when applying Sub-rule (0). Again, as illustrated several times in Sub-section 2.5, it is immaterial which of two equivalent atoms, in this case the two a-atoms of the selected near end, we choose as first in sequence. The other a-atom of the near end will be second, and that a-atom of the far end, from which exploration round the ring would lead to the first atom of the sequence, will come third. Structure *(46)* has the *R*-configuration.

[13] *K. Mislow*, Angew. Chem. *70*, 683 (1958).

A simple molecule having the symmetry of *(46)* is the bicyclic allene, whose *R*-enantiomer is shown at *(47)*. The first optically active compound of symmetry V to be prepared is the biaryl bis-sulphide, the *R*-form of which is shown at *(48)*. *Mislow* and *Glass*[14] obtained this compound, the *R*-enantiomer of which had $[\alpha]_D^{26} = +415°$.



*(47)*




*(48)*

An axis may be pseudo-asymmetric. If one of the ligand-pairs ab in structure *(44)* consisted of *R* and *S* modifications of the same substituent, we should expect two diastereoisomers, which would both be optically inactive, because each molecule now has a plane of symmetry. We should distinguish them by the lowercase symbols, *r* and *s*.

### 2.7. Planar Chirality: Procedure and Symmetry

A procedure for the specification of planar chirality was proposed in Paper II. We now wish to modify the method in a way that allows it to be prescribed more closely.

The first step is the selection of a plane of chirality, which must be derived by desymmetrisation of a plane of symmetry; but this easily satisfied geometrical condition may leave open various possibilities. In Paper II it was considered convenient to choose a plane containing as many atoms as possible; and in the illustrations there presented, atoms were brought on to the chiral plane by deformations giving structures which could be quite unlike the natural ones. The first change we would now make is to disallow such drastic formalism, and to employ only natural planes of atoms (with at most minor idealisation) as in systems of unsaturated, including conjugated unsaturated, and aromatic atoms, and the atoms directly bound to such systems. When a structure contains several chiral planes as thus defined, it is obviously necessary, at least in so far as the planes are non-equivalent, that the chiral description of each should indicate the plane to which it refers. Such non-equivalent planes may be stereospecifically unlinked or linked; but even if they are linked, in the sense that the chirality of one determines that of all, we consider that it would render interpretation easier and less liable to error, to specify them all.

The second step, which we do not modify, is to identify a preferred side of the plane, a "nearer" side under Sub-rule (0) of the Sequence Rule, that is, the side containing the locus from which observation of the model is made in applying the Chirality Rule, which requires remoteness of the locus from the lower precedences of the "further" side. This preferred side is identified by

[14] *K. Mislow* and *M. A. W. Glass*, J. Amer. chem. Soc. *83*, 2780 (1961); *Idem*, *H. B. Hopps*, *E. Simon*, and *G. A. Wahl*, *Jr.*, *ibid. 86*, 1710 (1964).

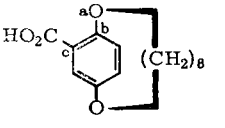
finding, among atoms of the set directly bound to the atoms of the plane, that which is most preferred by the Standard Sub-rules (1)–(5). In making the determinative comparisons, each atom is considered in the environment of the whole molecule, not merely in that of the set, or the relevant side of the chiral plane. The most preferred atom of the set directly bound to the plane, the leading atom or "pilot" atom, as we may call it, marks the preferred side of the plane. We call it the "pilot" atom, because of its function in the step next to be considered.

This third step is to develop the chirality-specifying sequence. And here we propose another departure from our previous procedure: instead of developing the sequence adjacently to the chiral plane, we develop it in the plane. So we pass from the already identified, off-plane, pilot atom to the in-plane atom to which it is directly bound, or, if there are several such, to that preferred by the Standard Sub-rules. This atom is now identified as the first atom of the inplane sequence, the atom of highest precedence in the pattern to which the Chirality Rule will be applied. The second atom in the sequence is that one of the in-plane atoms directly bound to it, which is most preferred by the Standard Sub-rules. The third in sequence is that atom (other than the first) directly bound to the second, which is most preferred by the same Sub-rules. As the sequence is to be continued until the Chirality Rule can be applied, a condition that might sometimes necessitate development of the sequence to more than three atoms (for instance, if linear acetylenic systems had to be passed through), we must add to the above the general prescription that the *n*th atom in sequence is that (other than the *n*-2nd) directly bound to the *n*-1st, which is most preferred by the Sub-rules. In making these comparisons by means of the Standard Sub-rules, we take the whole molecule, and not the plane only, as the relevant environment of each atom considered. We had an off-plane locus from which to observe the chiral plane, and now we have an in-plane sequence of the necessary number, three or more, of atoms to observe from the locus. We are accordingly in a position to apply the Chirality Rule.

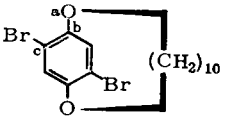
We summarise this procedure in the following Selection Rule for Planar Chirality, which defines the atoms that are to be taken as fiducial:

> Selection Rule for Planar Chirality. *Of atoms directly bound to atoms in the plane, that most preferred by the Standard Sub-rules, the pilot atom, marks the side of the plane from which, under the Chirality Rule, an in-plane sequence is observed; and the sequence starts with the in-plane atom directly bound to the pilot atom, and continues, to and through other atoms, by way of a succession of bonds along that in-plane path, which at each branch leads to the atom more preferred by the Standard Sub-rules.*

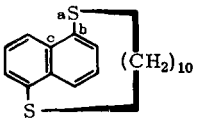
This change of method does change several assignments of chirality in Paper II (but none by other authors). *Lüttringhaus* and *Gralheer*'s quinol and naphthalene-1,5-dithiol polymethylene ethers, examples (LXXIX), (LXXX), and (LXXXIII) of Paper II, are shown at *(49)–(51)*, in what we must now call *R*-form. In each, the aromatic plane is taken as the chiral plane, and the in-plane sequence is marked a, b, c. In two of the examples, two equivalent sequences may be found: they give the same chiral specification. *Cram*'s cyclophane-type acid and anhydride, examples (LXXXV) and (LXXXVI) of Paper II, are shown at *(52)* and *(53)*, in *R*- and *S*-form, respectively, when aromatic planes are taken as chiral planes. The in-plane sequences are as marked. The reason for the change of label between the acid and anhydride is that the pilot atom in the former is a methylene-carbon atom, whereas in the latter it is an anhydride-oxygen atom. In the anhydride, two equivalent chiral planes are present.



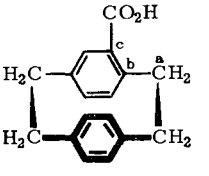
*(49)*



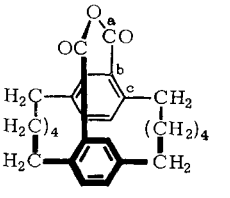
*(50)*



*(51)*



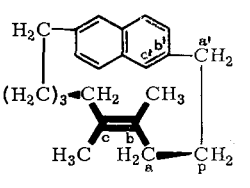
*(52)*



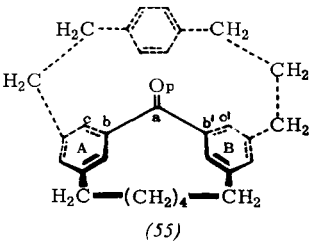
*(53)*

In the acid and anhydride depicted at *(8)* and *(9)* on p. 389, the aromatic planes constitute two non-equivalent chiral planes. The acid is in *R*-form with respect to the plane of the unbrominated benzene ring, and in *S*-form with respect to that of the brominated ring. In the anhydride these labels become reversed, for the reason just explained in another example. Obviously, the descriptions of chirality must show (for example, by numbering) to which planes they respectively refer.

Two further examples (as yet unrealised) will illustrate how two chiral planes may have a common pilot atom, and even a common atom among their in-plane sequences. Structure *(54)* has an ethylene plane and a naphthalene plane, and the carbon marked p is pilot for both. The marked sequences show that the model is *R* about the ethylene plane and *S* about the naphthalene plane. In structure *(55)* the benzenoid planes A and B are twisted from the plane abb′ about the lines ab and ab′, respectively; and so the carbonyl-oxygen, p, is off both planes, and is pilot to both; whilst the carbonyl-carbon, a, is the common first atom of the two in-plane sequences. The model is thus *R* about plane A, and *S* about plane B. Again one sees the need to attach indications of location to these descriptions of chirality.



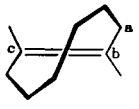
*(54)*



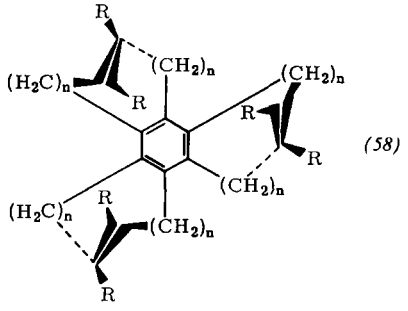
*(55)*

The *trans*-cyclo-olefins offer examples of planar chirality. Some compounds of this type have been optically resolved by Cope and his co-workers, who for *trans*-cyclo-octene itself have determined the absolute configurations of the enantiomers[15]. The double-bonded carbon atoms, and the four atoms bound to them, now provide the plane of chirality. There are two equivalent in-plane sequences, one of them marked a, b, c in *(56)*, and it follows from either that the *R*-enantiomer is being represented. Two of the three atoms in either in-plane sequence are equivalent.

*(56)*



*(57)*

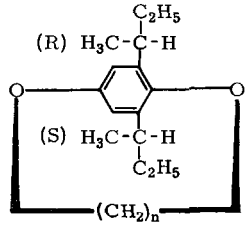



*(58)*

We conclude this sub-section with some remarks on the *symmetry classes* allowed in planar chirality. The examples already mentioned fall into two classes. Examples *(8)* and *(9)* on p. 389, and *(49)* and *(52)* above, have no symmetry (class $C_1$). Examples *(50)*, *(51)*, *(53)*, and *(56)* have one two-fold axis of rotation ($C_2$). The next higher class would have three two-fold axes of rotation (V). No case of such has yet been demonstrated, but a possible case would be furnished by a bis-(*trans*-polymethylene)ethylene, such as *(57)*. Again, the double-bonded atoms and the atoms bound to them define the chiral plane. There are now four equivalent off-plane atoms, any of which could be chosen as pilot to the corresponding in-plane sequence. Of course, there are four equivalent in-plane sequences. But whichever we work with, the result is the same: our diagram represents the *R*-form. Once again, two atoms of any of the in-plane sequences are equivalent.

We may consider the relation of an atomic plane to higher symmetry classes having chirality. An atomic plane of symmetry $D_{2ph}$ can be made the centre of a chiral molecule of symmetry $D_p$, characterised by one *p*-fold and *p* two-fold rotational axes of symmetry. We could, for example, build such a molecule round a central benzene ring ($p = 3$), by bridging its three pairs of *ortho*-situated bonds with three independent and completely equivalent bridges, each with a centrally situated plane of chirality in some definite, common, chiral form. Each bridge will destroy the plane of symmetry between the *ortho*-bonds, as well as that containing the bonds, but will preserve the two-fold rotational axis between the bonds. We might employ *trans*-olefin bridges, as in formula *(58)*. The chiralities of their planes being alike, the three-fold axis of rotation of the molecule is preserved, and the molecule has symmetry $D_3$. It is chiral, but its chirality depends on its girdle of chiral planes, which, however, induce no fixed chirality in the plane of the central ring.

A plane may be pseudo-asymmetric. If the path in the chiral plane turns in a particular sense only because of the distinction between symmetrically placed *R* and *S* varieties of the same group, as in the 2,6-di-s-butylquinol polymethylene ether *(59)*, we should expect two diastereoisomers both optically inactive, because each contains a plane of symmetry. We would distinguish them by the lower-case designations, *r* and *s*.




*(59)*

## 2.8. Secondary Structures

This chemical term of structural classification arose with the growth of our knowledge of protein structure. It has never been adequately defined; but it conveys a distinctive idea, which can be generalised. To what extent it will become generalised as chemistry advances, it is not possible to foresee.

The most celebrated example is the hydrogen-bonded α-helical form of polypeptides, first recognised by *Pauling* and *Corey*[16]. It is shown in *(60)*, opened out after making a cut parallel to the helical axis. If this projection is wrapped into a cylinder by joining the points AA, and the points BB, behind the paper, the peptide chain will describe an *M*-helix, whilst, if the junctions are made in front of the paper, the chain will describe a *P*-helix. It has been made very probable, both theoretically[17] and practically[18], that polypeptides derived from L-enantiomers of primary amino-acids favour the *P*-helix. Any such polypeptide has an optical rotation derived partly from the chirality of the primary structural units, and partly from the chirality of the secondary helical form. It has been estimated[19] that the partial rotation due to the *P*-helix of poly-*S*-alanine in chloroform is $[\alpha]_D = +82°$.

[15] *A. C. Cope, C. R. Ganellin*, and *H. W. Johnson, Jr.*, J. Amer. chem. Soc. *84*, 3191 (1962); *Idem, T. V. Van Auken*, and *H. J. S. Winkler, ibid. 85*, 3276 (1963); *A. C. Cope* and *A. S. Mehta, ibid. 86*, 5626 (1964).

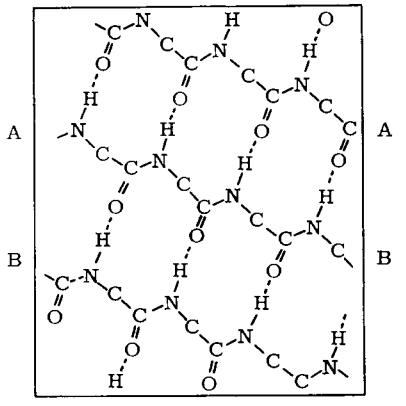
[16] *L. Pauling, R. B. Corey*, and *H. B. Branson*, Proc. nat. Acad. Sci. U.S.A. *37*, 205 (1951); *L. Pauling* and *R. B. Corey, ibid. 37*, 235 (1951); Proc. roy. Soc. (London) B *141*, 21 (1953).

[17] *W. Moffitt*, J. chem. Physics *25*, 467 (1956); Proc. nat. Acad. Sci. U.S.A. *42*, 736 (1956); *W. Moffitt. D. D. Fitts*, and *J. G. Kirkwood, ibid. 43*, 723 (1957); *S. F. Mason*, Nature (London) *199*, 139 (1963).

[18] *A. Elliott* and *B. R. Malcolm*, Proc. roy. Soc. (London) A *249*, 30 (1959); *J. C. Kendrew, R. E. Dickerson, B. E. Strandberg, R. G. Hart, D. R. Davies, D. C. Phillips*, and *V. C. Shore*, Nature (London) *185*, 422 (1960).

[19] *A. R. Downie, A. Elliott, W. E. Hanby*, and *B. R. Malcolm*, Proc. Roy. Soc. (London) A *242*, 325 (1957).

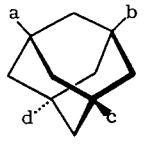
The helicenes, such as those with which axial chirality was illustrated in Paper II, might well, on grounds of obviousness, be treated as secondary structures. In the example shown at *(61)*, the benzene rings form an *M*-helix, and thus the chiral description *M*, as applied to the whole model, is very easily interpreted.




*(60)*

*(61)*

The adamantoid series could provide chiral structures, which might conveniently be treated as secondary, inasmuch as their gross structure is as obviously tetrahedral and amenable directly to the Chirality Rule, as that of the helicenes is obviously helical and directly responsive to the Helicity Rule. Although it has not yet been done, it would certainly be possible to substitute the four tertiary hydrogen atoms of adamantane with four different groups, as in *(62)*. The four carbon atoms thus made quaternary would all be asymmetric, and they could, of course, be specified separately with respect to their chirality as asymmetric atoms. But their chiralities are so interlinked that they can collectively produce only one pair of enantiomers. And so it would seem more convenient to specify their chirality, and hence that of the structure, collectively, by reference to a centre of chirality taken at the unoccupied centroid of the adamantane frame.




*(62)*

A still simpler chirally central, secondary structure would be furnished by the tetrahedral $X_4$ unit, well-known in inorganic chemistry, though not yet known in chiral form.

Catenanes are necessarily handled as secondary structures. The secondary chirality of any pair of interlinked rings may be described by selecting the most preferred and the next most preferred atoms, a and b respectively, of one ring, and the most preferred and next most preferred atoms, c and d, respectively, of the other ring, arranging the atom-pairs ab and cd as remotely from each other as possible, and then fitting them to the tetrahedron *(1)* on p. 388. If the pairs ab and cd are identical, we may use the tetrahedron *(44)* on p. 400. In either case, the Standard Sub-rules and the Chirality Rule are applied as for axial chirality [*].

## 3. Chirality to Ligancy Four: Nomenclature Problems

### 3.1. Specification of Chirality in Names

The specification of the chirality of a compound by the sequence-rule procedure is rigidly defined by the space-model. No such rigid procedure can be applied for adding symbols of chirality to the name of a compound, since that name may vary according to which of the various permissible systems of nomenclature is used, the purpose which the name serves, or linguistic characteristics.

In Paper II we recommended that the symbols of chirality be placed in front of the otherwise complete name, in parentheses, accompanied by any necessary indications of location, as, for instance, in (*R*)-2-methylpentan-1-ol, (2*S*,4*R*)-4-hydroxyproline, or (*S*)-methyl lactate. Partly owing to experience at the Beilstein Institute, for an account of which again we are indebted to the late Professor *F. Richter*, it now seems that this simple direction needs expansion or modification in various circumstances.

As a simple variant, of complete generality, it is immaterial if, for convenience in an index or for some linguistic reason, the symbols are written after the name, as in 4-hydroxyproline-(2*S*,4*R*). We adhere, however, to our view that these symbols of chirality should not normally be inserted in the interior of a name, for reasons given in Paper II (nevertheless see below, especially Sub-section 3.3).

In the remainder of this Section, we deal with five types of case, attempting to show by examples where general types of variation may be required; but one set of these cases, that discussed in Sub-section 3.4, needs some further preliminary remark.

We shall consider in Sub-section 3.4 how far it is necessary or desirable separately to include in a name the specifications of chirality for all the chiral elements present, in particular, the centres of chirality. Obviously, one must include them all when they could be independently inverted, as, *e.g.*, could those of (2*S*,4*R*)-4-hydroxyproline. However, structures exist in which such independent inversion is impossible, as, *e.g.* in camphor, which, despite its two chiral centres, has only two possible configurations, *viz.* 1*S*,4*S* and 1*R*,4*R*.

The routine of specifying all such stereospecifically linked chiral centres (at least if non-equivalent and non-enantiomeric) was established in Paper II. We favour a similar principle of individual treatment for chiral elements generally, because the resulting descriptions can be checked against one another, so providing more

[*] This is the central point in part of a paper by *S. J. Tauber* [20], to which the reader is referred for much interesting detail and development.

[20] *S. J. Tauber*, J. Res. nat. Bur. Standards *67* A, 591 (1963).

security against error; and furthermore, because we then have no need of any general rules to determine which of a stereospecifically linked assembly of chiral elements should be treated as titular for the assembly. This is a broad guiding principle, one to be applied reasonably. Cases will arise, for instance, among adamantoids and among ferrocenes, in which the inconvenience of specifying the chirality of every one of a considerable number of linked chiral elements will provide a dominating argument for not doing so. When linked chiral elements are equivalent or enantiomeric, it will usually be easy to decide (and will largely depend on whether other chiral elements are present) what elisions or condensations of chiral symbols can be made without risk of obscurity.

Against this general background, we have to recognize the important opportunities for simplifying the notation of chirality, which arise when some part of the name of a compound defines the relative configurations of a number of its chiral centres. How advantage may be taken of these opportunities is discussed in Sub-section 3.4.

### 3.2. Mixtures of Stereoisomers

The sequence rule has to analyse and specify some definite structure, and hence it must deal with one structure at a time. A racemate is a mixture of two structures – even when they do pack into the same crystal. But such a mixture is handled and described often enough to make it advisable to apply to it a single name, as though it were a compound in the molecular sense, and not only, at most, in the phase-rule sense.

When there is only one element of chirality, so that only one racemate can be formed, this may be designated (±), or, when appropriate, DL, or, in sequence-rule symbolism, (*RS*). We adopt here this alphabetical order *RS* as normal for the components of the composite symbol, in order that special significance may attach to its inversion to *SR*, as noted below.

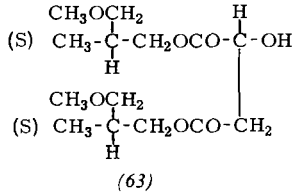
When in a component of a racemate there is more than one element of chirality, the one cited first (normally that which is located by the lowest number) is written *RS*, and the remainder are written as *RS* or *SR* in such a way that the first letter of each pair is associated with *R* of the first-cited pair and the second with *S* of the first-cited pair. For example, the racemate composed from (2*R*,3*S*)- and (2*S*,3*R*)-3-chlorobutan-2-ol would be designated (2*RS*,3*SR*)-; the other racemate would be designated (2*RS*,3*RS*)-.

Mixtures, which are racemic with respect to some centres but optically active with respect to others, could, if necessary, be named by simple extension of this method. A not uncommon case is that of the "failed resolution", involving, for example, an unseparated mixture of the salts (*R*)-base (*R*)-acid and (*R*)-base (*S*)-acid. The obvious course is to name this as (*R*)-base (*RS*)-acid.

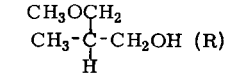
### 3.3. Broken Numbering

Collection of *R*,*S* symbols in front of a complete name is possible only when each can be unambiguously located. Ambiguity arises when the numbering of the complete name involves independent sets of numerals; such "broken numbering" is not infrequent, as many esters, amines, and compounds with side-chains present this feature.

It may then become necessary to place each stereochemical symbol next to its appropriate partial name, as in (*R*)-s-butyl (*S*)-lactate, or in (*R*)-α-methylbenzyl-(*S*)-β-methylphenethylamine. However, it cannot be too strongly emphasised that *R*,*S* symbols invariably refer to the whole molecule, not to any component parts *per se*. It is equally fundamental that *R*,*S* symbols do not refer to any actual or supposed chemical precursors; for example, the compound *(63)* is bis-(*S*)-3-methoxy-2-methylpropyl (*S*)-malate, even though it is the ester of the (*R*)-alcohol *(64)* and (*S*)-malic acid. Obviously this principle applies equally when the complication of broken numbering is absent: a simple case is (*R*)-glycerol 1,2-diacetate 3-methyl ether *(65)*, which has the label *R*, whether it be made from (*S*)-glycerol 1-methyl ether *(66)* or (*R*)-glycerol 1,2-diacetate *(67)*. A group can have an *R* or *S*, not in its own right, but only in the particular compound to which that symbol is assigned.



*(63)*



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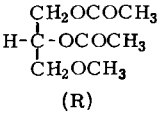
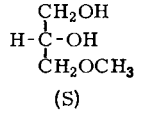


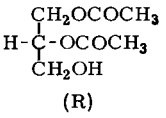
(R)

*(65)*



(S)

*(66)*



(R)

*(67)*

### 3.4. Chirality Symbols in Trivial Names that Specify Configurations

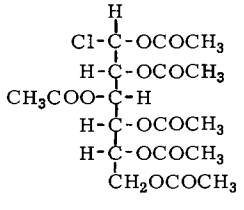
It was argued, particularly in Paper II, that a general system such as the present one need not displace a satisfactory "local" system within its own field. We suggest, however, that the general system may helpfully be "mixed" with a local system when the field of application of the latter is exceeded. It seems desirable now to illustrate how this mixing may be done, by examples that we shall choose from three of the widest local systems.

#### 3.4.1. Carbohydrates

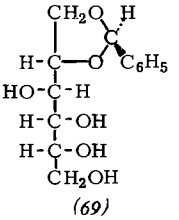
In a name such as methyl α-D-glucopyranoside, the prefix α and the syllable "gluc" jointly specify the relative configurations at positions 1, 2, 3, 4, and 5; the prefix D denotes a genetic relation at position 5 to

(+)-glyceraldehyde; and now our later-acquired knowledge of the absolute configuration of (+)-glyceraldehyde allows us also to specify absolute configurations on the basis of a name such as methyl α-D-glucopyranoside. Thus, unless it is desired to tie this stereochemistry to a general system, by writing, for instance, (1*S*,5*R*)-methyl glucopyranoside, the customary name suffices.

When, however, the limits of the local system are exceeded, as they are, for example, in compounds *(68)* and *(69)*, then to mix-in the sequence-rule system provides simple descriptions: compound *(68)* becomes (1*R*)-1-chloro-D-glucitol hexa-acetate, and compound *(69)* becomes (*R*)-1,2-*O*-benzylidene-D-glucitol.



*(68)*



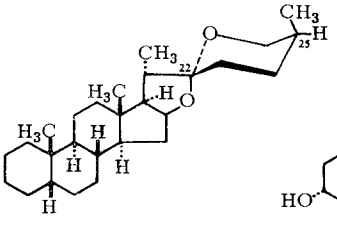
*(69)*

### 3.4.2. Inositols

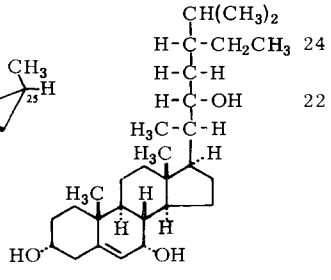
Optically active inositols are commonly distinguished from one another, either by use of prefixes denoting the relative stereochemistry of the ring atoms, or by a numerical device. As long as these practices give satisfaction, it is unnecessary to displace them by sequence-rule procedures. Absolute configurations of optically active compounds may be conveniently denoted by mixing-in the *R* or *S* symbol, as in the name (4*R*)-inositol for the laevorotatory compound (XLVIII) (p. 396). Mixing-in has wider scope in the name of an optically active compound derived from a cyclitol that is itself inactive. This was in fact done by *Angyal* and *Gilham*[21] when they named compound *(28)* (p. 397) (1*R*)-1-*O*-methylmyoinositol, a name entirely in consonance with the principles here advocated. We accept the general proposals by *Angyal* and *Gilham* for mixing in this field.

### 3.4.3. Steroids

For steroids, a small number of trivial names, and the symbols α and β, were originally used to denote relative configuration, and were coupled with an arbitrary method of writing the formulae. Here too, later knowledge showed that the arbitrary choice coincided with absolute configuration; and the trivial names and the prefixes α and β are commonly used now with an absolute connotation, and are well understood. Among steroids in particular, the relative stereochemistry of various parts of the molecule is of great importance for the chemical, physical, and pharmacological properties of the substances; so here it is particularly desirable to retain the simple local system in so far as it is unambiguous. It can certainly be retained for groups singly attached to the main tetracyclic ring system A–D. Where, however, spiro or other rings are attached, whose planes deviate strongly from the planes of the main system, the limits of the local system of trivial names and simple α and β symbols are exceeded. In these circumstances, to mix-in the sequence-rule system can be of value; and the chirality at positions in such attached rings, including the spiro atom itself, may well be expressed by sequence-rule symbols. Further, similar mixing-in may be appropriate for chirality in an open side-chain. This paper is not the place to discuss the merits of the various proposed systems in detail[22]; it will suffice to illustrate the mixing by reference to two compounds *(70)* and *(71)* selected from *Mueller* and *Pettit*'s paper. Compound *(70)* may be named (25*S*)-5β-spirostan or (22*R*,25*S*)-5β-spirostan, according to whether it is decided that the name spirostan by itself does or does not specify the stereochemistry at position 22 (a matter still under debate by specialists)[22]; and compound *(71)* may be termed (22*S*,24*R*)-stigmast-5-ene-3α,7α,22-triol.



*(70)*



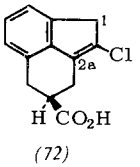
*(71)*

### 3.5. Molecules of Uncertain Structure

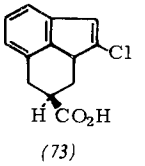
When there is uncertainty about the structure of a molecular model, a similar uncertainty may attach to the sequence-rule symbol to be applied. For example, prototropic substances present this problem: it may be necessary to specify chirality completely for a prototropic substance in spite of the structural uncertainty.

This must be done by choosing one of the possible structures – any convenient one. Often the choice will be self-evident, as for carbazole or fluorene; in other cases it must be indicated in the name chosen, *e.g.* 1-phenylazo-2-naphthol or 1,2-naphthoquinone 1-(phenylhydrazone), or again in the numbering chosen, *e.g.* 4-chloroimidazole or 5-chloroimidazole.

In practice it will be very rare that the different prototropic structures require different chiral symbols. If, however, such cases do arise, all that is needed is that the chiral symbol fits the name adopted. Thus, if one



*(72)*



*(73)*

[21] *S. J. Angyal* and *P. T. Gilham*, J. chem. Soc. (London) *1957*, 3691.

[22] International Union of Pure and Applied Chemistry, Information Bulletin No. 11, 50 (1960); *L. F. Fieser* and *M. Fieser*, Tetrahedron *8*, 360 (1960); *G. P. Mueller* and *G. R. Pettit*, Experientia *18*, 404 (1962).

were in doubt between structures *(72)* and *(73)*, one might arbitrarily select *(72)* and give its name as (4*S*)-2-chloro - 1,3,4,5 - tetrahydroacenaphthylene - 4 - carboxylic acid, or select *(73)* and give its name as (4*R*)-2-chloro-2a,3,4,5-tetrahydroacenaphthylene-4-carboxylic acid.

### 3.6. Specification of Axial, Planar, and Secondary Structural Chirality

It will often be desirable, for the sake of clarity, to indicate which type of chiral element, a centre, axis, or plane, is being specified as *R* or *S*. As axial and planar elements of chirality are less commonly used than are asymmetric atoms, we suggest that, when the symbols *R* and *S* apply to axes or planes of chirality, a signal to that effect should be associated with the symbols. We propose to add italic letters *a* (for axial) and *p* (for planar) immediately before the corresponding *R*'s and *S*'s, or *r*'s and *s*'s.

Whilst this would not be essential in simple cases such as (*aR*)-6,6′-dinitrodiphenic acid *(43)* (p. 400) it may be that a name such as (*aR*, α*R*, α′*R*)-6,6′-dilactoyldiphenic acid would be clearer than without the *a*; and it would be clearer still if written as (*aR*)-6,6′-di-(*R*)-lactoyldiphenic acid. In describing the quinol polymethylene ether *(59)* (p. 402), the symbol *pr* would bring out the distinctive character of the form of stereoisomerism being specified.

If a structure contains more than one chiral axis or plane, it is necessary when they are not stereospecifically linked, and in our view desirable in general when they are thus linked, separately to specify the chirality of each (cf. Sub-section 3.1). In every case one must identify the chiral element with its description, as by attaching some locating numbers or letters to the symbols *a* and *p*, in a form such as *x*,*y*-*aR*, where *x* and *y* locate the axis *a*.

The helicene *(61)* (p. 403) can be treated as a secondary structure; but it contains, and could be specified through, its two, stereospecifically linked, non-equivalent, chiral axes, both duplicated by the symmetry ($C_2$) of the structure. The model shown is *R* about the more interior, and *S* about the more exterior, biaryl axes. Formulae *(40)* and *(41)* (p. 399) illustrate structures with two chiral axes, which are not stereospecifically linked; this means that stereoisomers are possible in which the chirality of one axis only is reversed. It is obviously necessary in these cases to specify the chirality about each axis, even though in *(40)* the symmetry ($C_2$) of the structure renders the two equivalent. Formulae *(8)* and *(9)* (p. 389) and formulae *(54)* and *(55)* (p. 401) illustrate structures with non-equivalent chiral planes. As explained already, we consider it desirable to specify chirality about each plane separately, and to associate plane-identifying numerals with each chiral specification.

The assignment to secondary structures of chiralities *R* and *S* or *M* and *P* is again a circumstance which we think should be signalised in the notation; and so we propose to introduce for this purpose the prefix *sec*, to be placed, like *a* or *p*, immediately before the chiral symbol, as in *secR* or *secM*. The adamantoid enantiomers *(62)* (p. 403) would be designated *secR* and *secS*. The helicene enantiomer shown at *(61)* (p. 403) would be termed *secM*. Catenanes are secondary structures with axial chirality, but it would probably be sufficient to describe them as *secR* or *secS*.

## 4. Conformational Chirality to Ligancy Four

### 4.1. Basis of Treatment

The description of molecular conformations can be treated, according to a proposal by *Klyne* and one of us [7], in terms of partial conformations about the individual single bonds. One can thus specify, for a single bond between quadriligant atoms, the spatial relations between the two sets of up to three groups thereto bound. A fiducial group is chosen from each set by means of the following Conformational Selection Rules, and then the smallest torsion angle between the two fiducial groups will specify the conformation:

(A) *If all the groups of a set are different, the group most preferred by the Standard Sequence Sub-rules (p. 391) is fiducial.*

(B) *If an identity among the groups of a set leaves one group unique, the unique one is fiducial.*

(C) *If all the groups of a set are identical, that which provides the smallest torsion angle is fiducial.*

If the magnitude of the angle is only approximately known, semiquantitative terms (or their abbreviations), namely, synperiplanar (*sp*), synclinal (*sc*), anticlinal (*ac*), and antiperiplanar (*ap*), are used to describe conformations whose torsion angles are within ±30° of 0°, ±60°, ±120°, and 180°, respectively.

This system embodies the concept of a Conformational Helix, which may be defined as follows:

> Conformational Helix. *The single bond about which conformation is to be specified is made the axis, and the smallest torsion angle between the fiducial groups is made to define the pitch and sense of the helix (p.389).*

Right- and left-handed helices, thus defined, correspond to + and − torsion angles, and are designated by the Helicity Rule (p. 391) as *P* ("plus") and *M* ("minus"), respectively. A result of this symbolism is that, if, upon a specification of configuration in terms of *R* and *S*, one wishes to superpose a specification of conformational relations, the two types of description remain clearly distinguished.

Some generalisation is needed to provide for the specification of conformations in their widest possible connotation within the ligancy limit of four. The concept of phantom atoms is useful. They mark non-bonded electron-sites, and thus have their own individual spatial positions relative to neighbouring real atoms. They must therefore be considered, equally with real atoms, among the sets of "groups" from which fiducial groups have to be selected, as described above, for the

purpose of specifying conformation. For example, on account of Conformational Selection Rule (B), the phantom atom is fiducial in the amino-group.

The duplicate representations of atoms by the help of which multiple-bond unsaturation is represented are in a different case. They have no space-positions separate from those of their originals. Hence the only effect of introduced double bonds, whether localised, or blended as, for instance, in aromatic systems, is to create special cases by reducing below maximum the number of spatially distinct off-axis groups about a single bond, whose relative positions determine conformation. The two trios of groups flanking the single bond in the general case may, in the presence of unsaturation, degenerate to a trio and a pair, or to two pairs. The fiducial group of a pair, as of a trio, is to be chosen by the Selection Rules given above.

The introduction of a triple bond can reduce an original trio of groups to a single group. But, except in special circumstances, the latter is on-axis, and hence without conformational interest.

The number of conformational isomers that could be formed by relative rotation about just one single bond cannot be greater than the numbers of those torsional potential-energy hollows that are deep enough to contain total-energy levels. With like off-axis groups on either flank of the bond, the energy hollows will be equivalent. The number of them will be the least common multiple of the numbers of groups in the sets flanking the bond: two sets of three groups each will give three energy hollows, two sets of two will give two, and one set of three and one of two will give six. With inequalities between the groups, the number of energy hollows may rise as far as the product of the numbers of groups in the sets. The energy hollows will, however, tend rapidly to insignificance as their number rises, owing to increasing compensation in the angular variation of individual group-interaction energies. Potential-energy hollows, which are significant for conformational molecular states, very frequently arise because differences among the groups on either flank of the single bond enlarge some energy hollows at the expense of others. Thus, a theoretical maximum of six energy hollows might be represented by either three or two conformationally significant energy hollows, the remainder being reduced out of significance, or even out of existence. A theoretical maximum of three energy hollows may contain only two that are conformationally effective, the third having become either insignificant or non-existent. Of course, the number of significant energy hollows may in some cases be reduced to one; then conformational isomerism disappears. Thus, the most important cases for our considertation are those in which rotation round a single bond produces either three or two conformationally significant energy hollows. Each energy hollow must be deep enough to contain the ground energy-state of a conformational isomer, so protected that it either has been or could conceivably be isolated, or that it either has had or could conceivably have its separate existence proved by physical methods.

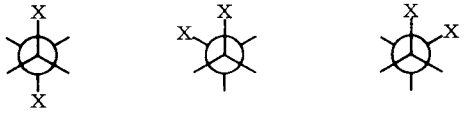
Out of these two important basic situations, one involving three, and the other two suitably stable torsional orientations about a single bond, develop all the compound situations, in which the conformational isomers arise from restricted rotation around several single bonds. In the absence of equivalences between such bonds, and in the absence of mutual interference, the number of conformational isomers will be the product of the numbers produced during rotation about the bonds, one at a time. However, these possibly large numbers are commonly much reduced by symmetry-equivalences, and very drastically by mutual interference as in rings.

We shall sometimes, either for convenience or lack of better knowledge, write of energy hollows as though they were symmetrically placed between their flanking barriers, even though it is well understood that intramolecular interactions, or intermolecular forces as in crystals, may render that assumption untrue.

### 4.2. Conformations Involving Three Torsional Energy Hollows [23]

We may take the 1,2-dihalogenoethanes as prototype examples. They have three conformationally isomeric forms, namely, the two enantiomeric synclinal forms, and the one antiperiplanar form, shown in *(74)–(76)*, where X denotes halogen.

The existence of such isomers [24] is shown, in the first place, by the Raman and infrared spectra of 1,2-dichloro- and 1,2-dibromo-ethane. Each spectrum consists of two superposed spectra, one of which fades as the temperature is reduced, thus indicating isomers of different stabilities in equilibrium. The low-temperature spectra show that the more stable isomers have the



Antiperiplanar *(74)* (M)-Synclinal *(75)* (P)-Synclinal *(76)*

antiperiplanar form. This conclusion is supported by the dipole moments, which fall as the temperature is reduced. The antiperiplanar isomers can be isolated in pure form merely by cooling: the solid substances consist of these pure isomers. From the effects of temperature on the spectra of the gases, it is inferred that the synclinal forms of 1,2-dichloro- and 1,2-dibromo-ethane are less stable by 1.2 and 1.5 kcal/mole, respectively, than their antiperiplanar forms.

In the n-propyl halides, whether as gases or as liquids, the balance of stability between the synclinal and antiperiplanar conformers, though somewhat small, is in

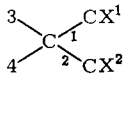
[23] *D. J. Millen* in *P. B. D. de la Mare* and *W. Klyne*: Progress in Stereochemistry. Butterworths Scientific Publications, London 1962, Vol. 3, Chapter 4.

[24] *S. Mizushima*: Structure of Molecules and Internal Rotation. Academic Press, New York 1954, Chapters 2 and 3.

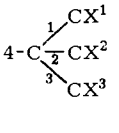
the opposite direction [25,26]. However, the solid chloride and the solid bromide are both pure antiperiplanar forms [26,27], presumably because these more symmetrical forms, despite their lesser molecular stability, have the larger lattice energies. The synclinal form of ethylene chlorohydrin is more stable by 1.0 kcal/mole than the antiperiplanar, in the gaseous and in the liquid state, and now the solid substance consists entirely of the synclinal racemate [28].

For the purpose of showing how several equivalent systems of three energy hollows in torsions about single bonds may yield conformational isomers limited in number by symmetry, we next consider the assemblies of *contiguous equivalent bonds*, illustrated by a trimethylene dihalide, a methylidynetrimethyl trihalide, and a pentaerythritol tetrahalide, each with like halogen atoms.

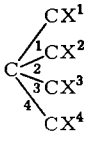
The energetically favoured conformations about each carbon-carbon bond will be assumed to be *M*- and *P*-synclinal and antiperiplanar, that is *Msc*, *Psc*, and *ap* in symbols, which we can here with convenience contract to *M*, *P*, and *a*, respectively, since other bond conformations are not in question. In order to locate these partial conformations, it is convenient to number 1–4 the bonds of the non-halogen-bearing carbon atom, and correspondingly number 1, 2, *etc.*, the halogens, as shown at *(77)–(79)*. Then, the numbers of the bonds being cited as pre-subscripts, and of the halogens as post-superscripts, the symbols ${}_2a^1$, ${}_2M^1$, and ${}_2P^1$, for example, will mean that halogen-1 is antiperiplanar, *M*-synclinal, and *P*-synclinal, respectively, to bond-2.



*(77)*



*(78)*



*(79)*

Each molecule has fewer than the 9, 27, or 81 conformationally distinct isomeric forms, which would be allowed in the absence of structural equivalences. The trimethylene dihalide has two achiral forms and two enantiomeric pairs (one asymmetric). The methylidynetrimethyl trihalide has three achiral forms and four enantiomeric pairs (three asymmetric). The pentaerythritol derivative has three achiral forms and three enantiomeric pairs (two asymmetric). The various conformers are specified in the Table by the method described above. Pairs of enantiomers are indicated by braces.

It should be understood that the conformational descriptions given in the Table are far from unique. For example, the model of any one conformer of a pentaerythritol halide can be numbered in 24 ways; and for

Table 1. Conformers with equivalent contiguous bonds in $H_{4-n}C(CH_2X)_n$.

| | Conformation | Symmetry |
|---|---|---|
| *(77)* | $H_2C(CH_2X)_2$ | |
| *(80)* | ${}_2a^1, {}_1a^2$ | $C_{2v}$; axis bisects bond-angles 12 and 34. |
| *(81)* | ${}_2M^1, {}_1P^2$ | $C_s$; plane contains bonds 3 and 4. |
| *(82)* | ${}_2M^1, {}_1M^2$ \| ${}_2P^1, {}_1P^2$ | $C_2$; axis bisects bond-angles 12 and 34. |
| *(83)* | ${}_2a^1, {}_1M^2$ \| ${}_2a^1, {}_1P^2$ | $C_1$; asymmetric. |
| *(78)* | $HC(CH_2X)_3$ | |
| | ${}_4a^1, {}_4a^2, {}_4a^3$ | $C_{3v}$; axis is along bond 4. |
| | ${}_4a^1, {}_1a^2, {}_1a^3$ | $C_s$; plane contains bonds 1 and 4. |
| | ${}_4a^1, {}_3a^2, {}_2a^3$ | $C_s$; plane contains bonds 1 and 4. |
| | ${}_4M^1, {}_4M^2, {}_4M^3$ \| ${}_4P^1, {}_4P^2, {}_4P^3$ | $C_3$; axis is along bond 4. |
| | ${}_4M^1, {}_4M^2, {}_4P^3$ \| ${}_4P^1, {}_4P^2, {}_4M^3$ | $C_1$; asymmetric. |
| | ${}_4a^1, {}_4M^2, {}_4M^3$ \| ${}_4a^1, {}_4P^2, {}_4P^3$ | $C_1$; asymmetric. |
| | ${}_4a^1, {}_4a^2, {}_4M^3$ \| ${}_4a^1, {}_4a^2, {}_4P^3$ | $C_1$; asymmetric. |
| *(79)* | $C(CH_2X)_4$ | |
| *(84)* | ${}_2a^1, {}_1a^2, {}_4a^3, {}_3a^4$ | $V_d$; axis bisects bond-angles 12 and 34. |
| *(85)* | ${}_4P^1, {}_1P^4, {}_3M^2, {}_2M^3$ | $S_4$; axis bisects bond-angles 14 and 23. |
| *(86)* | ${}_2a^1, {}_1a^2, {}_4P^3, {}_3M^4$ | $C_s$; plane contains bonds 1 and 2. |
| *(87)* | ${}_2a^1, {}_1a^2, {}_4M^3, {}_3M^4$ \| ${}_2a^1, {}_1a^2, {}_4P^3, {}_3P^4$ | $C_2$; axis bisects bond-angles 12 and 34. |
| *(88)* | ${}_2a^1, {}_1a^2, {}_4a^3, {}_3M^4$ \| ${}_2a^1, {}_1a^2, {}_4a^3, {}_3P^4$ | $C_1$; asymmetric. |
| *(89)* | ${}_2a^1, {}_1M^2, {}_4P^3, {}_3M^4$ \| ${}_2a^1, {}_1P^2, {}_4M^3, {}_3P^4$ | $C_1$; asymmetric. |

any fixed placing of the numbers, for instance, one satisfying the conditions ${}_2a^1 \equiv {}_3M^1 \equiv {}_4P^1$, these three completely equivalent descriptions will be available to specify the conformation of halogen-1; wherefore there will be 81 ways of describing that one conformation of the pentaerythritol halide. Some of these descriptions are more immediately informative than others as to the chiral status of the conformation; and, in the Table, we have chosen, often from among a number of alternatives that would have served equally well, descriptions which signalise in an obvious way the achiral and chiral forms, and the enantiomeric pairs among the latter.

The conformations of those trimethylene dihalides which are numbered in the Table are schematically represented at *(80)–(83)* below. The vibration spectra of trimethylene dichloride, dibromide, and di-iodide, each as liquid and in crystalline form, have been studied by *Brown* and *Sheppard* [29], who were able thus to specify certain features of the symmetry of the isomers present, and to distinguish fairly certainly between antiperiplanar and synclinal partial conformations about the carbon-carbon bonds. They found that the molecules of the stable solid forms of all three dihalides contain two synclinal partial conformations, and concluded that these forms consist of the $C_2$ racemates (one chiral variety at 82), because the $C_s$ *meso*-form *(81)* is expected to be rendered unstable by pressure between the halogen atoms. The iodide was obtained also in a metastable solid form, the molecule of which contains two antiperiplanar partial conformations, and

[25] *E. Hirota*, J. chem. Physics *37*, 283 (1962).

[26] *C. Komaki, I. Ichishima, K. Kuratani, T. Miyazawa, T. Shimanouchi*, and *S. Mizushima*, Bull. chem. Soc. Japan *28*, 330 (1955).

[27] *J. K. Brown* and *N. Sheppard*, Trans. Faraday Soc. *50*, 535 (1954).

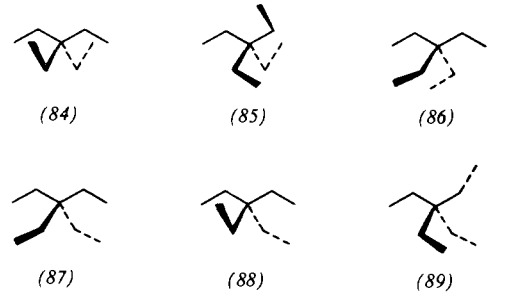
[28] *S. Mizushima, T. Shimanouchi, T. Miyazawa, K. Abe*, and *M. Yasumi*, J. chem. Physics *19*, 1477 (1951).

[29] *J. K. Brown* and *N. Sheppard*, Proc. roy. Soc. (London) A *231*, 555 (1955).

hence must be the $C_{2v}$ isomer *(80)*. The liquid dihalides were mixtures. Their main component was in each case the isomer of the stable solid form, the $C_2$ racemate. All three liquids contained a second isomer, shown by its spectrum to have one synclinal and one antiperiplanar partial conformation, and therefore to be the $C_1$ racemate [one chiral form at *(83)*]. The liquid dibromide and the liquid di-iodide contained a third isomer, characterised by two antiperiplanar partial conformations; this was the $C_{2v}$ isomer *(80)*. This di-iodide was identified with the metastable solid form of that dihalide.

*(80)* *(81)* *(82)* *(83)*

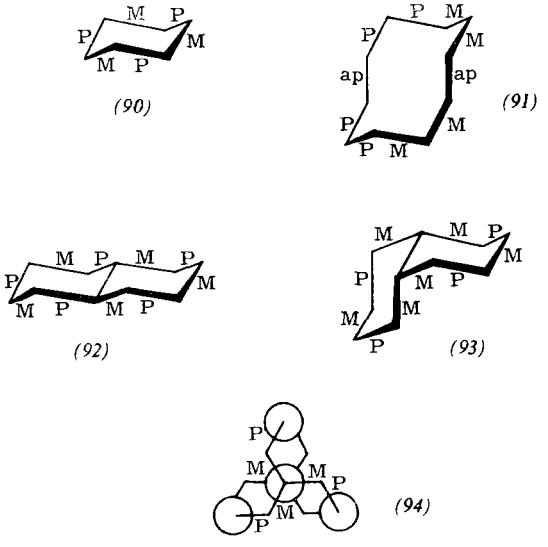
*Gilman* and his co-workers[30] isolated tetra-*o*-tolylsilane, $Si(C_6H_4Me\text{-}o)_4$, in four (optically inactive) forms having m.p.'s 145, 228, 300, and 344 °C, together with a possible fifth form of m.p. 270 °C. They stated that four *meso*-forms and two racemic mixtures (eight isomers in all) should be expected, but did not indicate what assumptions underlay this computation. If we assume four equivalent systems of three energy hollows, in which each methyl can bear the same space-relations to the three bonds holding other *o*-tolyl groups as each halogen in a pentaerythritol halide bears to the three bonds holding other halogenomethyl groups, we must expect isomers corresponding to the pentaerythritol isomers listed in the Table, namely, three achiral forms and three racemates (nine isomers in all). The forms of those numbered in the Table are shown at *(84)–(89)*. They can be derived by applying, with due allowance for enantiomers, conformations *(80)–(83)* independently to the 1,2-pair and the 3,4-pair of $CH_2Br$ groups, the upper and lower pairs, respectively, in *(84)–(89)*, and then eliminating overlap from the overall conformational representations thus obtained.



*(84)* *(85)* *(86)*

*(87)* *(88)* *(89)*

Conformations are strongly limited and selected by ring-formation. The chair-form conformation of cyclohexane has alternate *M*- and *P*-synclinal partial conformations about the ring-bonds *(90)*. An important conformation of cyclodecane[31] has two diametrically opposite antiperiplanar bonds, and, elsewhere, the balanced arrangement of *M*- and *P*-synclinal bonds shown at *(91)*. A *trans*-decalin composed of chair-form six-rings has an antiperiplanar bridge-bond, and otherwise alternate *M*- and *P*-synclinal ring-bonds *(92)*. A *cis*-decalin built from chair-form six-rings is chiral; one enantiomer has the bridge-heads joined by two tetramethylene loops of *MPMPM*-synclinal bonds (to specify them in order), as in *(93)*, and the other spans the bridge-heads by two *PMPMP*-loops. In 9,10-tetramethylene-*cis*-decalin, either all three tetramethylene loops are *MPMPM*, as shown in the Newman projection *(94)*, or else all are *PMPMP*.



*(90)* *(91)*

*(92)* *(93)*

*(94)*

### 4.3. Conformations Involving Two Torsional Energy Hollows

The normal conformation of hydrogen peroxide has been determined in a spectroscopic investigation by *Cross* and his co-workers[32]. There are only two effective energy hollows in the torsional potential-energy curve. These contain the energy levels of the *M*- and *P*-anticlinal conformations. Their valency angles are 94.8 °, and their torsion angles are ±119.8 °. Between the energy hollows rise, on the one hand, a synperiplanar barrier of 3.7 kcal/mole and, on the other, an antiperiplanar barrier of 0.85 kcal/mole.

The most important examples of optically stable conformers dependent on two energy hollows associated with torsions about single bonds are those of the biaryl series. These molecules have axial chirality, which may be specified, as has been described (Sub-section 2.6), on the basis of the Chirality Rule (p. 391). However, as already explained (Sub-section 1.5), we hold it allowable to regard the enantiomerically related structures as being conformationally distinct, and hence as suitable also for specifying chirality on the basis of the Helicity Rule (p. 391).

Throughout this field of examples, assignments *R* and *S* by the former method respectively correspond to assignments *M* and *P* by the latter, provided that the same sets of groups are employed in the two methods.

[30] *G. N. Russell Smart, H. Gilman,* and *H. W. Otto,* J. Amer. chem. Soc. *77*, 5193 (1955).

[31] *J. D. Dunitz* and *V. Prelog,* Angew. Chem. *72*, 896 (1960).

[32] *R. L. Redington, W. B. Olson,* and *P. C. Cross,* J. chem. Physics *36*, 1311 (1962).

And now that we have changed our procedure (cf. Sub-section 2.6) for choosing fiducial groups in the specification of axial chirality, making the effective chiral axes as short as possible, instead of, as formerly, as long as possible, the groups used for the defining of axial chirality in biaryl applications will always be the same as those, necessarily adjacent to the biaryl torsion bond, which are employed for the purpose of specifying its partial conformation.

These matters could be illustrated with a number of the biaryl examples treated in Paper II or in Sub-section 2.6 of this paper. It may suffice here to refer to formula *(39)* (p. 399). The axially chiral molecule represented is in the *R*-configuration, or, if we prefer, the *M*-conformation.

The second main group of examples of optically stable conformers conceptually derivable from two energy hollows in torsions around single bonds – often, in this area, around trunnion-like pairs of bonds – is in the group of the cyclophanes, or, more generally, that of bridged rings with aromatic bridge-heads. As described in Sub-section 2.7, these molecules have planar chirality, which may be specified on the basis of the Chirality Rule. However, some of the examples fulfil the wide definition of conformers given on p. 388; and, as explained in Sub-section 1.6, we consider it permissible to specify chirality of the conformations about the relevant bonds by means of the Helicity Rule. For such a specification, we propose to apply the Helicity Rule to the same atoms as served for the specification of planar chirality, namely, the pilot atom p and the atoms a, b, c, of the associated planar sequence (see p. 401), the torsion bond among the overall sequence of atoms p, a, b, c, being the bond a–b. This procedure yields, in this group of examples, a simple relation between the symbols of planar chirality and those of helicity: *R* and *S* correspond here, in contrast to the biaryls, to *P* and *M*, respectively.

A number of the examples of planar chirality given in Paper II, and several of those given in this paper, could be used in illustration. Thus, the planar chirality of the molecule *(8)* (p. 389) is *S* for the plane of the brominated benzene ring, and *R* for the plane of the other benzene ring. The corresponding conformational helicities are seen to be *M* and *P*, respectively. Similarly, the symbol *R* for the planar chiralities of molecules *(49)*, *(50)*, and *(52)* (p. 401) corresponds to the symbol *P* for the helicities of the conformations about the single bonds selected as described above.

### 4.4. Conformational Secondary Structures

The possibility of describing the chirality of secondary structures is attractive in that one may often thus achieve comprehensive but succint specifications. This was illustrated by means of the helicenes, in Sub-section 2.8. Among the conformations discussed in Sub-section 4.3, there are two in which a secondary-structural feature of readily definably chirality can be recognised.

The more obvious is 9,10-tetramethylene-*cis*-decalin, one chiral conformation of which is represented in *(94)*, on p. 409. It has been pointed out that each of the three tetramethylene loops in this molecule consists of five synclinal partial conformations in the chiral order *MPMPM*. We now note that the combined translation and rotation of a right-hand helix will carry the first atom of any of the three loops into the last atom of the same loop. This feature, if regarded as one of secondary structure, would allow the Helicity Rule to confer on the conformation as a whole the single symbol *P*, or, if the suggestion in Sub-section 3.6 is followed, *secP*, as an alternative to the longer designation in terms of individual partial conformations.

The other example is *cis*-decalin, one chiral conformation of which is shown in *(93)*. The same conformation could be represented more stereographically by a Newman projection, derived from *(94)* by omission of one tetramethylene loop. Each of the remaining loops would again be conformationally defined by the identical conformational order of its bonds, namely, *MPMPM*. And again the two ends of each loop would bear an identical helical inter-relation, which would allow the Helicity Rule to describe the whole conformation more simply as *P*, or, as we should prefer, *secP*.

## 5. Central Chirality to Ligancy Six

### 5.1. Outline of the Sequence-Rule Procedure for Ligancies Five and Six

By far the most important ligancy higher than four, for which the specification of chirality has yet presented any practical problems, is ligancy six of the octahedral atoms. These include non-metals, such as sexiligant phosphorus in the tris-2,2′-biphenylylenephosphate(VI) ion [33]; but the main family of examples comprises the transition metals in their six-co-ordinate complexes. We shall discuss in detail only the co-ordinatively sexiligant octahedral structures. The chirality of a quinqueligant atom could be specified after extension of its ligancy to six by means of a phantom atom, in a manner similar to that in which we specify the chirality of a trigonal pyramidal atom after extension of its ligancy to four. However, since we know of no molecule whose chirality depends on that of a configurationally stable, chiral, quinqueligant atom, we shall for the present refrain from detailing such a procedure. We shall also not attempt to treat ligancies higher than six, whether of atoms of the heavier elements, or of polyatomic elemental clusters.

We shall have to describe positional relations on the octahedral co-ordination figure in a more detailed way than has been done before. But we can start from some already used descriptions. *Werner*'s designations of the geometrical relations of pairs of ligands as *cis* or *trans*, according as they terminate an edge or body-diameter of the octahedron, are generally accepted.

[33] *D. Hellwinkel*, Angew. Chem. 76, 756 (1964).

*Werner* numbered the octahedron, with 1 and 6 in *trans*-positions, and 2–5 in cyclic order *cis* to each. Our method of distinguishing stereoisomers involves numbering the octahedral model according to that prescription, but allowing its unspecified features, namely, those of where to start, and in what sense to take the cyclic order, to be determined by a sequence of the ligands, as described hereunder. Having thus numbered the octahedral model, we designate its chiral sense according to a pattern read in the numbers.

The problem of arranging six ligands in sequence, for the purpose of specifying their spatial positions about a centre, is neither necessarily nor advantageously solved in the same way as for four ligands. Four points are the fewest that can constitute a three-dimensional figure, and hence possibly provide a chiral figure. When we have only four ligands, their properties have to determine the sequence which is required to describe the chirality of their space-distribution. With six ligands, more than this necessary minimum of working data would be furnished were exactly the same method followed; and then, some very difficult problems of selection would arise. We avoid these by designing our sequence of ligands, to be, not the sole instrument for placing a sequence of numbers on the octahedral model, but the means of completing a spatial distribution of numbers already delimited by the geometrical pre-condition of their octahedral arrangement.

With this simpler requirement in view, we have some freedom to adjust our sequence-forming procedure in order to reduce the intricacies that two features of co-ordination structures would otherwise frequently create.

The first feature is the occurrence about a chiral centre of identical ligands, as is possible when the total number of ligands exceeds four. In order to deal with this, we use the circumstance that, just because the number exceeds four, we are not dependent only on their internal properties in order to secure a chirality-defining sequence. We can allow their internal properties to order them as far as may be, and then leave co-operation with the octahedral pre-condition, implied in the Werner pattern of numbering, to complete the sequence-in-space.

The second feature of octahedral structures that could create considerable complications is the frequent occurrence of chelate ligands. However, we can largely forestall these difficulties by devising a special procedure, as described in the next Sub-section, for ordering groups in sequence.

The general circumstance which forces on us an elaboration of our procedure of chiral specification, when we come to complexes, is that, with more than four ligands to be arranged about a chiral centre, the various relations of geometrical isomerism, and the relations of chirality, arise together. Our procedure must therefore be competent to specify both, and not the latter only. That is why, after arranging the ligating atoms in sequence, we put in an additional step that takes the octahedral geometry into account, namely, the step of numbering the groups on the octahedron. At that stage, the geometrical isomerism, apart from any associated chirality, is completely described. All is then ready for the final step, which is to specify chirality.

Our procedure is thus as follows. With an octahedral structure, as with any molecule, the first step is to apply the *Factorisation Rule* (p. 391), so separating the chiral elements, in particular, the sexiligant chiral centre with the detailed description of which this Section is concerned.

Independently of ligancy, centres, axes, and planes of chirality are treated in that order. To the sexiligant chiral centre we apply in the second step the *Octahedral Sequence Rule* (Sub-section 5.2), which is a rule designed to order the ligating atoms in a "linear" series of priorities. The third step is to apply the *Octahedral Numbering Rule* (Sub-section 5.3), so assigning to the ligating atoms a set of numbers, which takes joint account of the already determined priorities and of the octahedrally geometrical relations. The geometrical relations, apart from chirality, are then fully specified, and the only remaining step, the fourth, is to apply the *Octahedral Chirality Rule* (Sub-section 5.4), so specifying the chiral sense of the sexiligant atom. We proceed now to describe these steps in detail.

### 5.2. The Octahedral Sequence Rule and its Sub-Rules

Our procedure must allow for ligands, which range from unidentate to sexidentate ligands. The classes from bidentate to sexidentate constitute the chelate ligands. They could create formidable complications, if we should try to handle them only by the machinery provided to deal with atomic ligancies of four and less. For they build rings round the sexiligant atom, bridged and even multiply bridged rings if the ligand is more than bidentate; and then the sexiligant atom becomes a common bridge-head of all the rings, and sometimes a spiro-atom in addition. It would be possible, but usually intricate, to explore such ring structures by means only of the Standard Sub-rules (p. 391). However, we offer below an extended system of sub-rules, better adapted to cope with such situations. The position of complex chemistry, as a main division of chemistry, potentially comparable with organic chemistry, justifies such a special measure. The extended system is comprised in three "Octahedral Sequence Sub-rules", as we may call them, which are to be successively applied. The second of these new sub-rules incorporates the Standard Sub-rules. We shall first describe the new sub-rules, and then state them formally.

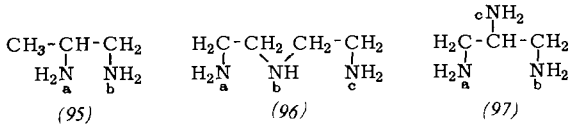
First, the ligands are ordered by classes, according to the number of atoms in each which are bound directly to the same sexiligant atom, a number which it will be convenient to call the *denticity* of a ligand. The denticity classes are ordered on the basis that higher denticities precede lower. The unidentate, that is, the non-chelate ligands will thus constitute the last class.

Secondly, the ligands of each denticity class are ordered, as far as possible, within their class. A ligand now takes its order from a *leading ligating atom*, which is a selected

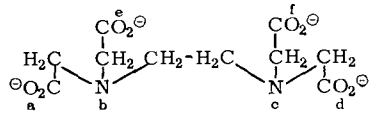
one of its terminal ligating atoms, or, if none is terminal as in an endless ligand, a selected one of its ligating atoms, selection being made by applying the Standard Sub-rules to the combined ligand. By "terminal" ligating atom is meant a terminal member of a series of ligating atoms contained in a ligand, regardless of whether or not it is at an extreme end of the ligand. The leading ligating atom of a non-chelate ligand is, of course, the only ligating atom that the ligand possesses. In each denticity class, the leading ligating atoms of the ligands, and hence the ligands themselves, are set in order, within the collective precedence of their denticity class, with terminal before non-terminal leading atoms, and otherwise as prescribed by the Standard Sub-rules (p. 391).

Thirdly, the ligating atoms of each chelate ligand are ordered within the collective precedence of the ligand. Apart from the leading ligating atom, the precedence of ligating atoms within a ligand is based on position in the ligand alone, and not on the properties used by the Standard Sub-rules. The leading ligating atom is given the first place; and then, proceeding from it along the longest continuous chain of linked atoms that leads to a terminal ligating atom, the successively situated ligating atoms, and, thereafter, the ligating atoms in the successively situated branches from that chain, are given successively lower places, all within the collective precedence of the chelate ligand. Direction round a cyclic ligand is taken as from the leading ligating atom to that one of the ligating atoms next on each side of it, which is given precedence over the others by the Standard Sub-rules. Any remaining ambiguity of direction in a bridged-ring ligand is resolved by taking at a bridgehead that path which would be preferred by the Standard Sub-rules.

In illustration of the described procedure, the internal priorities of the ligating atoms in some chelate ligands, assumed maximally ligated to the same central atom, are indicated by letter-labels (a > b > c > d, *etc.*) in formulae *(95)–(98)*. The first two of these are unbranched ligands, and the second two are branched ligands. In the latter, the ligating atoms in branches receive lower priorities than any in the main series. The only use of the Standard Sub-rules in these examples is to determine which of the non-equivalent ligating atoms of propylenediamine *(95)* is to be made the leading ligating atom.



*(95)* *(96)* *(97)*



*(98)*

We may now formally state the Octahedral Sequence Sub-rules which are to be successively applied:

(1) *Ligands of higher denticity precede those of lower.*

(2) *The leading ligating atom of a ligand being its terminal ligating atom most preferred by the Standard Sub-rules, or, in an endless ligand, the ligating atom which is so most preferred, the ligands are ordered, ended before endless, and otherwise as their leading ligating atoms would be ordered by the Standard Sub-rules.*

(3) *The ligating atoms of a ligand are ordered according to position, with diminishing precedence from the leading ligating atom along the longest continuous chain of atoms that leads to a terminal ligating atom, and thereafter in the successively situated branches from that chain. The sense of the succession in a cyclic ligand is taken as from the leading ligating atom to that next ligating atom which is preferred by the Standard Sub-rules, or, in case a choice remains, by following the path preferred by the Standard Sub-rules.*

### 5.3. The Octahedral Numbering Rule and its Sub-Rules

The Octahedral Sequence Rule gives to the differing ligating atoms a "linear" sequence, which has now to be converted into an "octahedral" sequence, by the use of a numbering scheme, preconditioned to describe octahedral arrangements, but capable of registering such information contained in the linear sequence as is significant for the description of the geometrical relations of the ligating atoms.

The pattern of the octahedral numbering scheme is *Werner*'s. This is prescribed in the first two of the following set of four sub-rules. The last two of these sub-rules adapt the priorities of the ligating atoms, as given by the Octahedral Sequence Rule, to the octahedral numbering pattern. The Octahedral Numbering Sub-rules, which are to be successively applied, are as follows:

(a) *The numbers 1 and 6 mark trans-positions.*

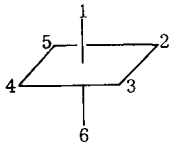
(b) *The numbers 2–5 form a cyclic sequence.*

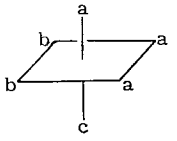
(c) *With the number 1 is associated the ligating atom which is most preferred by the Octahedral Sequence Rule; or, in case a choice is open, that most preferred ligating atom which allows the least preferred possible to be associated with the number 6; or, if a choice is still open, that which allows more preferred ligating atoms to be associated with lower numbers in the range 2–5.*

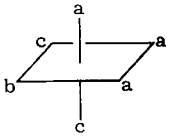
(d) *The numbers 2–4 are successively associated with the most preferred of the ligating atoms remaining available to each.*

In order to show how the Octahedral Numbering Sub-rules work with sexiligant atoms, we number some illustrative formulae, in the first place achiral formulae, below. Chelate ligands are represented by symbols such as A–A, A–B, B–A–B, the leading ligating atoms of which are A, A, and B, respectively. The order of precedence of the ligating atoms, as this would be given by the Standard Sub-rules, is taken to be A > B, *etc.* It is assumed, as is the usual situation, that successive ligating atoms of chelate ligands ligate in *cis*-positions.

Non-chelate ligands are represented by a, b, *etc.* Their order, as given by the Standard Sub-rules, is taken to be a > b, *etc.*


*(99)*


*(100)*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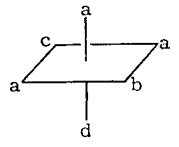
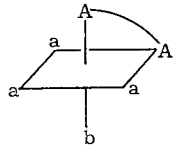
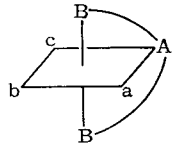
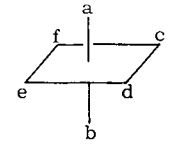

*(102)*

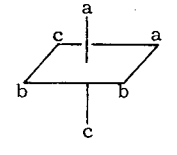

*(103)*

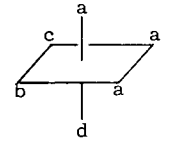

*(104)*

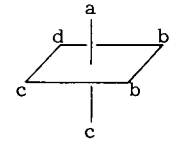
A set of numbers consistent with the Octahedral Numbering Sub-rules (a) and (b) is shown at *(99)*. The formulae *(100)–(104)* are so drawn that these numbers can be superposed on them by a translation alone, consistently with the Numbering Sub-rules (c) and (d). Now these are all achiral structures, and it is an easily proved characteristic of such that they can be numbered by the Octahedral Numbering Sub-rules in two completely equivalent ways, only one of which is illustrated in the diagrams. The alternative numberings are all obtainable by mirror-reflexions. For *(100)*, we reverse the positions of the numbers 2 and 3, and also 4 and 5. For *(101)*, we reverse 1 and 3, and also 5 and 6. For *(102)*, we reverse numbers 2 and 4; for *(103)*, numbers 3 and 5; and for *(104)*, 1 and 6. In every case, either of the alternative distributions of numbers on the octahedron, if carried into the name of the structure, produces an identical name, which, conversely, uniquely defines the achiral structure.

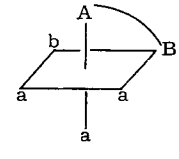
Formulae *(105)–(119)* illustrate application of the Octahedral Numbering Sub-rules to chiral structures. Again the formulae are so drawn that the numbering shown at *(99)* can be superposed by a pure translation consistently with the Octahedral Numbering Sub-rules. For many such structures, the numbering thus obtained is the only allowable one. But for others it is one of two or more completely equivalent number-distributions, inter-related by rotations. Structures *(113)*, *(116)*, and *(119)* each have two, structure *(117)* has four, and structure *(114)* has six such equivalent number-distributions. Obviously, these apparent alternatives, lead to the same name, which conversely, describes the same model, except only with respect to its chirality.

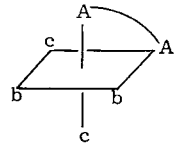

*(105)*

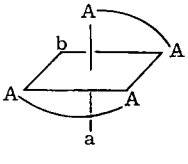

*(106)*

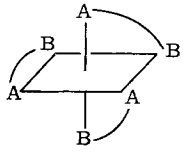

*(107)*

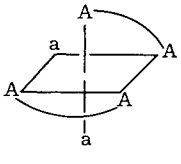

*(108)*

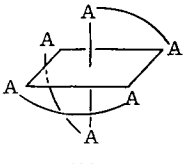

*(109)*

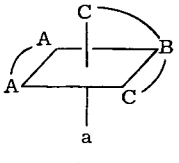

*(110)*

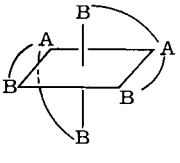

*(111)*

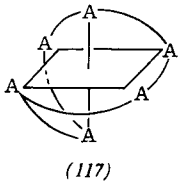

*(112)*

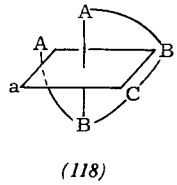

*(113)*

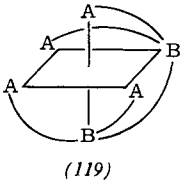

*(114)*


*(115)*


*(116)*


*(117)*


*(118)*


*(119)*

### 5.4. The Octahedral Chirality Rule

The Numbering Sub-rules are such that, when any chiral structure, such as one of those shown at *(105)* to *(119)*, is reflected in a plane, and the resulting structure is re-numbered, the result is the same as if the numbering as well as the structure, had suffered the reflexion. In other words, any chiral isomer and its enantiomer have their ligating atoms identically numbered, and, if the numbers are incorporated in a name, are represented by the same name. Thus the numbering system takes care of every feature of diastereoisomerism, excepting only associated chirality.

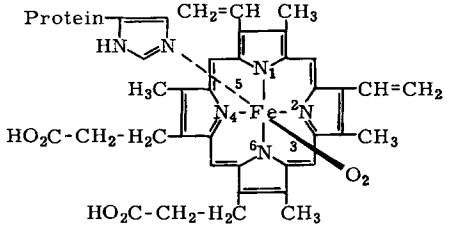
The outstanding matter of the specification of chirality is, however, very easily dealt with by reference to the numbering. The rule for so doing is as follows:

> **Octahedral Chirality Rule.** *The chiral centre of the numbered model is specified as R or S, according as the path of the numbers 1, 2, 3 in order appears right- or left-handed from the side of the model remote from 4, 5, 6.*

According to this rule, all the structures figured at *(105)–(119)* are in *R*-form. So also is that represented by *(120)*, which shows the iron atom and one valence-bond structure of the haem of the oxygen-myoglobin adduct[34]. The iron atom is σ-complexed, and two phantom atoms must make up the ligancy deficiencies in the two tertiary nitrogen atoms present in any valence-bond structure. Tertiary and quaternary nitrogen atoms in any such structure are always linked by conjugation, in the manner, already illustrated in the cyanine ion *(16)* (p. 394). Hence, in the blended structure, each of the four nitrogen atoms carries half a phantom atom, and each nitrogen atom and each ring-carbon atom has

[34] *J. C. Kendrew, H. C. Watson, B. E. Strandberg, R. E. Dickerson, D. C. Phillips,* and *V. C. Shore,* Nature (London) *190*, 666 (1961); cf. *R. E. Dickerson* in *H. Neurath*: The Proteins. Academic Press, New York 1964, Vol. 2, p. 634.

a delocalised valency. The atomic numbers associated with these delocalised valencies are 3 for nitrogen atoms, $6^1/_3$ for carbon atoms adjacent to nitrogen, and 6 for other carbon atoms. The Octahedral Sequence Subrules place the quadridentate ligand ahead of the nonchelate ligands, and identify in the former the leading ligating atom, and the sense of the cyclic ordering. Thus, the first two ligating atoms will belong to the vinyl-bearing pyrrole rings, and their relative order will follow from comparative explorations from N-1 to vinyl-2 and from N-2 to methyl-6 (if we distinguish the substituted pyrrole moieties with their side-chains by the numbers here attached to their nitrogen atoms). Then, the Octahedral Numbering Rule completes the association of ligating atoms with numbers on the octahedron, as shown in *(120)*, and the designation of chirality follows.




*(120)*

### 5.5. Symmetry in Central Chirality with Ligancy Six

Octahedral chiral systems can belong to any of the following five symmetry classes. First, there is the asymmetric class, $C_1$, illustrated by models *(105)* to *(111)*, *(115)*, and *(118)*. Next higher in symmetry stands the $C_2$ class, which has one two-fold rotational axis as its only symmetry, and is illustrated in models *(113)*, *(116)*, and *(119)*. Then comes the $C_3$ class, which has one three-fold rotational axis as its only symmetry, as illustrated in model *(112)*. Above that stands the V class, whose symmetry comprises three two-fold rotational axes, as exemplified by model *(117)*. Finally, the highest class, $D_3$, whose symmetry is constituted from one three-fold and three two-fold rotational axes, is exemplified by model *(114)*. In these five classes, the "multiplicities" (of group theory), or "symmetry numbers" (of statistical mechanics), are also the numbers of equivalent number-distributions on the octahedral figure, namely, one, two, three, four, and six, respectively.

The first octahedral complexes to be assigned absolute configurations were of the $D_3$ class. The self-contained method of diffraction by a favourable crystal structure of X-rays of a critical wavelength [35] was applied to the ion tris(ethylenediamine)cobalt(III) by *Saito* and his coworkers [36], who thus showed that the isomer with $[M]_D = +600°$ in water has structure *(114)* (AA = en), and so is the *R*-enantiomer. By a comparative analysis of the relevant circular dichroism spectra, Mason and his co-workers have correlated this configuration with those of a number of other complexes of like symmetry, and thus have established that $[Cr(en)_3]^{3+}$ giving $[M]_D = +300°$, $[Co(ox)_3]^{3-}$ giving $[M]_D = -7500°$, and $[Cr(ox)_3]^{3-}$ giving $[M]_D = +8000°$ in water, all have the *R*-configuration [37]. These workers have given the rule, applying to complexes with $D_3$ symmetry of $d^3$ and $d^6$ metals, that according as the longest-wave, spin-allowed absorption along the axis of the uniaxial crystal has a positive or negative rotational strength, the configuration of the complex will be *R* or *S*. They also evolved a second self-contained method of determining absolute configuration, a method wholly based on the theoretical analysis of suitable circular dichroism spectra. Thus they showed [38], without reference to any substance of known chirality, that (−)-tris-(*o*-phenanthroline)ruthenium(II) has the *R*-configuration *(114)* (AA = *o*-phen).

Again, by comparative analyses of circular dichroism spectra, the same workers have shown [37] that certain ions of $C_2$ symmetry, *viz.* (+)-*cis*-diammine- and (+)-*cis*-dicyano-(bisethylenediamine)cobalt(III), have the *R*-configuration *(113)* (AA = ethylenediamine; a = $NH_3$, $CN^-$).

They have similarly shown that some $C_1$ (asymmetric) ions, *viz.* (+)-*cis*-chloro-, (+)-*cis*-bromo-, and (+)-*cis*-aquo-ammine(bisethylenediamine)cobalt(III), have the *R*-configuration *(111)* (AA = ethylenediamine; a = $Cl^-$, $Br^-$, $OH_2$; b = $NH_3$).

### 5.6. Secondary Structures Involving Ligancies Six

When a unique helical relation is apparent in a structure, the Helicity Rule (p. 391) affords a particularly easy description of the chirality. We have applied this description to conformations and to secondary structures; and, because of its convenience when applicable, we have treated as secondary some organic structures which are so only marginally, such as the helicenes. We now propose a similar liberty in the field of octahedral structures, again taking advantage of the circumstance that the term "secondary structure" is not defined.

Octahedral structures with three *cis*-pairs of ligating atoms, like within each pair, but either like or unlike as between the pairs, contain a helical axis. This property bears no uniform relation to symmetry. Some, though not all, $C_1$ structures, which, being asymmetric, contain no axis of symmetry, nevertheless possess a helical axis. Model *(110)* is an example: it has *secM*-helicity. A $C_2$ structure may have zero, one, or two helical axes. Such axes never coincide with the symmetry axis. Model

[35] *J. M. Bijvoet, A. F. Peerdeman,* and *A. J. van Bommel,* Nature (London) *168*, 271 (1951).

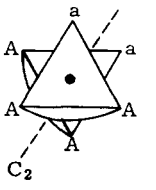
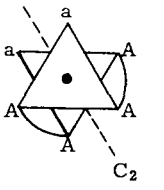
[36] *Y. Saito, K. Nakatsu, M. Shiro,* and *H. Kuroya,* Acta crystallogr. *8*, 729 (1955).

[37] *R. E. Ballard, A. J. McCaffery,* and *S. F. Mason,* Proc. chem. Soc. (London) *1962*, 331; *A. J. McCaffery* and *S. F. Mason, ibid. 1962*, 388; Trans. Faraday Soc. *59*, 1 (1963); Mol. Physics *6*, 359 (1963); *S. F. Mason,* Quart. Reviews *17*, 57 (1963); *A. J. McCaffery, S. F. Mason,* and *B. J. Norman,* Chem. Commun. *1965*, 132; *A. J. McCaffery, S. F. Mason,* and *R. E. Ballard,* J. chem. Soc. (London) *1965*, 2883.

[38] *A. J. McCaffery* and *S. F. Mason,* Proc. chem. Soc. (London) *1963*, 211.

*(113)* has two helical axes: about one it has *secM*, and about the other *secP*-helicity. All $D_3$ structures, without exception, contain four helical axes. One of these is co-incident with the three-fold axis of symmetry. None of the other three helical axes is co-incident with any of the three two-fold axes of symmetry. Model *(114)* is an example: with respect to the helical axis co-incident with the three-fold symmetry axis, it has *secM*-helicity: with respect to any of the other three helical axes, it has *secP*-helicity. The former assignment of helicity will probably be preferred on grounds of obviousness, but it is clearly not definitive unless the relevant axis of helicity is specified.

This discussion would modify the helicity symbols given to ions of $C_2$ symmetry, referable to model *(113)*, in a paper [39] which appeared while the present paper was in press: P($C_2$) would become *secP* or *secM*, according to the helical axis chosen; or, in the system which is always unequivocal, it would be *R*. The symbols *M* and *P* should refer to a helical axis, such as those shown in end-projection in the alternative representations *(113')* of *(113)*. Under octahedral geometry, the rotational axis $C_2$ is not a helical axis, because, *inter alia*, the chelate ligands AA spread apart along the direction of $C_2$.

(sec P)   (sec M)

*(113')*

*We thank Dr. H. H. Westen, not only for the German translation, but also for discussions and proposals arising therefrom that stimulated many improvements in the paper as a whole.*

Received: August 12th, 1965 [A 516/292 IE]
German version: Angew. Chem. *78*, 413 (1966)

[39] *A. J. McCaffery, S. F. Mason*, and *B. J. Norman*, J. chem. Soc. (London) *1965*, 5094.

# COMMUNICATIONS

## A Novel Synthesis of Adipic Acid from Acetylene and Acetic Acid

By Dr. J. DiPietro and Dr. W. J. Roberts

Research Laboratories of Celanese Corporation of America, Summit, New Jersey (U.S.A.)

It is known that carboxylic acids are formed when acetic acid is reacted with olefins in the presence of radical-producing agents [1,2].

We wish to report a novel synthesis of adipic acid by the free-radical addition of acetic acid to acetylene. A rocking bomb was charged with 1.8 kg of glacial acetic acid and 3.3 g (0.02 mole) of di-t-butyl peroxide. The bomb was then closed, purged with $N_2$ and heated. Once the temperature of the solution inside the bomb had reached 110 °C, anhydrous acetylene gas (4.94 g) was slowly introduced. The bomb was rocked and heated up to 120 ± 5 °C for 18 hours, after which it was cooled down to room temperature. The liquid portion of the reaction mixture was then distilled under nitrogen until most of the acetic acid was removed. Addition of cold $H_2O$ separates water-clear crystals of adipic acid from an oily product; the latter possesses a molecular weight of about 300, with a carboxyl content of 36 % by weight and has no unsaturation detectable by infrared spectroscopy. Based on the acetylene charged the yield of adipic acid was 10 %. Unreacted acetylene (64 %) can be recovered.

It remains to be established whether the reaction proceeds step-wise through the formation of vinylacetic acid, or by a simultaneous free-radical addition of two moles of acetic acid to acetylene. It is of interest in this respect that vinylacetic acid, when added to a large excess of boiling acetic acid in the presence of di-t-butyl peroxide, yields adipic acid.

Received: October 4th, 1965 [Z 102/929 IE]
German version: Angew. Chem. *78*, 388 (1966)

[1] *W. Banes, F. J. Fitzgerald*, and *M. C. Nelson*, U.S.-Patent 2585723 (1952).

[2] *J. C. Allen, I. G. Cadogan*, and *H. D. Hey*, Chem. and Ind. *1962*, 1621.

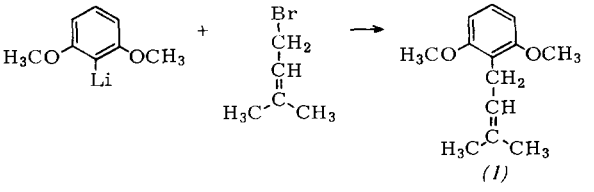
## New Synthesis of 5-Chromanol Derivatives and of Dihydroseselin [1]

By Dr. K.-H. Boltze and Dr. H.-D. Dell

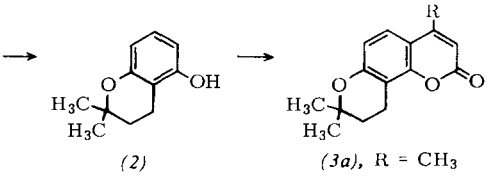
Chemische Abteilung der Troponwerke, Köln-Mülheim (Germany)

Dihydroseselin *(3b)* [2] previously has been obtained by cyclization from osthenol or, during ether cleavage, from osthol [3] (two-stage synthesis; 3.7 % yield).

2-Lithioresorcinol dimethyl ether, prepared from resorcinol dimethyl ether and phenyl-lithium [4], was treated with 3-methyl-2-butenyl bromide, affording the new compound 2-(3-methyl-2-butenyl)resorcinol dimethyl ether *(1)*, a colorless liquid of b.p. 101 °C/0.55 mm, $n_D^{20} = 1.5320$ (98 % yield). Ether cleavage of this product by heating with pyridinium chloride at 210–220 °C for 5 h gave 2,2-dimethyl-5-chromanol (dihydro-β-tubanol) *(2)* as yellowish needles, m.p. 120–122 °C (from light petroleum, b.p. 80–100 °C) in 74 % yield. This procedure constitutes a new and simple synthesis of compound *(2)*, which was previously obtained from 5-methoxycoumarin in five stages (15–36 % yield; 1.9–4.6 % overall yield) or from dihydro-2-isoprenylresorcinol in mediocre yield.



*(1)*



*(2)* *(3a)*, R = $CH_3$
*(3b)*, R = H

When kept with 1 mole of ethyl acetoacetate in the four-fold volume of concentrated $H_2SO_4$ at room temperature (24 h) or when heated with malic acid and concentrated $H_2SO_4$ until gas evolution ceases [molar ratio *(2)*:malic acid:$H_2SO_4$ = 1:1:15], compound *(2)* affords 3',4'-dihydro-4-methylseselin *(3a)*, needles, m.p. 164.5–165 °C (from 2-propanol/water; *ca.* 60 % yield), or 3'4'-dihydroseselin *(3b)*, m.p. 104–105 °C (from light petroleum; *ca.* 50 % yield), respectively.

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German version: Angew. Chem. *78*, 389 (1966)

[1] Part II of Experiments in the Coumarin Series.-Part. I: *K.-H. Boltze* and *H.-D. Dell*, Angew. Chem. *78*, 114 (1966); Angew. chem. internat. Edit. *5*, 125 (1966).

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[3] *E. Späth* and *H. Holzen*, Ber. dtsch. chem. Ges. *67*, 264 (1934).

[4] Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim 1963, Vol. I, p. 476.

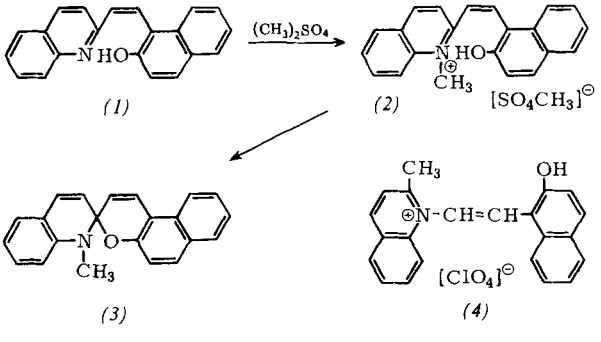
## Synthesis of 1'-Methylspiro[3*H*-naphtho[2,1-*b*]-pyran-3,2'(1,2-dihydroquinoline)]

By Dr. C. Schiele and H. O. Kalinowski

Forschungsinstitut der Telefunken AG., Ulm (Germany)

It has hitherto been assumed that 1'-methylspiro[3*H*-naphtho-[2,1-*b*]pyran-3,2'(1,2-dihydroquinoline)] *(3)* can be isolated only in an intramolecularly ionised form, as "spirain" [1].

We have found that compound *(3)* is obtained as spiran if quinaldine and 2-hydroxy-1-naphthaldehyde are heated with anhydrous $ZnCl_2$ at 150 °C for 1.5 hr and the resulting compound *(1)* is then treated in ethanolic suspension with methyl sulfate. The product, 2-[2-(2-hydroxy-1-naphthyl)vinyl]-1-methylquinolinium methyl sulfate *(2)*, can be cyclized to the spiran *(3)* by means of a basic ion-exchange resin (Merck III) in methanol. Yields amount to *ca.* 80 % calculated on *(1)*.




*(1)* *(2)* *(3)* *(4)*

Compound *(3)* forms yellow needles, m.p. 205–206 °C, from methanol; it is converted by acid into salts corresponding to *(2)*. Its infrared spectrum includes the $\nu C_{spiro}$-O stretching vibration at 970 $cm^{-1}$, characteristic of spiropyrans [2], that is absent from the spectra of compounds *(2)* and *(4)*. Compound *(3)* is, to the best of our knowledge, the first spiran of pyran and quinoline.

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[Z 152/985 IE]
German version: Angew. Chem. *78*, 389 (1966)

[1] *R. Wizinger* and *H. Wenning*, Helv. chim. Acta *23*, 247 (1940); *C. F. Koelsch*, J. org. Chemistry *16*, 1362 (1951); *E. B. Knott*, J. chem. Soc. (London) *1951*, 3038; *O. Chaude*, Cahiers de Physique *50*, 17 (1954); *51*, 6 (1954); *52*, 3 (1954).

[2] *G. Arnold*, Z. Naturforsch. *21b*, in press.

## Cycloaddition of Azosulfones and Sulfonylimines

By Doz. Dr. F. Effenberger and Dipl.-Chem. R. Maier

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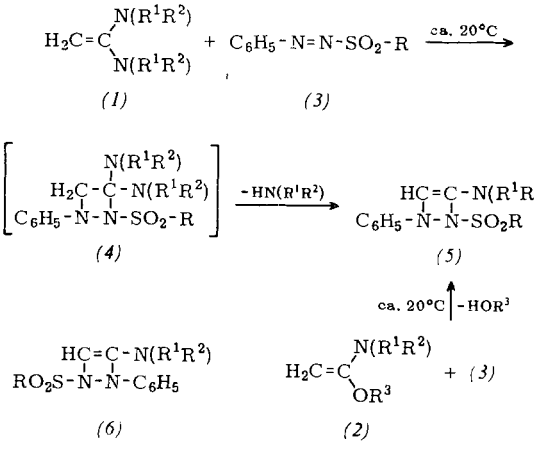
Ketene N,N-acetals *(1)* and ketene O,N-acetals *(2)* containing hydrogen in the 2-position afford β-substitution products when treated with compounds such as isocyanates and isothiocyanates that contain an electrophilic double bond system [1,2].

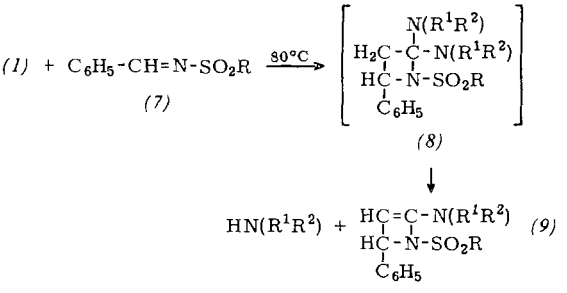
However, azosulfones *(3)* [3] and *N*-sulfonylimines *(7)* [4] react with ketene N,N-acetals *(1)* by cycloaddition, affording the hitherto unknown 1,2-dihydro-1,2-diazetes *(5)* (Table 1) and 1,2-dihydroazetes *(9)* (Table 2), respectively. Ketene O,N-acetals *(2)* and azosulfones *(3)*, under comparable conditions, also give 1,2-dihydro-1,2-diazetes *(5)*.




*(1)* *(3)* *(4)* *(5)* *(6)* *(2)*

Table 1. 1,2-Dihydro-1,2-diazedes *(5)* obtained from *(1)* or *(2)* and *(3)* in benzene.

| *(1)* | | *(2)* | | | *(3)* | *(5)* | |
|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^1$ | $R^2$ | $R^3$ | R | Yield [%] | M.p. [°C] |
| $-(CH_2)_5-$ | | | | | $C_6H_5$ | 50.5 | 148–149 |
| $-(CH_2)_5-$ | | | | | $p$-$CH_3$–$C_6H_4$ | 75.7 | 177–178 |
| $-(CH_2)_5-$ | | | | | $p$-Cl–$C_6H_4$ | 66.8 | 172–173 |
| $CH_3$ | $CH_3$ | | | | $p$-$CH_3$–$C_6H_4$ | 77 | 148–149 |
| $CH_3$ | $CH_3$ | | | | $p$-Cl–$C_6H_4$ | 72.5 | 153–154 |
| | | $CH_3$ | $CH_3$ | $C_2H_5$ | $C_6H_5$ | 60.2 | 142–144 |
| | | $CH_3$ | $CH_3$ | $C_2H_5$ | $p$-$CH_3$–$C_6H_4$ | 67 | 148 |




*(1)* + *(7)* → *(8)* → *(9)*

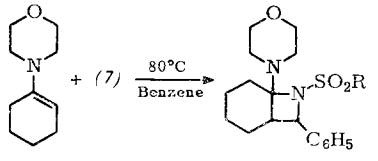
Table 2. 1,2-Dihydroazetes *(9)* from *(1)* and *(7)* in benzene at 80 °C.

| *(1)* $R^1 + R^2$ | *(7)* R | *(9)* Yield [%] | M.p. [°C] |
|---|---|---|---|
| $-(CH_2)_5-$ | $C_6H_5$ | 68 | 132–133 |
| $-(CH_2)_5-$ | $p$-$CH_3$–$C_6H_4$ | 60 | 179–181 |
| $-(CH_2)_5-$ | $p$-Cl–$C_6H_4$ | 66.8 | 196–198 |
| $-(CH_2)_2-O-(CH_2)_2-$ | $C_6H_5$ | 35 | 146–149 |
| $-(CH_2)_2-O-(CH_2)_2-$ | $p$-$CH_3$–$C_6H_4$ | 34.3 | 166 |

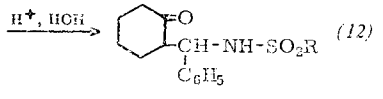
Equimolar quantities of the ketene derivative *(1)* or *(2)* and the sulfonyl derivative *(3)* or *(7)*, separately dissolved in anhydrous benzene, are mixed and, depending on the reactivity of the sulfonyl derivative, are kept at room temperature for 2 days or heated under reflux for 2 hr. After removal of the benzene by distillation, the products, which mostly separate as oils, crystallize when rubbed with ether or petroleum ether and can be obtained analytically pure by recrystallization from acetonitrile or ethyl acetate. Elemental analysis, molecular weight determinations, as well as infrared and NMR spectra show these to be 1,2-dihydro-1,2-diazetes and -azetes, respectively. The 1:1 adducts *(4)* and *(8)* that are presumably formed as primary products could not be isolated under the conditions used.

The direction of cycloaddition of the sulfonylimines *(7)* is proved by NMR investigations (AB spectrum at $\delta \approx 6.7$ ppm, $J_{AB} = 17$ cps). However, formation of the isomeric compound *(6)* in reactions of azosulfones *(3)* could not be excluded, although we consider formation of compounds *(5)* more probable because of the electronic influence of the sulfonyl group on the N=N double bond.

*N*-Sulfonylimines *(7)* react also with 4-(cyclohexen-1-yl)-morpholine *(10)* (molar ratio 1:1, in boiling benzene), although the latter is less reactive than compounds *(1)* and *(2)*; cycloaddition affords compounds *(11)* (elemental analysis, molecular weight determination, infrared and NMR spectra). Compounds *(11)* are hydrolysed to ketones *(12)* in acidic solution.




*(10)* *(11)*




*(12)*

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German version: Angew. Chem. *78*, 389 (1966)

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## Synthesis of Monodisperse Oligoamides on Macromolecular Carriers[1]

By Priv.-Doz. Dr. M. Rothe and Dipl.-Chem. Hj. Schneider

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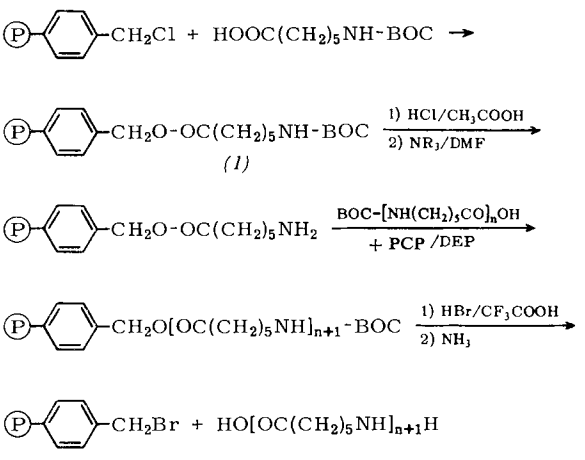
We have worked out a synthesis of molecularly homogeneous linear oligomers $H[NH(CH_2)_5CO]_nOH$ of 6-aminohexanoic acid with a degree of polymerization up to n = 11 by using *Merrifield*'s procedure[2] for the synthesis of peptides (covalent bonding to an insoluble macromolecular carrier of the oligoamide chain that is to be extended stepwise)[3]. For formation of the amide linkage we have used phosphorous ester chlorides[4], which have not been previously used for this purpose; they give quantitative conversions, even in heterogeneous reaction with the oligomers bound on the carrier, which is a prerequisite for homogeneity of the products.

For instance, *N*-t-butoxycarbonyl-mono- or -bis-(6-aminohexanoic acid), m.p. 41 °C or 66 °C, respectively, was converted by *o*-phenylene chlorophosphite (PCP) into a mixed anhydride, and this was treated on a shaker at 100 °C with 6-aminohexanoic acid *(1)* bound as benzyl ester to the carrier (chloromethylated polystyrene, cross-linked with 2 % of divinylbenzene, particle size 200–400 mesh). The mode of linkage of the monomer to the carrier and removal of the butoxycarbonyl protecting group and, after several repetitions of the process, of the whole oligomer chain, will be evident from the reaction scheme below and is performed under standardized conditions[2].

Excess of starting material and by-products can be easily removed by means of diethyl phosphite (DEP) as solvent, even when higher butoxycarbonyl-oligoamides are used as "carboxyl components" in the chain extension.




The molecular homogeneity of the oligoamides obtained was established by thin-layer electrophoresis at pH 1.9 and 0.3. The products were identified by comparison with authentic specimens[4,5].

Yields were in excess of 90 % for the lower, water-soluble oligoamides and 60 to 70 % for the higher oligoamides that were more difficult to isolate.

The prospects for synthesis of much longer, monodisperse chains by this procedure appear to be good, since solubility difficulties that have so far precluded the preparation of homogeneous macromolecules do not occur.

Received: January 28 th, 1966; revised: February 7th, 1966
[Z 150/983 IE]
German version: Angew. Chem. *78*, 390 (1966)

[1] Part XVI of Linear and Cyclic Oligomers. – Part XV: *M. Rothe et al.*, Makromolekulare Chem. *91*, 23 (1966).

[2] *R. B. Merrifield*, J. Amer. chem. Soc. *85*, 2149 (1963).

[3] *M. Rothe*, Lecture at Marl (Germany) on June 16th, 1965.

[4] *G. W. Anderson et al.*, J. Amer. chem. Soc. *74*, 5304, 5307 (1952); *M. Rothe et al.*, Makromolekulare Chem. *75*, 122 (1964).

[5] *M. Rothe et al.*, Liebigs Ann. Chem. *609*, 88 (1957).

## Preparation and Crystallographic Data of Vanadium Chlorimide Trichloride, $Cl_3VNCl$

By Dr. J. Strähle and Dr. H. Bärnighausen

Chemisches Laboratorium der Universität Freiburg
(Germany)

The compound $Cl_3VNCl$ is remarkable in that it contains a metal-nitrogen multiple bond and is a metal derivative of chloramine. It was first obtained on reaction of chlorazide with vanadium tetrachloride[1]. We have now found a more expedient preparation of $Cl_3VNCl$, which eliminates the

necessity of working with the sensitive and explosive compounds $ClN_3$ and $VCl_4N_3$ (obtained as intermediate):

$$VN + 2\,Cl_2 \rightarrow Cl_3V{=}N{-}Cl$$

At the reaction temperatures required (between 120 and 140 °C) the product sublimes and deposits in the cooler part of the apparatus as needle-shaped crystals, often twinned; the vanadium tetrachloride formed as by-product is removed in the stream of chlorine (*ca.* 4 liters/hr). In three hours, 500 mg of vanadium nitride can be converted.

Weissenberg photographs and Buerger precession diagrams show that $Cl_3VNCl$ is triclinic with lattice parameters

| | | |
|---|---|---|
| $a = 7.64$ Å | $b = 7.14$ Å | $c = 5.91$ Å |
| $\alpha = 112.4°$ | $\beta = 94.9°$ | $\gamma = 107.8°$ |

The volume of the unit cell set up by *Delaunay's* method [2] is 276.6 Å$^3$. This value is about twice that estimated for one molecule from the ionic increments [3], so that the unit cell must contain two formula units of $Cl_3VNCl$. From these results a value of 2.48 g/cm$^3$ is derived for the density.

It is not yet possible to decide between the two space groups P1 and $P\bar{1}$, but preliminary results of a complete structure determination make the centrosymmetric space group appear the more probable.

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German version: Angew. Chem. *78*, 450 (1966)

[1] *J. Strähle* and *K. Dehnicke*, Z. anorg. allg. Chem. *338*, 287 (1965).

[2] *B. Delaunay*, Z. Kristallogr., Mineralog. Petrogr., Abt. A. *84*, 132 (1933).

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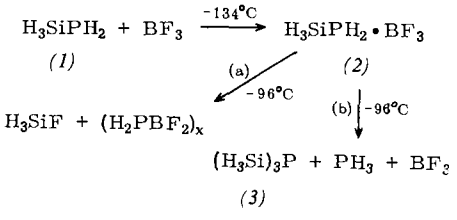
## Cleavage and Addition Reactions of Silylphosphines and Silylarsines [1]

By Dr. C. R. Russ and Prof. Dr. A. G. MacDiarmid

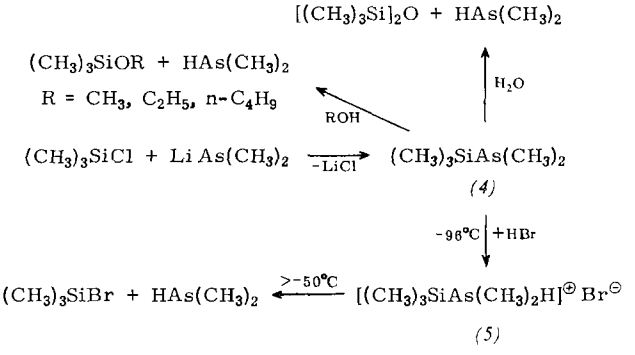
John Harrison Laboratory of Chemistry and
Laboratory for Research on the Structure of Matter
Philadelphia, Penn. (U.S.A.)

Silylphosphine *(1)* [2] and $BF_3$ form an adduct *(2)* at −134 °C which decomposes at −96 °C in two ways:




Reactions (a) and (b) occur to approximately equal extents. Trisilylphosphine *(3)* is apparently less susceptible to attack by $BF_3$ than *(1)*, as evidenced by the coexistence of $BF_3$ and *(3)* during separation.

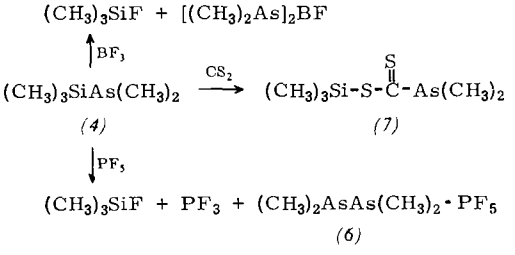
Dimethyl(trimethylsilyl)arsine *(4)*, m.p. −87.6 °C, b.p. 136.4 °C, was obtained in 76 % yield by the reaction of dimethylarsinyl-lithium with chlorotrimethylsilane. At −96 °C *(4)* forms an adduct *(5)* with HBr, which decomposes quantitatively between −50 °C and room temperature to bromotrimethylsilane and dimethylarsine. Compound *(4)* is hydrolysed instantly and almost quantitatively by pure water at room temperature to dimethylarsine and hexamethyldisiloxane; it also reacts rapidly with alcohols to give trimethylsilyl ethers. It does not react with ammonia or dimethylamine.




The Si–As bond in *(4)* is cleaved by a deficit of $CH_3I$ at room temperature to give iodotrimethylsilane, trimethylarsine, and a little tetramethylarsonium iodide.

Reaction betwen *(4)* and $BF_3$ commences at −50 °C, but heating at 90 °C is required for quantitative formation of bis(dimethylarsinyl)boron fluoride and fluorotrimethylsilane. In contrast to the reaction with dimethyl(trimethylsilyl)-amine [3], phosphorus pentafluoride reacts with *(4)* above −50 °C to give fluorotrimethylsilane, phosphorus trifluoride, and the adduct *(6)* of $PF_5$ and tetramethyldiarsine.

Carbon disulfide was found to insert in the Si–As bond in *(4)* just as it inserts in the Si–N bond [4]. The product, *S*-trimethylsilyl-*C*-dimethylarsinyl dithioformate *(7)*, decomposes completely at 90 °C.




Received: February 1st, 1966 [Z 147/980 IE]
German version: Angew. Chem. *78*, 391 (1966)

[1] This work was supported by the Advanced Research Projects Agency, Office of the U.S. Secretary of Defendse.

[2] *G. Fritz* and *H. O. Berkenhoff*, Z. anorg. allg. Chem., *289*, 250 (1957).

[3] *G. C. Demitras*, *R. A. Kent*, and *A. G. MacDiarmid*, Chem. and Ind. *1964*, 1712.

[4] *H. Breederveld*, Recueil Trav. Chim. Pays-Bas *81*, 276 (1962).

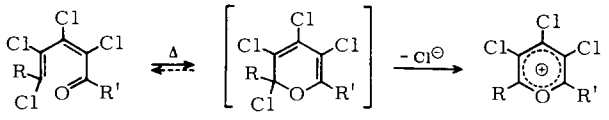
## Synthesis of Chlorinated Pyrylium Salts

By Prof. Dr. A. Roedig, Dr. M. Schlosser, and
Dipl.-Chem. H.-A. Renk

Institut für Organische Chemie
der Universität Würzburg (Germany)

A pentachloro-2*H*-pyran has been considered as an intermediate in the chloroaldehyde-carbonyl chloride rearrangement of perchloro-2,4-pentadienal [1] on the basis of results obtained in kinetic investigations [2]. We have now found that this aldehyde and other chlorinated pentadienals and pentadienones *(1)* afford complex pyrylium salts *(2)* when warmed with Lewis acids [$SnCl_4$ or $SbCl_5$ in $CS_2$, or $FeCl_3$ in $CS_2$ (with a little ether)] for 10 to 15 h at 40–50 °C. A prerequisite for ring closure is that the α,β-double bond in *(1)* is in the *cis*-configuration [3] and for salt formation that at least one halogen atom is in the δ-position. It is thus probable that the pentadienone tautomerizes to a 2*H*-pyran, which is converted into the pyrylium cation on abstraction of a chloride ion.

δ-Chlorinated *cis*-2,4-pentadienoyl chlorides *(1)* with R = H or $C_6H_5$ and R′ = Cl react in the same way but more slowly (reaction time: 4 days).



*(1)* *(2)*

| R | *(2)* R′ | Anion | Decomp. p. [°C] | Yield [%] | Method |
|---|---|---|---|---|---|
| Cl | H | $SnCl_5^{\ominus}$ | 170–171.5 | 87 | [a] |
| | | | | 27.6 | [b] |
| H | H | $FeCl_4^{\ominus}$ | 155–160 | 13 | [a] |
| Cl | $C_6H_5$ | $SnCl_6^{2\ominus}$ | 177–183 | 40.9 | [a] |
| | | $SnCl_5^{\ominus}$ | 176–180 | 17.2 | [b] |
| $C_6H_5$ | H | $SnCl_5^{\ominus}$ | 118–120 | 60 | [a] |
| $C_6H_5$ | $C_6H_5$ | $FeCl_4^{\ominus}$ | 219–222 | 52 | [a] |
| | | $SbCl_6^{\ominus}$ | 128–133 | 28.9 | [a] |
| | | $ClO_4^{\ominus}$ | 240 | 20 | [c] |

[a] From aldehyde or ketone.
[b] From acid chloride.
[c] From the chloroferrate with $NaClO_4$ in acetonitrile.

The pyrylium salts can be stored only if completely free from solvent and with rigid exclusion of air and moisture. The tetrachloro derivatives (R = Cl) are particularly sensitive. They decompose rapidly in moist air with formation of the corresponding 2-pyrones.

Received: February 3rd, 1966 [Z 156/989 IE]
German version: Angew. Chem. *78*, 448 (1966)

[1] *A. Roedig* and *G. Märkl*, Liebigs Ann. Chem. *659*, 1 (1962); *A. Roedig, R. Kohlhaupt*, and *G. Märkl*, Chem. Ber. *99*, 698 (1966).

[2] *A. Roedig*, Angew. Chem. *76*, 276 (1964); Angew. Chem. internat. Edit. *3*, 317 (1964).

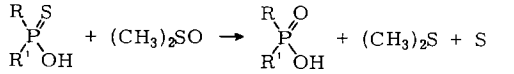
[3] The *trans*-ketone (R = Cl, R′ = $C_6H_5$) does not react with $SnCl_4$ in $CS_2$.

## Desulfuration of Thio-Acids with Dimethyl Sulfoxide

By Dr. M. Mikołajczyk

Institute of Organic Chemistry of the Polish Academy of Sciences, Lodz (Poland)

It was found that *O,O*-diethyl hydrogen thiophosphate *(1)* and *O*-ethyl hydrogen ethylthiophosphonate *(2)* are converted into the sulfur-free analogues when allowed to stand with an equimolar amount of dimethyl sulfoxide for one week at 20 °C. Yields are about 75–80%. After reaction the dimethyl sulfide formed is distilled off and the residue is dissolved in methanol and filtered from sulfur.



*(1)*, R = R′ = $OC_2H_5$
*(2)*, R = $OC_2H_5$, R′ = $C_2H_5$

Diphenyldithiophosphinic acid *(3)* undergoes a strongly exothermic reaction with 2 moles of dimethyl sulfoxide, yielding similarly (up to 90%) the sulfur-free acid.

$(C_6H_5)_2PS_2H + 2\,(CH_3)_2SO \rightarrow (C_6H_5)_2PO_2H + 2\,(CH_3)_2S + 2\,S$
*(3)*

Monothioacetic acid is also desulfurated by dimethyl sulfoxide; the yield is 70% after one week at 20 °C.

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German version: Angew. Chem. *78*, 393 (1966)

## Alkylation of Amine Oxides with Sultones

By Dr. W. D. Willmund

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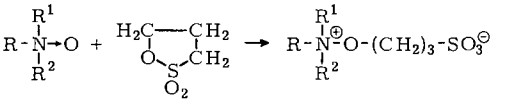
Alkoxyammonium halides are formed on reaction of tertiary amine oxides with alkyl halides [1].

We have found that alkylation of tertiary amine oxides with 1,3-propanesultone *(1)* in acetone or ethanol leads to alkoxyammonium sulfobetains *(2)*. Reaction conditions: dropwise addition of an equimolar amount of sultone to a boiling solution of the amine oxide in acetone, removal of the crystalline sulfobetaine after 2 hr, washing with acetone and vacuum drying. For pyridine oxide: reaction in the melt or in a little ethanol.

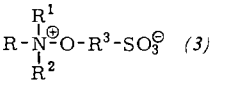


*(1)* *(2)*

| R | $R^1$ | $R^2$ | *(2)*, M.p. [°C] | *(2)*, Yield [%] |
|---|---|---|---|---|
| $C_{12}H_{25}$ | $CH_3$ | $CH_3$ | 172 | 64.6 |
| $C_{14}H_{29}$ | $CH_3$ | $CH_3$ | 174 | 79 |
| $C_{16}H_{33}$ | $CH_3$ | $CH_3$ | 175.5 | 70.3 |
| $C_{18}H_{37}$ | $CH_3$ | $CH_3$ | 178 | 79 |
| Benzyl | $CH_3$ | $CH_3$ | 174 | 29.3 |
| Cyclohexyl | $CH_3$ | $CH_3$ | 155 | 36.6 |
| Phenyl | $CH_3$ | $CH_3$ | [a] | 45 |
| | Pyridyl | | 194.5–195 | 54.4 |
| | Quinolyl | | 182 [b] | 61.3 |

[a] Very violent reaction; the oily product was not obtained pure.
[b] Contains 1 mole of water of crystallization.

The reaction is not confined to 1,3-propanesultone. Butanesultone (1,2-oxathiane 2,2-dioxide), *o*-toluenesultone [the sultone from *o*-(hydroxymethyl)benzenesulfonic acid], and tridecanesultone (formed on reaction of $SO_3$ with 1-tridecene [2] with amine oxides afford similar *O*-alkylation products of type *(3)*.



*(3)*

| R | $R^1$ | $R^2$ | $R^3$ | *(3)*, M.p. [°C] | *(3)*, Yield [%] |
|---|---|---|---|---|---|
| $C_{12}H_{25}$ | $CH_3$ | $CH_3$ | $-C_4H_8-$ | Paste | 86 |
| $C_{12}H_{25}$ | $CH_3$ | $CH_3$ | $-CH_2-o-C_6H_4-$ | 42–43 | 71 |
| | Pyridyl | | $-CH(C_{10}H_{21})-(CH_2)_2-$ | 149 | 69.4 |

Alkoxyammonium sulfobetaines are stable in neutral or acidic aqueous solution. In an alkaline medium (pH 12) they are cleaved at the N–O bond, yielding the tertiary amines and ω-formylsulfonates.

Received: February 7th, 1966 [Z 151/984 IE]
German version: Angew. Chem. *78*, 391 (1966)

[1] *W. R. Dunstan* and *E. Goulding*, J. chem. Soc. (London) *75*, 792 (1899); *J. Meisenheimer*, Liebigs Ann. Chem. *397*, 273 (1913); *K. B. Augustinsson* and *H. Hasselquist*, Acta chem. scand. *15*, 817 (1961).

[2] German Patent Application 1159430 (Aug. 9th, 1962/Dec. 19th, 1963); Henkel & Cie., inventors: *H. Baumann, W. Stein*, and *M. Voss*.

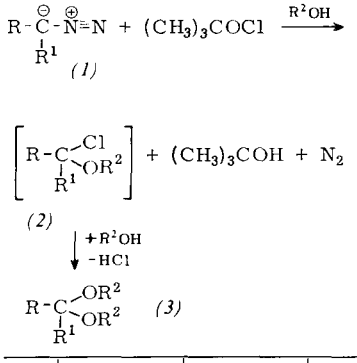
## Synthesis of Acetals by Reaction of Diazoalkanes with t-Butyl Hypochlorite [*]

By Prof. Dr. H. Baganz and Dr. H.-J. May

Institut für Organische Chemie der Technischen Universität Berlin (Germany)

Organic sulfur chlorides react with diazoalkanes to give aldehyde derivatives[1]. Corresponding reactions are not yet known for the analogous oxygen compounds, *i.e.* esters of hypochlorous acid.

We have found that diazoalkanes *(1)* are converted by t-butyl hypochlorite in the presence of alcohols into acetals *(3)* in good yields. The α-halogeno ethers *(2)* postulated as intermediates cannot be isolated.



| | R | $R^1$ | $R^2$ | Yield [%] |
|---|---|---|---|---|
| *(3a)* | H | H | $C_2H_5$ | 70 [a] |
| *(3b)* | H | H | n-$C_3H_7$ | 76 [a] |
| *(3c)* | H | H | 2 $R^2$ = $-CH_2CH_2-$ | 57 [a] |
| *(3d)* | $C_6H_5$ | H | $C_2H_5$ | 49 [b] |
| *(3e)* | $C_6H_5$ | $C_6H_5$ | $C_2H_5$ | 43 [b] |
| *(3f)* | R + $R^1$ = 9-Fluorenylidene | | $C_2H_5$ | 63 [c] |

[a] Determined by gas chromatography.
[b] Determined as 2,4-dinitrophenylhydrazone.
[c] Isolated in quantity.

Most methods for preparation of acetals depend on removal of water formed during the reaction from the equilibrium mixture. The present method avoids these difficulties and may therefore be important in special cases.

*Experimental*:

An ethereal solution of 0.2 mole of a diazoalkane (previously dried over KOH pellets) is treated with 100 ml of the anhydrous alcohol and cooled to −10 °C. 21.7 g (0.2 mole) of t-butyl hypochlorite is then dropped in slowly with stirring. The mixture is colorless at the end of the addition. The hydrogen chloride formed, and the solvent, are then removed under slightly diminished pressure and the residue is distilled or recrystallized.

Received: February 14th, 1966 [Z 161/993 IE]
German version: Angew. Chem. 78, 448 (1966)

[*] We thank the Deutsche Forschungsgemeinschaft, the Fond der Chemischen Industrie, and the Gesellschaft von Freunden der Technischen Universität Berlin for supporting this work.

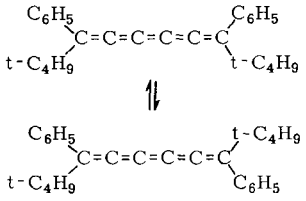
[1] *A. Schönberg, O. Schütz*, and *J. Peter*, Ber. dtsch. chem. Ges. *62*, 1663 (1929); *A. Schönberg* and *T. Stolpp, ibid. 63*, 3102 (1930); *H. Brintzinger* and *H. Ellwanger*, Chem. Ber. *87*, 300 (1954).

## cis-trans-Isomerism of 1,6-Diphenyl-1,6-di-t-butylhexapentaene [1]

By Prof. Dr. R. Kuhn, Dr. B. Schulz, and Dr. J. C. Jochims

Max-Planck-Institut für Medizinische Forschung, Heidelberg (Germany)

*Van't Hoff*'s prediction[2] that *cis-trans*-isomerism should occur in hexapentaenes has so far not been confirmed. We tried unsuccessfully to apply to the homologous hexapentaene[4] the methods with which we separated the *cis*-form (m.p. 142–143 °C) from the *trans*-form (m.p. 127–128 °C) of 1,4-diphenyl-1,4-di-t-butylbutatriene[3]. The hexapentaene was obtained crystalline only in one form (m.p. 128 °C).



The nuclear magnetic resonance spectrum, at 100 MHz, of the hexapentaene in [$^2H_6$]dimethyl sulfoxide contains, however, two sharp bands, at 1.25 and 1.29 ppm, which must be assigned to the two equivalent tert-butyl groups of the *cis* and the *trans*-form, respectively. When the solution is warmed these bands move closer together, and at 100 °C they coalesce to one broad band, which becomes sharp when the temperature is raised further. Cooling regenerates the original spectrum. From the coalesce temperature of the two bands the free energy of activation of the *cis-trans* isomerization in dimethyl sulfoxide can be calculated as $\Delta G^{\neq} = 20$ kcal/mole, whereas a value of 30 kcal/mole had been found[5] for the corresponding butatriene under the same conditions. The equilibrium constant is 1 in both cases. This is the first time that *cis-trans* isomerism has been demonstrated for a hexapentaene, albeit only in solution.

Received: February 14th, 1966 [Z 160/992 IE]
German version: Angew. Chem. 78, 449 (1966)

[1] Communication XXIII on Cumulenes. – Communication XXII: *D. Rewicki*, Chem. Ber. *99*, 392 (1966).

[2] *J. H. van't Hoff*: Die Lagerung der Atome im Raume. Verlag F. Vieweg und Sohn, Braunschweig 1877, p. 14.

[3] *R. Kuhn* and *B. Schulz*, Chem. Ber. *98*, 3218 (1965).

[4] *F. Bohlmann* and *K. Kieslich*, Chem. Ber. *88*, 1211 (1955).

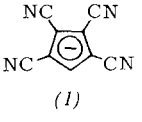
[5] *R. Kuhn, B. Schulz*, and *J. C. Jochims*, unpublished work.

## Reactions of Cyano-Substituted Cyclopentadienyl Anions

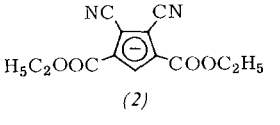
By Dr. K. Friedrich

Department of Chemistry, The University, Southampton (England) [*]

The tetracyanocyclopentadienyl anion *(1)*[1] and the 2,3-dicyano-1,4-diethoxycarbonylcyclopentadienyl anion *(2)* form stable salts. In distinction from the unsubstituted cyclopentadienyl anion, which yields dihydrosesquifulvalene with tropylium bromide in tetrahydrofuran[2], the tetramethylammonium salts of *(1)* and *(2)* give tropylium salts (m.p. 183 °C and 160 °C, respectively) when treated with tropylium fluoroborate in aqueous solution.

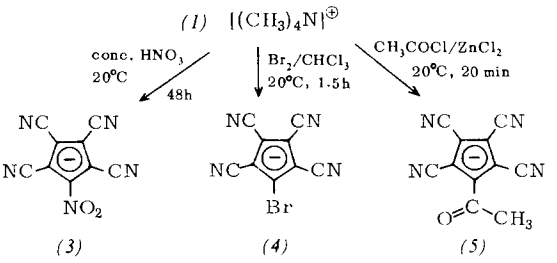


*(1)*



*(2)*

Electrophilic substitution can be effected on salts of *(1)* under mild conditions. The tetramethylammonium salt (m.p. 217–220 °C) with concentrated nitric acid gives the tetracyanonitrocyclopentadienyl anion *(3)* (m.p. of the tetramethylammonium salt >385 °C). With bromine in chloroform the bromo derivative *(4)* (m.p. of the tetramethylammonium salt 360–362 °C) is formed; and shaking a solution in acetyl chloride with zinc chloride gives the anion *(5)* (m.p. of the tetramethylammonium salt 335 °C).




(3) (4) (5)

The tetracyanocyclopentadienyl anion *(1)* described by *Webster*[1] can also be obtained from all-*trans*-1,2,3,4-cyclopentanetetracarboxylic acid[3]. With phosphorus pentachloride in benzene this acid yields the tetrachloride (b.p. 172–173 °C/4 mm Hg) which is converted by ammonia in benzene into the tetraamide (m.p. 335 °C). Dehydration with phosphorus oxide chloride in acetonitrile with addition of sodium chloride then yields all-*trans*-1,2,3,4-tetracyanocyclopentane (m.p. 221 °C), which is converted directly into tetracyanocyclopentadiene when heated with phosphorus pentachloride at 125–130 °C; addition of tetramethylammonium chloride to an aqueous solution of the reaction products precipitates the tetramethylammonium salt of *(1)*.

For preparation of the 2,3-dicyano-1,4-diethoxycarbonylcyclopentadienyl anion *(2)*, diethyl 2,3-dioxo-1,4-cyclopentanedicarboxylate[4] was converted by anhydrous hydrocyanic acid into the biscyanohydrin (m.p. 144 °C), whose diacetate (m.p. 120–121 °C) yields the potassium salt of *(2)* on addition of potassium t-butoxide; the tetramethylammonium salt precipitated from aqueous solution melts at 169 °C. An attempted extension of this reaction sequence to 3,5-dicyanocyclo-1,2-cyclopentadione (m.p. 225 °C), obtained from glutaronitrile and oxalic ester, was unsuccessful.

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German version: Angew. Chem. *78*, 449 (1966)

[*] Present address: Chemisches Laboratorium der Universität Freiburg (Germany).

[1] *O. W. Webster*, J. Amer. chem. Soc. *87*, 1820 (1965).

[2] *W. v. E. Doering* and *H. Krauch*, Angew. Chem. *68*, 664 (1956).

[3] *K. Alder, H.-H. Mölls*, and *R. Reeber*, Liebigs Ann. Chem. *611*, 7 (1958).

[4] *W. Dieckmann*, Ber. dtsch. chem. Ges. *27*, 965 (1894).

## Preparation and Properties of Tungsten Dioxide Diiodide, $WO_2I_2$

By Dr. J. Tillack and Dr. P. Eckerlin
Philips Zentrallaboratorium, Aachen (Germany)

and by J. H. Dettingmeijer
N. V. Philips, Hauptindustriegruppe Licht,
Forschungsabteilung, Eindhoven (The Netherlands)

When tungsten, tungsten trioxide, and an excess of iodine are subjected in a sealed quartz tube to a temperature gradient of 800/300 °C, previously unknown $WO_2I_2$ separates analytically pure in the cooler zone:

$$W + 2\,WO_3 + 3\,I_2 = 3\,WO_2I_2$$

$WO_2I_2$ decomposes above 200 °C in a vacuum with loss of iodine but can be sublimed unchanged under an iodine pressure of about 3 atm (equivalent to 14 mg of iodine per ml of tube volume) in a temperature gradient of 450/300 °C. Owing to the reversibility of the reactions, $WO_2I_2$ can also be obtained by reaction of iodine with tungsten and oxygen or with tungsten dioxide.

$WO_2I_2$ forms very thin platelets, several millimeters in size, with metallic luster, that gradually decompose in the air. It is insoluble in water, dilute mineral acids, or organic solvents (*e.g.* alcohol, ether, benzene, light peroleum, and chloroform). In dilute alkalis it gives colorless solutions from which acidification precipitates tungstic acid.

The properties of $WO_2I_2$ correspond to a considerable extent with those of a $WI_2$ described by *Roscoe*[1].

$WO_2I_2$ has a strongly disordered layer structure with a monoclinic unit cell: $d_{X\text{-ray}} = 6.40$; $d_{pyc} = 6.39$; $a = 17.095$ Å; $b = 3.899$ Å; $c = 7.492$ Å; $\beta = 102.66°$; probable space groups: C2/c and Cc.

$WO_2I_2$ plays an important part in the iodine lamp. The necessity for the presence of oxygen in quantitative re-transport of the evaporated tungsten to the filament can now be unambiguously explained.

Received: February 21st, 1966 [Z 167/999 IE]
German version: Angew. Chem. *78*, 451 (1966)

[1] *H. E. Roscoe*, Liebigs Ann. Chem. *162*, 366 (1872); Chem. News *25*, 73 (1872).

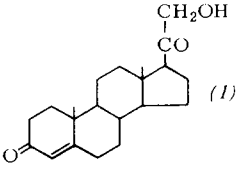
## A Vertebrate Hormone as Defensive Substance of the Water Beetle (Dytiscus marginalis) [1]

By Prof. Dr. H. Schildknecht, Dipl.-Chem. R. Siewerdt, and Dr. U. Maschwitz

Organisch-Chemisches Institut der Universität Heidelberg (Germany)

More attention has been paid to the defense glands in the pectoral section of dytiscids than to the function and contents of the pygidial vessels. In 1721 *Frisch* correctly assumed that the poisonous secretion of the water beetle constituted "foul drops that afford internal torment to a pike or other animal" that swallows it.

When merely firmly held, and certainly on application of slight pressure to the head, the beetle secretes the glandular liquid. When the secretion is taken up in a capillary the active ingredient (m.p. 135–140 °C) sometimes crystallizes; it is better isolated by thin-layer chromatography. Its ultraviolet absorption maximum at 241 mμ, its reaction with 2,4-dinitrophenylhydrazone[2], and its infrared absorption bands at 1613 $cm^{-1}$ (ν-C=C vibration) and 1668 $cm^{-1}$ (ν-C=O vibration) indicate an α,β-unsaturated ketone. A second keto group can be recognized from absorption at 1693 $cm^{-1}$. The active component was characterized as a steroid diketone by its optical circular dichroism, absorption having extrema at 283 and 321 mμ. By comparison with literature data[3] we concluded that the compound is a $\Delta^4$-3-keto steroid as well as a 20-keto steroid. However, the infrared absorption at 1693 $cm^{-1}$ indicated that the 20-keto group is hydrogen-bonded to an OH group that was disclosed by its absorption at 3475 $cm^{-1}$. All these findings pointed to 21-hydroxy-4-pregnene-3,20-dione (11-deoxycorticosterone, cortexone) *(1)*.




*(1)*

Commercial cortexone and its acetate agree in their physical properties with the natural product and its acetate. The physiological properties of cortexone explain the action of the *Dytiscus* toxin, for cortexone is a mineralocortical hormone of vertebrates. Since the beetle stores up to 0.4 mg of hormone – an amount that can be isolated from more than a thousand ox suprarenal glands[4] – it must strongly upset the sodium-potassium balance of vertebrates. Accordingly, and in agreement with *Blunck*'s results[5], we observed that pike and trout suffer deep narcosis, often within

a short time of being fed with *Dytiscus* secretion or cortexone solutions *per os*. Cortexone has no action on the beetle since it is a hormone foreign to the insects.

Received: February 22nd, 1966 [Z 168/1 IE]
German version: Angew. Chem. 78, 392 (1966)

[1] Communication XXI on Arthropod Defensive Substances. – Communication XX: *H. Schildknecht* and *W. F. Wenneis*, Z. Naturforsch., in press. The investigations were made possible by financial support from the Deutsche Forschungsgemeinschaft. We thank Messrs. Merck, Darmstadt, for a gift of cortexone. Mr. *H. Schaeflein* (Straubing) helped us by supplying water beetles.

[2] *H. Schildknecht* and *K. Holoubek*, Angew. Chem. *71*, 524 (1959).

[3] *L. Velluz* and *M. Legrand*, Angew. Chem. *73*, 603 (1961).

[4] *L. F. Fieser* and *M. Fieser*: Organische Chemie. Verlag Chemie, Weinheim 1965, p. 1623.

[5] *H. Blunck*, Z. wiss. Zool. *117*, 205 (1917).

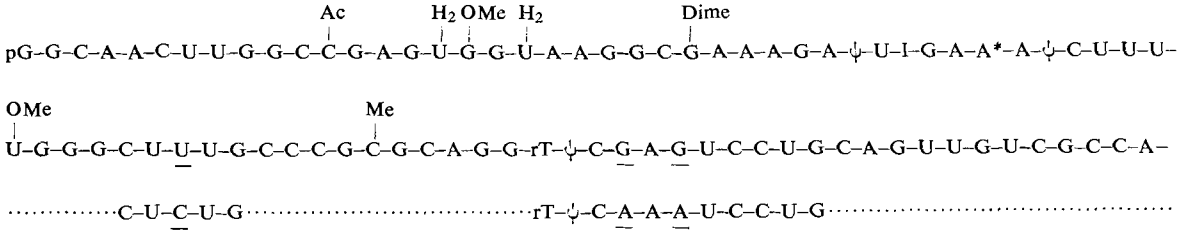
## Nucleotide Sequences of two Serine-Specific Transfer Ribonucleic Acids [1,2]

By Prof. H. G. Zachau, Dr. D. Dütting, and Dr. H. Feldmann

Institut für Genetik der Universität Köln (Germany)

Structural studies on transfer-ribonucleic acids (tRNA's [3]) recently entered a new phase when *Holley et al.* [4] established the primary structure of an alanine-specific tRNA. We have been able for the first time to elucidate the nucleotide sequences of two tRNA's specific for the same amino acid, *i.e.* of the two main serine-specific tRNA's from brewer's yeast. Thus the second complete nucleotide sequence of a nucleic acid can now be reported. In earlier stages of this work, *F. Melchers* [5] and *W. Karau* [6] made important contributions.

The serine-specific tRNA's were split with pancreatic RNase and $T_1$-RNase into oligonucleotides, the structures of which were determined by further enzymatic degradation. Sequences of up to 25 nucleotides could be constructed by comparing the two sets of oligonucleotides. In addition to the partial digestion with $T_1$-RNase [4], the elucidation of the complete sequences required partial digestion with pancreatic RNase, a second partial splitting of large oligonucleotide fragments, and sequential degradation with snake venom phosphodiesterase of oligonucleotides obtained by partial $T_1$-RNase digestion.




Serine-specific tRNA I and II from brewer's yeast.
Upper line: Nucleotide sequence common to both tRNA's.
Middle line: Continuation of the upper line for tRNA II.
Lower line: Continuation of the upper line for tRNA I.

The two serine-specific tRNA's differ only in three nucleotides (which are underlined in the formula). The differences may originate from transitions in the tRNA cistrons. The chain length (84 nucleotides) and the probable anticodon sequence I–G–A are the same in both tRNA's.

Thirteen odd nucleotides occur in the serine-specific tRNA's. *N*(6)-acetyl-Cp, A*p (the structure of which is not yet completely known [7]), and the two nucleotides methylated in the ribose have been found in tRNA-sequences for the first time. Models of the secondary structure of the two serine-specific tRNA's were constructed using only the principle of maximal base pairing. They show that *ca.* 60% of the nucleotides can be arranged in five paired regions. Almost all odd nucleotides appear in loops and unpaired regions. Probably the three nucleotides in which the two tRNA's differ are also located in loops.

The primary structures of the serine-specific tRNA's are very different from that of the alanine-specific tRNA. The distances, however, between I, DimeG, and one of the $UH_2$'s are the same. It is noteworthy that the distance between rT and the C–C–A-end is also the same in the three tRNA's. The sequence G–rT–ψ–C–G, however, which has been considered as a possible constituent of all tRNA's [4], is replaced by G–rT–ψ–C–A in serine-specific tRNA I.

Received: February 23rd, 1966 [Z 155/988 IE]
German version: Angew. Chem. 78, 392 (1966)

[1] Serine-specific transfer-ribonucleic acids, part VIII. – Part VII: *H. G. Zachau, D. Dütting, F. Melchers, H. Feldmann*, and *R. Thiebe* in: Ribonucleic Acid – Structure and Function, Symposium of the Federation of European Biochemical Societies, Vienna 1965. Pergamon Press, Oxford 1966, p. 21.

[2] We are indebted to Misses *H. Heusinger*, *S. Notz*, and *G. Schulz* for expert technical assistance. The work was supported by grants from the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Bundesministerium für Wissenschaftliche Forschung.

[3] Abbreviations: tRNA = transfer ribonucleic acid; RNase = ribonuclease; p and – are used to represent a phosphate residue; A = adenosine; G = guanosine; C = cytidine; U = uridine; ψ = pseudouridine; $UH_2$ = 4,5-dihydrouridine; rT = ribothymidine; I = inosine; A*, see text; MeC = 5-methylcytidine; AcC = *N*(6)-acetylcytidine; DimeG = *N*(2)-dimethylguanosine; OMeG = 2'-*O*-methylguanosine; OMeU = 2'-*O*-methyluridine.

[4] *R. W. Holley, J. Apgar, G. A. Everett, J. T. Madison, M. Marquisee, S. H. Merrill, J. R. Penswick*, and *A. Zamir*, Science (Washington) *147*, 1462 (1965).

[5] See, for example, *F. Melchers* and *H. G. Zachau*, Biochim. biophysica Acta *91*, 559 (1964).

[6] *W. Karau* and *H. G. Zachau*, Biochem. biophysica Acta *91*, 549 (1964).

[7] Note added in proof: (March 16th, 1966): Investigations by high-resolution mass spectrometry suggest that A* from serine tRNA is an *N*(6)-isopentenyladenosine (*K. Biemann* and *S. Tsukanawa*, personal communication). Nuclear magnetic resonance studies in collaboration with *J. Sonnenbichler* showed that two methyl groups are located on C–3 and the double bond is between C–2 and C–3 of the side chain.

## Complex Formation between Copper and Organic Disulfides

By Doz. Dr. P. Hemmerich

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Prof. Dr. H. Beinert and Dr. T. Vänngard

Institute for Enzyme Research, University of Wisconsin Madison, Wisconsin (U.S.A.)

In general, mercaptide complexes of copper(II) are unstable, because of the reaction [1,2]

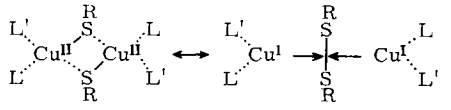
$$2Cu^{2+} + 2RS^- \overset{\alpha}{\rightleftharpoons} 2(Cu^{II}SR)^+ \overset{\beta}{\rightleftharpoons} 2Cu^+ + (RS)_2 \qquad (a)$$

Equilibrium β, however, can be displaced towards the right only in those cases where

a) the $Cu^+$ generated is stabilized by $Cu^I$-specific ligands, most easily by an excess of $RS^-$ (to form colorless $(Cu^ISR)_n$[3]), and where

b) the reaction is kinetically feasible, *i.e.* the hypothetical $(Cu^{II}SR)^+$ must either be able to dissociate into radicals ($\rightarrow Cu^+ + RS\cdot$) or to react with itself [$\rightarrow (CuSR)_2^{2+}$].

The formation of a binuclear complex *(1)*[4] is clearly the easiest way to fulfil condition b). In such a complex, $Cu^{II}$ mercaptide and $Cu^I$ disulfide are isoelectronic and chemically indistinguishable.



*(1)*

Of prime importance in this context is the affinity for $Cu^I$ of digonal sulfur, as found in the very stable, colorless $Cu^I$-methionine chelate[3]. In aqueous solution cystamine also forms a chelate with $Cu^+$ which, however, is deep violet in color and is maximally developed after liberation of one $H^+$ per Cu[3]. This complex may be formed according to Eq. (b) in agreement with structure *(1)* or according to Eq. (c) leading to structure *(2)*, which corresponds to the structure of a similar complex arising from thiomalic acid and $Cu^{2+}$ as found by *Klotz et al.*[5].

$$(RSSRH_2)^{2+} + 2\,Cu^+ \rightleftharpoons [Cu^I_2(RS) \leftrightarrow (Cu^{II}SR_2]^{2+} + 2\,H^+ \quad \text{(b)}$$

*(1)*

$$2(RSSRH_2)^{2+} + 8\,Cu^+ \rightarrow [(Cu^IRS)_4Cu^{II}]^{2+} + 3\,Cu^{2+} + 4\,H^+ \quad \text{(c)}$$

*(2)*

These equations differ essentially in the concomitant formation of $Cu^{2+}$. Hence we followed the formation of $Cu^{2+}$ during pH-titration of cystamine in the presence of $Cu^+$ by quantitative EPR spectroscopy in the solid (−170 °C) and liquid phase. In the pH-region 3–7 we found an increase in $Cu^{II}$ from 1 %[6] to not more than 7 % of total Cu. At pH 7, one mole of $H^+$ per mole Cu is liberated and the maximum color is reached with an extinction of *ca.* $5 \times 10^3$ $cm^{-1}$ per mole Cu[7]. The reaction, therefore, must follow Eq. (b) to more than 90 %, *i.e.* the contribution of a complex *(2)* cannot be more than 10 %. If the color were due to this complex exclusively, the molar extinction per $Cu^{II}$ would be as high as $10^5$ $cm^{-1}$, which is unlikely.

At pH 7, the violet complex disproportionates irreversibly with precipitation of $Cu(OH)_2$. If, on the other hand, a mercaptide-specific reagent, $ArHg^+$, is added, oxidoreduction ensues. In both cases the stoichiometric amount of $Cu^{2+}$ is found by EPR spectroscopy.

Hence, we take these results as strong evidence for the existence of copper mercaptides of type *(1)* with $R{-}L = CH_2CH_2NH_2$. Their strong color points to extensive electron delocalization in the – presumably diamagnetic – cluster $Cu\overset{S}{\underset{S}{}}Cu$. Their potential biological importance stems from the fact that certain Cu chromophores in redox enzymes, which may contain cyst(e)ine sulfur, are found to contain 2 or more Cu atoms (cytochrome oxidase, coeruloplasmine), which are redox-active, but not fully detectable by EPR spectroscopy[8]. Binuclear complexes of type *(1)* might explain this behavior when kinetically stabilized by a protein environment, whilst O- and N-ligands cannot be expected to allow for redox activity in Cu complexes unless accompanied by molecular rearrangements[3].

Received: February 16th, 1966 [Z 157/2 IE]
German version: Angew. Chem. *78*, 449 (1966)

[1] $Cu^+$ and $Cu^{2+}$ indicate free solvated ions, while $Cu^I$ and $Cu^{II}$ indicate oxidation states in any ligand field.

[2] *I. M. Kolthoff* and *W. Sticks*, J. Amer. chem. Soc. *73*, 1728 (1951).

[3] *P. Hemmerich* in *P. Aisen*, *W. E. Blumberg*, and *J. Peisach*: The Biochemistry of Copper. Academic Press, New York 1966, in press.

[4] *D. H. Busch*, *D. C. Jicha*, *M. S. Thompson*, *W. J. Wrathall*, and *E. Blinn*, J. Amer. chem. Soc. *86*, 3648 (1965).

[5] *I. M. Klotz*, *G. H. Czerlinski*, and *H. A. Fiess*, J. Amer. chem. Soc. *80*, 2920 (1958).

[6] The 1 % $Cu^{II}$ present at the beginning represents the inevitable impurity of the starting material $Cu^I(CH_3CN)_4ClO_4$; *P. Hemmerich* and *C. Sigwart*, Experientia *19*, 488 (1963).

[7] This order of magnitude corresponds to the chromophore of deeply colored Cu-proteins; cf. *W. E. Blumberg*, *W. G. Levine*, *S. Maroglis*, and *J. Peisach*, Biochem. biophys. Res. Commun. *15*, 277 (1954).

[8] Cf. *H. Beinert* and *G. Palmer* in *T. E. King*, *H. S. Mason*, and *M. Morrison*: Oxidases and Related Redox Systems. Wiley, New York 1965, Vol. II, pp. 567–585; *B. G. Malmström*, *ibid.* Vol. I, p. 207; *B. F. van Gelder* and *E. C. Slater*, Biochim. biophysica Acta *73*, 663 (1963).

# CONFERENCE REPORTS

## Association of Aliphatic Hydroxy Compounds in n-Heptane

*G. Geiseler*, Leipzig (Germany)

Infrared-spectroscopic and thermodynamic studies of the association of isomeric alcohols, oximes, carboxylic acids, and hydroperoxides derived from n-heptane and n-octane have shown that chains and three-dimensional structures are preferably formed by monofunctionally associating isomers, but that only cyclic dimers and trimers are formed from bifunctionally associating isomers[1].

Indirect insight into the mode of association can also be obtained from the thermodynamic excess functions, as has been found in studies of binary mixtures of octanols or octanone oximes with n-heptane. The excess free energy determined from phase equilibria depends significantly on the position of the functional group in the chain. However, the excess enthalpy determined calorimetrically provides much more information: the excess enthalpy has a maximum at the same mole fraction ($x_{hept} \approx 0.55$) for all the oximes. From this it must be concluded that substantially the same type of order applies to all the (undiluted) oximes; structural differences have only slight effect.

The excess enthalpy has a maximum at $x_{hept} \approx 0.65$ for 1- and 2-octanol, but for 3- and 4-octanol the maximum is shifted to $x_{hept} \approx 0.75$. Clearly the type of order is different for the two alcohols (when undiluted or in concentrated solution). For the first two it is assumed that the molecules form linear associates, but for the second that they are joined in parallel.

The excess entropies, which pass through a minimum, show a completely analogous behavior. They indicate that in the region up to $x_{hept} \approx 0.95$ the associtates behave on the average as stoichiometrically uniform components and that on admixture with n-heptane they force a definite type of order on it. Only in highly dilute solution are the associates broken; this is particularly evident for the alcohols as the excess entropy then becomes positive.

[Lecture at Hamburg, November 9th, 1965, and at Kiel, November 11th, 1965] [VB 974/281 IE]

German version: Angew. Chem. *78*, 395 (1966)

[1] *G. Geiseler*, Angew. Chem. *77*, 352 (1965); Angew. Chem. internat. Edit. *4*, 367 (1965); „Monofunctionally" and "bifunctionally" associating molecules differ by the number of atoms with acceptor effect in the associating group; the first type has one, the second two such atoms.

## Relations between Structural and Electrical Properties of Vanadium Spinels

*B. Reuter*, Berlin (Germany)

Mixed crystals of general composition $Mg(Mg_xV^{IV}_xV^{III}_{2-2x})O_4$ (ions in the octahedral positions are placed in parentheses) are obtained from the spinels $Mg(V^{III}_2)O_4$ and $Mg(MgV^{IV})O_4$ in the region $0 \leqslant x \leqslant 0.66$ [the vanadium(IV) spinel cannot be isolated pure because of partial disproportionation]. Since two $V^{3+}$ ions are replaced by $(Mg^{2+} + V^{4+})$ on increase of x, one has here a semiconductor system with controlled valence that is comparable with *e.g.* the system $Li_xNi^{III}_xNi^{II}_{1-2x}O$. By analogy with the views developed for this system in particular by *Jonker et al.*[1] the electronic properties of the system $Mg(Mg_xV_{2-x})O_4$ can be interpreted on a model for localized 3d-electron levels. The specific resistance $\rho$ is a minimum at $x = 0.15$. Consideration of the values of the thermoelectric power $\Theta$ indicates that part of the $V^{3+}$-ions may be replaced by two defect electrons.

The corresponding titanium system $Mg(Mg_xTi^{IV}_xTi^{III}_{2-2x})O_4$ can, however, be obtained phase-pure only in the region $x \geqslant 0.65$. Disproportionation of the $Ti^{4+}$ ion is excluded by its inert-gas configuration, as seen from the values of $\rho$ and $\Theta$.

The system $Mn(Mn_xV_{2-x})O_4$ behaves analogously to the Mg system, but the vanadium spinels of the iron group behave quite differently. The system $Fe(Fe_xV_{2-x})O_4$ includes a continuous range of solid solutions over the whole range $0 \leqslant x \leqslant 1$. The facts that in this case there is no disproportionation at high values of x, that $\rho$ is a minimum at $x = 1$, and that n-conduction occurs when $x > 0.65$, as well as the appearance of the products, show that $Fe_2VO_4$ contains $Fe^{2+}$, $Fe^{3+}$, and $V^{3+}$ ions, but no $V^{4+}$ ions. In the system $Co(Co_xV_{2-x})O_4$ ($0 \leqslant x \leqslant 0.9$) the minimum value of $\rho$ occurs at $x = 0$, which may be ascribed to separation of metallic cobalt. It is impossible to prepare a compound $NiV_2O_4$ because $Ni^{2+}$ ions do not occupy tetrahedral positions in the spinel lattice. However, $Ni^{2+}$ ions can be placed at octahedral positions in the spinel lattice of the systems $Mg(Ni_xV_{2-x})O_4$ ($x \leqslant 0.47$) and $Co(Ni_xV_{2-x})O_4$ ($x \leqslant 0.89$). The electrical properties of the system $Mg(Ni_xV_{2-x})O_4$ show considerable resemblance to those of the system $Mg(Mg_xV_{2-x})O_4$.

The octahedral positions of all these spinel systems are occupied not only by $V^{3+}$ and $V^{4+}$ ions, but also by ions other than vanadium, so that $\rho$ is increased and $\rho_{min}$ is shifted from $V^{3+}:V^{4+} = 1:1$ to smaller contents of $V^{4+}$ and foreign ions. The situation is different for $Li(V^{III}V^{IV})O_4$, which is almost as good a conductor as $Fe^{III}(Fe^{II}Fe^{III})O_4$. A continuous range of solid solutions $Li_xMg_{1-x}(V^{III}_{2-x}V^{IV}_x)O_4$ is formed; $\rho$ increases markedly in this series as x increases; $\Theta$ is almost zero at $x > 0.5$.

*Jaskowsky*[2] was able to describe the changes of $\Theta$ in the systems $Mg(Mg_xV_{2-x})O_4$ and $Li_xMg_{1-x}(V_2)O_4$ quantitatively by means of a model in which the influence of the non-vanadium ions was considered. By statistical analysis based on these considerations he deduced correctly the activation energy for hopping of the charge carriers and thus the value of $\rho$.

[Lecture at Stuttgart (Germany), November 25th, 1965]

[VB 973/280 IE]

German version: Angew. Chem. *78*, 394 (1966)

[1] *G. H. Jonker* and *S. van Houten* in *F. Sauter*: Halbleiterprobleme VI. F. Vieweg & Sohn, Braunschweig 1961, p. 118.

[2] *J. Jaskowsky*, Ber. Bunsenges. physik. Chem., in press.

## Synthesis from Sugar Mercaptals

*H. Zinner*, Rostock (Germany)

*Hann* and *Hudson*'s rules[1] permit prediction of the tendency to formation of cyclic acetals from polyalcohols. The acetal rings are denoted as βC-, β-, αT-, α-, βT-, γT-, or αC-[2] according to the steric arrangement of the acetal-forming hydroxyl groups and according to the ring size. For benzylidene derivatives the tendency to ring formation decreases in the above order. These rules, set up first for benzylidene derivatives of glycitols, are valid also for extended (acyclic) structures, as is shown for the benzylidene derivatives of pentose mercaptals, pentose dialkyl acetals, and esters of pentonic acids. In the D-ribose, D-xylose, and D-lyxose series the 2,4:3,5- and in the D-arabinose series the 2,3:4,5-dibenzylidene derivatives are formed. The structures of the products are proved by synthesis and by oxidation of intermediates with lead tetraacetate.

2,3,4,5-Di-*O*-benzylidene derivatives of pentoses can be obtained by loss of thiol from the dibenzylidenepentose mercaptals and are oxidized by $CrO_3/H_2SO_4$ in dimethylformamide to the corresponding acids. The methyl esters of these acids are convertible into readily crystallizing dibenzylidene derivatives of the corresponding pentitols, pentonohydrazides, pentoamides, 1-amino-1-deoxypentitols, and 5-methyl-1,2,3,4,5-hexanepentols.

Treatment of acetates of aldose mercaptals with bromine gives acetates of 1-alkylthio-1-bromo-1-deoxyglycitols, which are reduced by $LiAlH_4$ to 1-alkylthio-1-deoxyglycitols and are converted by alcohols and silver carbonate into acetates of 1-alkoxy-1-alkylthio-1-deoxyglycitols. The last-named compounds afford 1-*O*-alkylglycitol acetates when boiled with Raney nickel in ether.

[Lecture at Hamburg, December 3rd, 1965] [VB 976/283 IE]

German version: Angew. Chem. *78*, 394 (1965)

[1] *R. M. Hann* and *C. S. Hudson*, J. Amer. chem. Soc. *66*, 1909 (1944).

[2] *S. A. Barker* and *E. J. Bourne*, Advances Carbohydrate Chem. *7*, 137 (1952).

## Use of Tetrazolium Salts in the Early Diagnosis of Cardiac Infarcts

*F. Bölsing*, Hannover (Germany)

Ischemic damage to the heart muscle can be recognized by a reduced enzyme content resulting from changes in structure and permeability of the mitochondria in the necrotic region. Changes in the content of succinate dehydrogenase (SDH) can be detected by means of tetrazolium salts.

Detection of very small changes in SDH concentration requires a color test that is as intense as possible and gives a color tone different from that of the tissue as well as a strong contrast between sound and ischemically damaged areas. In place of the usual ditetrazolium salts one can use monotetrazolium salts, more simply and without the disadvantages of the former, if the red formazans formed are converted into intensely colored complexes of heavy-metal compounds. For this reason the complex-chemical behavior towards some heavy-metal salts was studied for triphenylformazan and its derivatives containing a nitro and a methoxy group (each in *para*-position in a phenyl residue) in the 27 possible arrangements. Only mercuriacetamide gave results suitable for tissue staining. Triphenylformazan itself with mercuriacetamide gives an intensely bluish-violet complex.

This method permitted detection of a 35 – minute – old experimental cardiac infarct (rat, ligature of the main stem of the left coronary artery).

For the human heart, residual blood is removed from the heart cavities and the coronary vessels with physiological Ringer solution, then the coronary vessels are washed out with a solution of triphenyltetrazolium bromide, and finally the whole heart is immersed in the solution. After incubation for 10 to 20 minutes at 37 °C, the heart is washed out and the process is repeated with the mercuriacetamide solution.

Triphenyltetrazolium bromide is obtained by oxidation of triphenylformazan with hypobromite solution.

[Lecture at Hannover (Germany) on January 20th, 1966]

[VB 978/284 IE]

German version: Angew. Chem. *78*, 394 (1966)

## Structure and Magnetism of Ternary Fluorides

*D. Babel*, Tübingen (Germany)

The magnetic behavior of transition-metal ions $M^{2+}$ = $Mn^{2+}$, $Co^{2+}$, $Ni^{2+}$, and $Cu^{2+}$ in ternary fluorides $AMF_3$ and $A_2MF_4$ ($A^+$ = alkali-metal ion or $Tl^+$) is related to the structure of the compounds. Compounds $AMF_3$ crystallize in rhombic, cubic, or hexagonal perovskite lattices depending on the Goldschmidt tolerance factors. Hexagonal lattices are present, above all, in the Cs compounds $CsMnF_3$ (hexagonal $BaTiO_3$ type; also $RbNiF_3$), $CsCoF_3$ ($BaRuO_3$ type), and $CsNiF_3$ ($BaNiO_3$ type). The number of $MF_6$ octahedra sharing faces increases in the order given. Except for $Na_2CuF_4$ (monoclinic, individual type), compounds $A_2M_4$ are formed only when A = K, Rb, Tl, or Cs; they occur in the tetragonal $K_2MgF_4$ type, with the exception that cesium fluorides $Cs_2MF_4$ crystallize in a hexagonal structure, details of which are not known.

The magnetic properties range from antiferromagnetism ($KMF_3$) through normal paramagnetism ($CsMF_3$, $A_2CuF_4$) to strong ferrimagnetism ($RbNiF_3$), and can be explained by considering the distances and coordination relations in the lattices. In particular, consideration of superexchange [*] and its dependence on the electron configuration of the cation and the arrangement of ions in the crystal permits qualitative interpretation of the magnetic properties. Thus, cases of 3-, 2-, 1-, and 0-dimensional superexchange can be differentiated which, in conjunction with the dependence on M–F distances and M–F–M angles, account for the variations in magnetic behavior.

[Lecture at Erlangen (Germany), on February 10th, 1966]

[VB 982/289 IE]

German version: Angew. Chem. 78, 451 (1966)

[*] Superexchange is the magnetic interaction between paramagnetic cations by means of intermediary anions.

## Homopolar and Heteropolar Halogeno Esters of Phosphorus, Arsenic, and Antimony

*L. Kolditz*, Berlin (Germany)

Compounds of pentavalent phosphorus, arsenic, and antimony that carry both halogen and OR groups (R = alkyl or aryl) on the central atom, like the analogous simple pure and mixed halides, appear in homopolar and salt-like forms. In polar solvents equilibria are established between these two forms, the homopolar form undergoing association by means of halogen or OR bridges even in relatively dilute solution (*e.g.* 0.01 M in $CH_3CN$). The behavior of chloro(ethoxo)antimony compounds is typical, leading to equilibria according to (L = solvent):

$$2\,SbCln(OR)_{5-n}\cdot L \rightleftharpoons [SbCl_{n+1}(OR)_{5-n}L_2]^+ + [SbCl_{n+1}(OR)_{5-n}]^- \quad (a)$$

The situation is, however, complicated by exchange reactions between Cl and OR.

Alkoxofluorohydroxoarsenic compounds behave similarly; in the forms $HO(RO)_3AsF$ and $HO(RO)_2AsF_2$ they show a strong tendency to condense, with elimination of OH groups and formation of oligomers containing As–O–As linkages.

On reaction with $KOCH_3$ in $C_2Cl_3F_3$, arsenic pentafluoride gives the compound $AsF_4OCH_3$ as well as $K[AsF_6]$. The reaction mechanism is interpreted as:

$$2\,AsF_5 \rightleftharpoons AsF^+ + AsF^-$$
$$AsF_4^+ + KOCH_3 \rightarrow AsF_4OCH_3 + K^+ \quad (b)$$

Equilibrium (c) was found when $AsF_3$ was used as solvent:

$$(AsF_4OCH_3)_2 \rightleftharpoons [AsF_2(OCH_3)_2][AsF_6] \rightleftharpoons [AsF_2(OCH_3)_2]^+ + [AsF_6]^- \quad (c)$$

Compounds $P(OR)_2F_3$ and $[P(OR)_4][PF_6]$ are formed by exchange of Cl ligands in $PCl_2F_3$ (homopolar) and $[PCl_4][PF_6]$ (salt-like) for OR groups. In polar solvents (*e.g.* $CH_3CN$) the homopolar substance is transformed into the salt-like one in an equilibration of the above type. On decomposition of the salt-like compound the cation yields $OP(OR)_3$.

[Lecture at Mainz (Germany) on January 22nd, 1966]

[VB 979/286 IE]

German version: Angew. Chem. 78, 451 (1966)

## Chemistry of Phosphorus, Arsenic, and Antimony Halides

*L. Kolditz*, Berlin (Germany)

We have studied the reactions of phosphorus, arsenic, and antimony halides with polar solvents. $PF_5$, $AsF_5$, and $SbF_5$ form adducts with $CH_3CN$, and these dissociate in acetonitrile according to Eq. (a) (A = P, As, Sb):

$$2\,AF_5\cdot CH_3CN \rightarrow [AF_4(CH_3CN)_2]^+ + [AF_6]^- \quad (a)$$

An analogous formulation holds for $SbCl_5\cdot CH_3CN$. The dissociation can be demonstrated by conductivity measurements and hydrolysis experiments. Hydrolysis occurs only at the cation for A = P, As, the anions remaining unchanged. This is true also for the compound $PF_5\cdot N(CH_3)_3$, but $AsF_5\cdot N(CH_3)_3$ occurs only in the "homopolar" form and is unaffected by moisture; the arsenic compound is not even wetted by water.

A solution of chlorine in $AsCl_3$, which contains the solvate $AsCl_3–Cl_2$ but no $AsCl_5$, is a very strong chlorinating agent. Arsenic and antimony compounds that contain a $CF_3$ group as well as halogen (general formula $AX_2(CF_3)_3$) are more stable than the corresponding simple halides.

$[SbBr_6]^-$ ions decompose in $CH_3CN$ according to Eq. (b). The structure of $[SbBr_6]^-$ may thus be represented by the

$$[SbBr_6]^- \rightarrow SbBr_3 + Br\cdot Br_2^- \quad (b)$$

formula $[SbBr_4\cdot Br_2]^-$. Easy loss of bromine occurs also with $SbBr_5\cdot O(C_2H_5)_2$, which can be prepared only with an excess of antimony (*e.g.* Br:Sb = 4.7:1). $SbBr_5$, like $AsCl_5$, is not known in the pure form.

The system $SbCl_5/SbF_5$ contains associated apolar and also polar forms. The most stable compound is $SbCl_4F$, which is tetrameric in the solid state: distorted $SbCl_4$ tetrahedra are linked by asymmetrical fluorine bridges (varying Sb–F distances).

All the compounds mentioned tend to exchange halogen. The equilibria occurring in solution are dependent on solvent, concentration, and temperature, and the halogen-transferring action of the apolar substances differs from that of the salt-like forms, so that halogenation can be readily controlled.

[Lecture at Aachen and Frankfurt/Main (Germany), on January 21st and 27th, 1966] [VB 980/287 IE]

German version: Angew. Chem. 78, 452 (1966)

## Structures and Reactions of the Products of Reaction of Hydrogen Cyanide with Hydrogen Halides

*E. Allenstein, A. Schmidt*, and *V. Beyl*, Stuttgart (Germany)

Structural investigation of the "sesquihalides of hydrocyanic acid," $2\,HCN\cdot 3\,HX$ (X = Cl or Br), mostly by infrared spectroscopy but also by chemical methods, has shown that they are *N*-(dihalogenomethyl)formamidinium halides [2], $[HX_2C–NH–CH=NH_2]^+X^-$, in accordance with the view of *Gattermann* and *Schnitzspahn* [1].

On hydrolysis with an equivalent amount of water in ether, *N*-formylformamidinium bromide *(1)*[2] [obtainable by reaction of *N*-(dibromomethyl)formamidinium bromide with dimethyl sulfoxide] yields *N*-formylformamide *(2)* (m.p. 42 °C; b.p. 119 °C/12 mm Hg) in accord with Eq. (a).

$$[O{=}CH{-}NH{-}CH{=}NH_2]^+Br^- + H_2O \rightarrow$$
$$\underset{(1)}{} \qquad O{=}CH{-}NH{-}CH{=}O + NH_4Br \quad (a)$$
$$\underset{(2)}{}$$

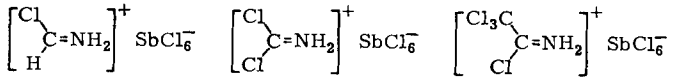
*N*-Formylformamide *(2)* can also be prepared by hydrolysis of *N*-(dichloromethyl)formamidinium chloride with traces of water in the presence of an excess of sodium hydrogen carbonate:

$$[Cl_2CH{-}NH{-}CH{=}NH_2]^+Cl^- + 2\,H_2O \rightarrow$$
$$O{=}CH{-}NH{-}CH{=}O + NH_4Cl + 2\,HCl \quad (b)$$

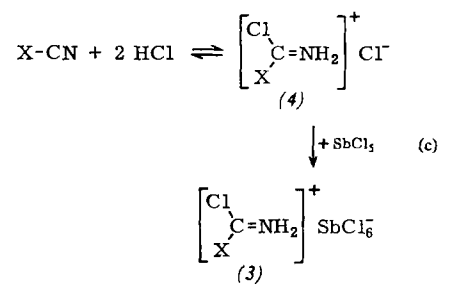
$$2\,HCl + 2\,NaHCO_3 \rightarrow 2\,NaCl + 2\,CO_2 + 2\,H_2O$$

The latter process is suitable also for the preparation of *N*-alkyl-*N*-formylformamides, starting with the *N,N'*-dialkyl-*N*-(dichloromethyl)formamidinium chlorides $[HCl_2C{-}NR{-}CH{=}NHR]^+Cl^-$ obtained by *Jentzsch*[3].

Hydrogen cyanide, chlorocyanogen, and trichloroacetonitrile, without or in the presence of hydrogen chloride, afford *N*-(dichloromethyl)formamidinium chloride[2], cyanuric chloride[4], and 2,4,6-tris(trichloromethyl)-*s*-triazine[5], respectively, by di- or trimerisation of the cyano compounds or of the hydrogen chloride adducts that are the primary products. However, we have shown that in the presence of antimony(V) chloride and hydrogen chloride, hexachloroantimonates *(3)* are produced. The antimony(V) chloride takes part in the reaction of the cyano compounds with hydrogen chloride according to Eq. (c):



*(3a)* [6] *(3b)* [7] *(3c)* [8]



The unstable imidium chlorides *(4)*, which are in equilibrium with the starting materials, are rapidly trapped as the stable hexachloroantimonates *(3)*; the slow dimerization or trimerization is thus prevented.

[Lecture at Clausthal-Zellerfeld (Germany), on January 21st, 1966] [VB 981/288 IE]

German version: Angew. Chem. *78*, 452 (1966)


[1] *L. Gattermann* and *K. Schnitzspahn*, Ber. dtsch. chem. Ges. *31*, 1770 (1898).

[2] *E. Allenstein, A. Schmidt* and *V. Beyl*, Chem. Ber. *99*, 431 (1966).

[3] *W. Jentzsch*, Chem. Ber. *97*, 1361, 2755 (1964).

[4] *A. Hantzsch* and *L. Mai*, Ber. dtsch. chem. Ges. *28*, 2466 (1895).

[5] *H. Herlinger*, Angew. Chem. *76*, 437 (1964); Angew. Chem. internat. Edit. *3*, 378 (1964).

[6] *E. Allenstein* and *A. Schmidt*, Chem. Ber. *97*, 1863 (1964).

[7] *E. Allenstein* and *A. Schmidt*, Chem. Ber. *97*, 1286 (1964).

[8] *E. Allenstein* and *A. Schmidt*, unpublished work.


# SELECTED ABSTRACTS

**The synthesis of 2-aminoethylphosphines** $(C_2H_5)_2N{-}(CH_2)_2{-}PR_2$ by reactions (a) to (d) has been reported by *K. Issleib* and *R. Rieschel*.

$$(C_2H_5)_2N(CH_2)_2Br + KP(C_6H_5)_2 \xrightarrow[-KBr]{THF} (C_2H_5)_2N(CH_2)_2P(C_6H_5)_2 \quad (a)$$
$$\underset{(1)}{}$$

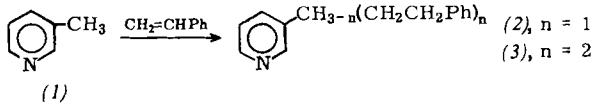
$$(C_2H_5)_2N(CH_2)_2Br + LiP(c\text{-}C_6H_{11})_2 \xrightarrow[-LiBr]{THF} (C_2H_5)_2N(CH_2)_2P(c\text{-}C_6H_{11})_2$$
$$\underset{(2)}{} \quad (b)$$

$$(C_2H_5)_2N(CH_2)_2Br{\cdot}HBr + HP(C_2H_5)_2$$
$$\rightarrow [(C_2H_5)_2HN(CH_2)_2PH(C_2H_5)_2]Br_2 \quad (c)$$
$$\underset{(3a)}{}$$

$$(3a) + 2\,Na \xrightarrow[-2\,NaBr]{-H_2} (C_2H_5)_2N(CH_2)_2P(C_2H_5)_2 \quad (d)$$
$$\underset{(3)}{}$$

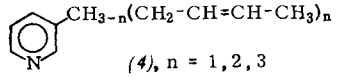
Reaction (c) is carried out in chlorobenzene, so that the phosphonium salt *(3a)* precipitates; after separation, *(3a)* is decomposed in ether in accordance with Equation (d). The products *(1)* to *(3)* can be isolated as colorless oils by vacuum distillation. They are soluble in ether, tetrahydrofuran, dioxane, benzene, and acetone, but not in water. The infrared spectra of *(1)* to *(3)* contain the triethylamine stretching bands, which are still present after the reaction with excess ethyl iodide. Thus only the phosphorus is quaternized. Oxidation of *(1)* to *(3)* with $H_2O_2$ in ether leads to the formation of the phosphine oxides. / Chem. Ber. *98*, 2086 (1965) / –Gn. [Rd 426/635 IE]

**The sodium-catalysed alkylation of 3-picoline** with styrene and butadiene has been achieved by *Y. I. Chumakov* and *V. M. Ledovskikh*. 3-Picoline *(1)* was boiled (145 °C) under $N_2$ with sodium [0.1 g-atom per mole of *(1)*]. An equimolar quantity of styrene was added dropwise over half an hour, and the mixture was refluxed for a further two hours. The products obtained included those resulting from monoalkylation [*(2)*, 23.2 % yield] and from dialkylation [*(3)*, 17.4 %].



*(1)* *(2)*, n = 1; *(3)*, n = 2

When butadiene was used instead of styrene, 2.4 % of the triply-substituted product was obtained, as well as 35.4 % of the mono-adduct and 16.4 % of the di-adduct. It was assumed that these adducts have the structure *(4)*. *(4)*, n = 1 could



*(4)*, n = 1, 2, 3

be reduced to n-amylpyridine, and yielded acetaldehyde on ozonolysis, indicating a 1,4-addition. A small quantity of the 1,2-addition product was also detected by infrared spectroscopy. The additions must take place on a derivative of *(1)* that has been metalated at the methyl group. The proton mobility was comparable to that of the 2- and 4-isomers. / Tetrahedron *21*, 937 (1965) / –Eb. [Rd 423/632 1E]

**The synthesis of substituted vinyl trialkylsilyl ethers** is described by *J. I. Baukov, G. S. Burlachenko,* and *I. F. Lutsenko.* Trimethylchlorosilane reacts with α-trialkylstannyl ketones to give excellent yields of α-alkylvinyl trimethylsilyl ethers *(1)*

$$(CH_3)_3SiCl + R_3Sn\text{-}CH_2\text{-}COR' \longrightarrow$$

$$(CH_3)_3Si\text{-}O\text{-}\underset{R'}{C}{=}CH_2 + R_3SnCl$$

*(1)*

[when R′ = $CH_3$, b.p. 92 to 94 °C/758 mm Hg, yield 80 %]. The infrared spectra of the products contain a band at 1652 $cm^{-1}$, which is assigned to the C=C double bond.

$$(C_2H_5)_3SiI + (C_3H_7)_3Sn\text{-}CH_2\text{-}COOCH_3 \longrightarrow$$

$$CH_2{=}C(OCH_3)(OSi(C_2H_5)_3) + (C_3H_7)_3SnI$$

*(2)*

1-Methoxy-1-triethylsiloxyethene *(2)*, b.p. 63 to 65 °C/7 mm Hg, is formed in the reaction of methyl tripropylstannylacetate with triethyliodosilane. / J. organomet. Chemistry *3*, 478 (1965) / –Sch. [Rd 431/640 IE]

**In the biosynthesis of insulin** the two peptide chains are formed separately and are then linked by the disulfide bridges. *R. E. Humber* has carried out labelling experiments using the Brockmann body of the anglerfish. The biosynthesis of insulin follows the general scheme of protein synthesis (it can be inhibited, *e.g.*, by puromycin) and proceeds from the amino end to the carboxyl end. Insulin obtained from the anglerfish contains three proline units, one roughly in the middle of the A chain ("A") and two in the B chain, in positions 2 and 28 ("$B_2$" and "$B_{28}$"). If the insulin synthesis is allowed to proceed for 8 hours in the presence of [$^{14}$C]-proline, the insulin is labelled to the same extent in all three proline residues. The synthesis is then allowed to continue for a further 15 to 30 min in the presence of [$^{3}$H]-proline; labelling of the proline units of the insulin with tritium increases with proximity to the carboxyl end. In the isolated insulin, the ratio $^{3}H/^{14}C$ was greatest in the $B_{28}$ proline unit, lower in the A proline, and lowest of all in the $B_2$ proline. If the insulin had been synthesized as a single peptide chain, which was subsequently cleaved (as is the case with chymotrypsin), the $^{3}H/^{14}C$ ratio should have decreased in the order $B_{28} > B_2 >$ A or A $> B_{28} > B_2$. / Proc. nat. Acad. Sci. USA *53*, 853 (1965) / –Hö. [Rd 411/620 IE]

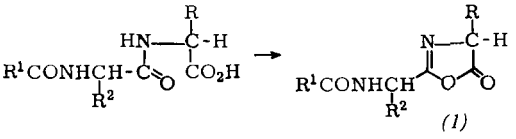
**Acetyl-CoA: D-amino acid α-*N*-acetyltransferase** has been concentrated by a factor of 2000 from baker's yeast by *M. H. Zenk* and *J. H. Schmitt.* The enzyme catalyses the reaction:

acetyl-CoA + D-amino acid → α-*N*-acetyl-D-amino acid + CoA

The reaction is irreversible, and cofactors are not required. D-Tryptophan was used as the substrate for the test, and acetyl-CoA was produced *in situ* from acetyl phosphate and CoA. The acetyl-D-tryptophan formed was extracted with ether and determined colorimetrically with *p*-dimethylaminobenzaldehyde. The reaction is specific for the D-amino acids, although D-proline and D-aspartic acids (in contrast to asparagine) react very poorly. The enzyme can be used for the preparative separation of D- and L-amino acids. Its biological function is probably to bind the D-amino acids and so render them non-toxic. / Biochem. Z. *342*, 54 (1965) / –Hö. [Rd 412/621 IE]

**Regulatory and functional sub-units in aspartate transcarbamylase** have been found by *J. C. Gerhart* and *H. K. Schachman.* With the aid of *p*-mercuribenzoate, these authors divided the enzyme (ATCase, MW = 310000) from *Escherichia coli* into two types of sub-units, two having a molecular weight of 96000 and four one of 30000. The larger sub-units carried the whole of the catalytic activity, but they were not inhibited by cytidine triphosphate, the feedback inhibitor for ATCase. The bonding sites for the inhibitor are located on the smaller sub-units, two to each sub-unit, as was shown by reaction with 5-bromocytidine triphosphate. On incubation in the presence of mercaptoethanol, the sub-units recombines to form the hexameric enzyme, which possesses the same catalytic and regulatory properties as the native allosteric enzyme. / Biochemistry *4*, 1054 (1965) / –Hö. [Rd 413/622 IE]

**A new method for the determination of C-terminal amino acids** in peptides and proteins is discussed by *H. Matsuo, Y. Fujimoto,* and *T. Tatsuno.* The C-terminal amino acid of an *N*-acetylpeptide is converted into the oxazolone *(1)* by boiling



*(1)*

$$R^1CONHCHCONH\text{-}\underset{D}{C}(R)\text{-}CO_2H \quad (2)$$

for a short time with acetic anhydride or dicyclohexylcarbodiimide in anhydrous dioxane. After the addition of a drop of pyridine, the compound *(1)* in dioxane is treated with $D_2O$ (or $T_2O$) to form the deuterated (or tritiated) compound *(2)*. The labelled amino acid can be determined after hydrolysis. / Tetrahedron Letters *1965*, 3465 / –Ma. [Rd 393/602 IE]

**A new method for the rapid cleavage of ethers** under mild conditions is described by *L. H. Long* and *G. F. Freeguard.* The method is based on the discovery that boranes or metal borohydrides and halogen (especially $I_2$) cleave O–C bonds with formation of O–B and C-halogen bonds. The resulting borates are completely hydrolysed within a few minutes at room temperature.

$$6\ PhOCH_3 + 3\ I_2 + B_2H_6 \rightarrow 2B(OPh)_3 + 6\ CH_3I + 3\ H_2$$

$$3\ PhOCH_3 + 2\ I_2 + NaBH_4 \rightarrow B(OPh)_3 + 3\ CH_3I + NaI + 2\ H_2$$

$$B(OPh)_3 + 3\ H_2O \rightarrow 3\ PhOH + H_3BO_3.$$

Boranes higher than diborane react more slowly. $NaBH_4$ is rather less reactive than $LiBH_4{\cdot}Br_2$, and interhalogen compounds such as ICl react more vigorously than $I_2$, but they are less convenient to use. The ethers may be symmetrical, unsymmetrical, aliphatic, aromatic, or cyclic. The cleavage can also be used for preparative purposes; for example, the cleavage of tetrahydrofuran with $B_2H_6$ and $I_2$ leads to the formation of 4-iodobutan-1-ol in a yield of more than 90 %. / Nature (London) *207*, 403 (1965) / –Ma. [Rd 394/603 IE]

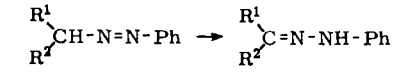
**The "trans effect" of ligands in square-planar palladium(II) and platinum(II) complexes,** *i.e.* the fact that the replacement of a ligand is more strongly promoted by a ligand *trans* to it than by a *cis* ligand, has been studied by *J. R. Durig, R. Layton, D. W. Sink,* and *B. R. Mitchell.* They examined the infrared spectra of *cis* and *trans* palladium(II) complexes $PdL_2Cl_2$ to find how the frequency of the Pd–Cl stretching vibration depends on the ligand L (see Table; of the two

Pd–Cl stretching vibrations of the *cis* complex, only the antisymmetric are given). The *trans* effect of L acts on the Pd–Cl bonds of the *cis* complex, but not on those of the *trans* complex. From the results given in the table, it is concluded that the *trans* effect of saturated compounds containing nitrogen is due simply to electrostatic weakening of the *trans* bond (the substitution of H by electron-donating alkyl groups causes a shift of $\nu_{Pd-Cl}$ towards longer wavelengths, corresponding to an increase in the *trans* effect).

| Ligand | $NH_3$ | $CH_3NH_2$ | $C_2H_5NH_2$ | Pyridine | $CH_3SC_2H_5$ | 3,6-Dithiaoctane |
|---|---|---|---|---|---|---|
| $\tilde{\nu}_{Pd-Cl}$ [cm$^{-1}$] (*trans*-compound) | 333 | 341 | 336 | 358 | 360 | |
| $\tilde{\nu}_{Pd-Cl}$ [cm$^{-1}$] (*cis*-compound) | 327 | 317 | 317 | 342 | | 323 |

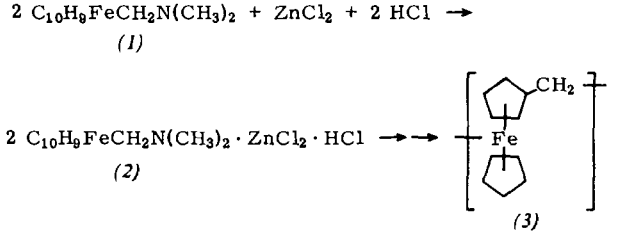
The shift to longer wavelengths does not occur in the case of ligands in which the nitrogen forms part of an aromatic system, or ligands containing sulfur. It may therefore be concluded that in ligands of this type, the *trans* effect is also due in part to $\pi$-bonding with the $d_\pi$-orbitals of the metal. / Spectrochim. Acta *21*, 1367 (1965) / –Hz. [Rd 395/604 IE]

**The rearrangement of phenylazoalkanes to phenylhydrazones** has been studied by *A. J. Bellamy* and *R. D. Guthei*, using free-radical, basic, and acidic catalysts.



The reverse reaction did not take place. Reaction of phenylazocyclohexane with catalytic quantities of benzoyl peroxide in $CHCl_3$ or hexane at 100 °C led to a 54 or 71 % yield, respectively, of cyclohexanone phenylhydrazone after 24 h. 1-Phenylazobutane refluxed for 1 h in $NaOCH_3/CH_3OH$ gave a 78 % yield of n-butyraldehyde phenylhydrazone. This last compound is obtained in 64 % yield after 5 min at 0 °C with concentrated $H_2SO_4$ in ethanol. All the reactions must be carried out in the absence of air to prevent autoxidation of the phenylhydrazones. Under the conditions used in the Fischer indole synthesis (anhydrous $ZnCl_2$ at 180 °C), the phenylazoalkanes react to form indoles. Thus 1-phenylazobutane gives 3-ethylindole (46 %), and 2-phenylazopropane gives 2-methylindole (27 %). / J. chem. Soc. (London) *1965*, 3528 / –Kü. [Rd 417/626 IE]

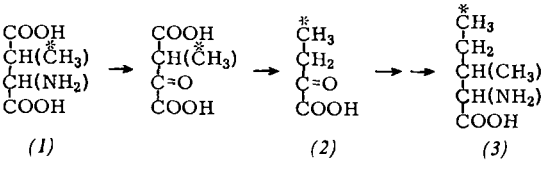
**The autocondensation of *N,N*-dimethylaminomethylferrocene** *(1)* in the presence of a $ZnCl_2$/HCl catalyst system, according to *E. W. Neuse* and *E. Quo*, leads to the formation of soluble polymers consisting of ferrocenylene units linked by methylene bridges. The crude condensation products prepared in the melt have a number-average molecular weights of 4000



to 8000. Elementary analysis and infrared spectroscopy, as well as viscometric data, indicate that the polymer has the formula *(3)*. The authors were able to isolate the intermediate *(2)* from the reaction mixture. / J. Polymer Sci. *3A*, 1499 (1965) / –Hl. [Rd 418/627 IE]

**Solutions of ethylmagnesium bromide in ether** have been studied by *E. C. Ashby*, who used triethylamine as a solvating agent. A solution of ethylmagnesium bromide was prepared from ethyl bromide and magnesium in ether, and was added to a large excess of triethylamine with vigorous stirring. This immediately resulted in the formation of crystals in a yield of more than 90 %; the molecular weight of the crystals, as found by the ebullioscopic method at 15 mm Hg, corresponded to the formula $C_2H_5-MgBr(C_2H_5)_3N$. Earlier ebulliscopic measurements had shown that in the absence of triethylamine, ethylmagnesium bromide in ether is largely dimerized, probably *via* symmetrical halogen bridges. The present work showed that ethylmagnesium bromide in ether cannot be decomposed to any great extent into diethylmagnesium and magnesium bromide (as had been suggested by *Schlenk* and *Schlenk*), and that the formation of the $C_2H_5MgBr(C_2H_5)_3N$ solvate is faster than this disproportionation. If this were not so, $MgBr_2(C_2H_5)_3N$ would precipitate as the least soluble component present. / J. Amer. chem. Soc. *87*, 2509 (1965) / –Eb. [Rd 422/631 IE]

**The preparation of isoleucine from β-methylaspartic acid with the aid of** *Escherichia coli* W has been reported by *T. Abramsky* and *D. Shemin*. These authors added DL-*threo*-β-methylaspartic acid *(1)* labelled with $^{14}C$ to growing bacteria cultures, and found that $^{14}C$ was incorporated into the baterial protein. Hydrolysis of the protein revealed that the only labelled amino acid present was isoleucine *(3)*. The same result was obtained on the addition of [4-$^{14}$C]-α-ketobutyric acid *(2)*. The following reaction scheme was assumed:



α-Ketobutyric acid is known to be an intermediate in the synthesis of isoleucine from threonine. The results are supported by the fact that during the growth of leucine-deficient mutants (*E. coli* IHM 544), isoleucine could be replaced by β-methylaspartic acid. The mutants lacked the threonine dehydrase required for the synthesis of isoleucine from threonine. / J. biol. Chemistry *240*, 2971 (1965) / –Hö. [Rd 404/613 IE]

**The preparation of iridium pentafluoride** from the elements has been described by *N. Bartlett* and *P. R. Rao*. Yellow, crystalline $IrF_5$ (m.p. 104.5 °C) separates at the cooler end of a monel reaction vessel containing a stoichiometric mixture of the elements at 350 to 380 °C. $IrF_5$ can also be obtained by the reaction of $IrF_5$ with glass powder. Earlier workers had assumed the formation of $IrF_4$[1]; however, the properties of the product are unlike those of other tetrahalides, but agree closely with those of the pentafluorides. The monoclinic $IrF_5$ is isomorphous with $RuF_5$ and $OsF_5$, and probably crystallizes with the $RuF_5$ structure. The magnetic behavior of $IrF_5$ is typical of the electronic configuration $d^4$ in octahedrally coordinated fluorides of the third transition series. / Chem. Commun. *1965*, 252 / –Gn. [Rd 427/636 IE]

[1] *G. J. Westland* and *P. L. Robinson*, J. chem. Soc. (London) *1956*, 4481.

**During the digestion of ribonuclease A from ox-pancreas by pancreas elastase,** *W. A. Klee* has isolated an enzymatically active degradation product. The reaction begins after an induction period, and ends with the decomposition of the ribonuclease into more than 20 fragments. In the course of the experiment, the reaction was stopped when roughly one peptide bond had been broken per ribonuclease molecule. Ribonuclease E was isolated by chromatography on Amberlite XE 64. Unlike ribonuclease A, ribonuclease E consists of two peptide chains with the N-terminal amino acids lysine and serine (A: lysine). Moreover, alanine is absent from position 20. Thus the primary attack of the elastase consists in the hydrolysis of two adjacent peptide linkages. The two fragments are held together by non-convalent bonds, and can be separated by trichloroacetic acid (the fragment consisting of 19 amino acids is soluble in trichloroacetic acid) with loss of enzyme activity. The equimolar mixture of the two fragments possesses 80 % of the original enzyme activity. In contrast to ribonuclease A, ribonuclease E is very sensitive to trypsin. Apart from the missing alanine, ribonuclease E is the same as the ribonuclease S obtained by the action of subtilisin. / J. biol. Chemistry *240*, 2900 (1965) / –Hö. [Rd 403/612 IE]

**Postasium dioxofluoroselenate(IV)** has been obtained by *R. Paetzold* and *K. Aurich* by the fusion of equimolar quantities of KF and $SeO_2$ and by reaction of $K_2SeO_3$ with $SeOF_2$.

$$KF + SeO_2 \rightarrow FSeO_2K \quad KSeO_2F$$

$$K_2SeO_3 + SeOF_2 \rightarrow 2\ SeO_2FK$$

Potassium fluoroselenate(IV) is a white crystalline substance which melts at 250 °C without decomposing, and which is very sensitive to water. Study of the hydrolysis by infrared spectroscopy showed that the products include potassium hydrogen selenite, potassium hydrogen fluoride, and selenous acid. The hydrolysis proper:

$$KSeO_2F + H_2O \rightarrow KSeO_2OH + HF$$

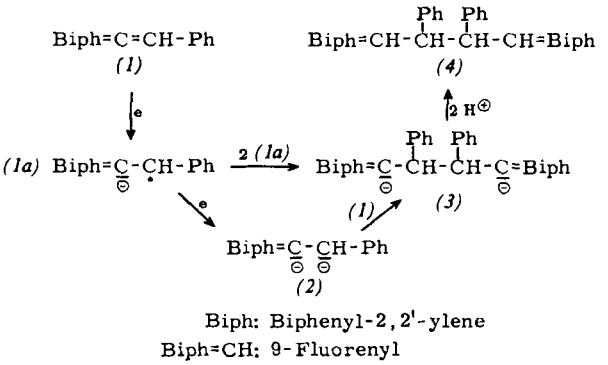
is followed by the reaction:

$$2\ HF + KSeO_2OH \rightarrow KHF_2 + (HO)_2SeO$$

which evidently takes place because of the high stability of $KHF_2 \cdot KSeO_2F$ reacts with methanol in the same way as with water. / Z. anorg. allg. Chem. *335*, 281 (1965 / –Sch. [Rd 434/643 IE]

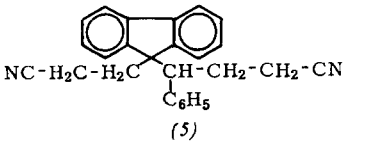
**The semiconducting properties of polymeric Schiff bases** synthesized by condensation of di-, tri-, and tetra-amino derivatives of benzene, fluorene, and anthraquinone with glyoxal or terephthalaldehyde have been studied by *J. Danhäuser* and *G. Manecke*. The polymers are light brown to black, insoluble, and infusible. The conductivities of these products are strongly dependent on the pressure (up to 8000 atm) used in the molding of the amorphous substances. There appears to be a relationship between the conductivity, color, and free-radical concentration, which points to an electronic conduction mechanism. The condensates with the best conductivities (*e.g.* glyoxal-triaminophenol, $\varkappa = 1.7 \times 10^{-10}\ \Omega^{-1}\ cm^{-1}$) are black. The relationship is probably similar to that prevailing in the case of the polyenes: the greater the number of delocalized π-electrons in the conjugated double bonds, the greater is the conductivity. / Makromolekulare Chem. *84*, 238 (1965) / –Hl. [Rd 420/629 IE]

**The electrolytic reductive dimerization of 9-benzylidenefluorene** *(1)* has been studied by *M. M. Baizer* and *J. D. Anderson*. 1,2-Diphenyl-1,2-bis-(9-fluorenyl)ethane *(4)* was obtained with an electrochemical yield of 66 % in DMF/water, the supporting electrolyte being tetraalkylammonium tosylate. In the course of the electrolysis, the Hg cathode became covered with a red film, which indicated the presence of carbanions. Two possible routes for the formation of the hydrodimer *(4)* are:




Biph: Biphenyl-2,2'-ylene
Biph=CH: 9-Fluorenyl

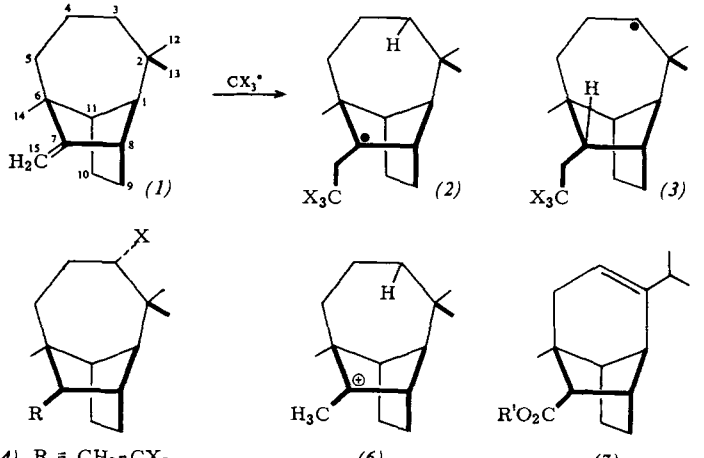
The dimeric dianion *(3)* is protonated to *(4)*. 8,8-Diphenylbenzofulvene gave a monomeric product, since dimerization is sterically hindered in this case.




*(5)*

In the presence of a ten-fold molar excess of acrylonitrile, *(1)* gave the product *(5)* of a double cyanoethylation in 76 % yield (Michael addition of *(2)* to two molecules of acrylonitrile). Compound *(2)* cannot be obtained by deprotonation of 9-benzylfluorene. / J. org. Chemistry *30*, 1348 (1965) / –Eb. [Rd 421/630 IE]

**Homolytic and heterolytic transannular 1,5-hydrogen shifts** occur in longifolene *(1)* and its derivatives. *D. Helmlinger* and *G. Ourisson* have obtained the adduct *(4)* by the free-radical reaction of *(1)* with tetrahalogenomethanes $CX_4$ ($CCl_4$, $CBrCl_3$, $CBr_4$), the reaction proceeding *via* the intermediates *(2)* and *(3)*. During the elucidation of the structure *(4)*, the compound *(5)* was isolated; on mild hydrolysis or slow chromatography on silica gel, *(5)* is converted quantitatively into pure *(1)*. If the carbonium ion *(6)* resulting from the




transannular 1,5-hydrogen shift is destabilized by the presence of electron-attracting groups on C-7, the solvolysis leads to a retro-pinacolone rearrangement, accompanied by ring contraction [*e.g.* to *(7)*]. / Liebigs Ann. Chem. *686*, 19 (1965) / –Bu. [Rd 436/645 IE]

**Rubredoxin, a new crystalline iron protein with a redox function,** has been isolated by *W. Lovenberg* and *B. E. Sobel* from *Clostridium pasteurianum*. It is red in the oxidized state ($\lambda_{max}$ = 490, 380, and 280 mμ) and colorless in the reduced state ($\lambda_{max}$ = 333, 311, and 275 mμ), has a molecular weight of approximately 6000, and contains one atom of iron (ferredoxin has 8) and four –SH groups per molecule. The

redox potential $E'_0$ at pH 7.0 and 25 °C is −0.057 V (ferredoxin: −0.41 V); only one electron is given up on oxidation (as in ferredoxin). Like ferredoxin and thioredoxin, rubredoxin contains many more acidic amino acids than basicones: 12 Asp, 6 Glu, compared with only 4 Lys. No specific reactions of rubredoxin have been found as yet. It catalyses the ferredoxin-catalysed reactions (*e.g.* the reduction of NADP by hydrogen and hydrogenase), but the reaction rates are only about 20 % of those obtainable with ferredoxin. / Proc. nat. Acad. Sci. USA *54*, 193 (1965) / −Hö. [Rd 414/623 IE]

**Fulvene containing less than 2 % of impurities** is formed in 74 % yield when a mixture of the acetoxymethylcyclopentadienes *(1)* and *(2)* is allowed to react with the equivalent quantity of triethylamine. *H. Schaltegger, M. Neuenschwander*, and *D. Meuche* prepared *(1)* and *(2)* from cyclopentadienylsodium and chloromethyl acetate in tetrahydrofuran

*(1)*, R = −CO−CH$_3$ *(2)*, R = −CO−CH$_3$
*(3)*, R = −CH$_3$ *(4)*, R = −CH$_3$

at −30 °C (yield 30 %). No fulvene is obtained from a mixture of *(3)* and *(4)* under the same conditions. / Helv. chim. Acta *48*, 955 (1965) / −Bu. [Rd 437/646 IE]

**The biosynthesis of the biotin enzymes from apoenzyme and biotin** has been studied by *Th. Höpner* and *J. Knappe*. They used the β-methylcrotonyl-CoA carboxylase from *Achromobacter* 1Vs-W. Even under oprimal growth conditions, this biotin-auxotrophic organism (grown with isovaleric acid as the only source of carbon) synthesizes a β-methylcrotonyl-CoA carboxylase in which only 80 to 90 % of the active centers are occupied by biotin. In the presence of a holocarboxylase synthetase which had been concentrated by a factor of 150, the remaining apo-centers could be saturated with biotin, this saturation being accompanied by stoichiometric regeneration of carboxyl reactivity. The course of the reaction [Equations (1) and (2)] was demonstrated by the following synthetase-catalysed reactions:

$$\text{biotin} + \text{ATP} \overset{\text{synthetase}}{\rightleftharpoons} \text{biotinyl-AMP} + \text{pyrophosphate} \quad (1)$$

$$\text{biotinyl-AMP} + \text{apoenzyme} \xrightarrow{\text{synthetase}} \text{holoenzyme} + \text{AMP} \quad (2)$$

a) ATP-dependent formation of biotin hydroxamate from biotin and hydroxylamine; b) biotin- and hydroxylamine-dependent formation of AMP from ATP; c) biotin-dependent exchange between ATP and $^{32}$P-pyrophosphate; d) synthesis of ATP from biotinyl-AMP and pyrophosphate; e) incorporation of biotin from biotinyl-AMP into β-methylcrotonyl-CoA carboxylase. / Biochem. Z. *342*, 190 (1965) −Hö. [Rd 415/624 IE]

# BOOK REVIEWS

**Cyclooctatetraen** (Cyclooctatetraene). By *G. Schröder*. Monograph No. 73 to "Angewandte Chemie" and "Chemie-Ingenieur-Technik". Verlag Chemie GmbH. Weinheim/Bergstr. 1965. 1st Edit., viii + 88 pp., many illustr., cardboard DM 23.– (about $6.–).

In recent years cyclooctatetraene has been the subject as well as the starting material of a large number of investigations, and these are comprehensively covered in this monograph. A description of the syntheses and a short chapter on the structure is followed by much the longest section, which is devoted to the chemical properties of cyclooctatetraene and its derivatives. The following are discussed in detail: reduction and oxidation products of cyclooctatetraene, its behavior towards acids, bases, and free radicals, the adducts formed with carbenes, halogens, and dienophiles, its organometallic complexes, valence-bond isomers, substitution products, and dimers with particular emph sis on bullvalene (obtainable from them). Finally there are selected recipes for preparation of 20 derivatives. The author restricts himself to short but clear restatement of the literature, which is considered up to the middle of 1964. Yet owing to the modernity of the subject, several sections already need expansion or correction (inversion of cyclooctatetraene, its bromination, and the structure of the dimer of m.p. 53 °C). Anyone interested in the unusually varied chemistry of cycloctatetraene will find this volume an ideal source of information. Unfortunately the price of this little book is not in proportion to its size.

*W. Roth* [NB 461/314 IE]

**Die komplexometrische Titration** (Complexometric Titration). Volume 45 of "Die chemische Analyse" (Chemical Analysis). By *G. Schwarzenbach* and *H. Flaschka*. Ferdinand Enke Verlag, Stuttgart 1965. 5th revised Edit., xvi + 339 pp., 42 figs., 12 tables, 48.– DM (about *fi* 12.–).

The present fifth edition of this part of "Die chemische Analyse" (Chemical Analysis) appears 20 years after the introduction of complexometric titration and 10 years after the first edition. Written in collaboration with *H. Flaschka* it has become a completely new book. The volumetric procedure established by *G. Schwarzenbach* is characterized by the use of specific complex-formers and indicators for metal ions, and its explosive development has necessitated an expansion of the text from 119 to 339 pages. Division of the text into two parts of equal length – one theoretical and the other practical – has been maintained. The first part contains general information about titration reagents, the theory of the course of the reactions and the mode of action of dye and fluorescent indicators in complexometry, the methods of visual and instrumental end-point determination and the various types of titration, their accuracy and selectivity. In the second part practical details are given, first for the preparation of volumetric and indicator solutions, then for complexometric determination of almost all the elements; in the last section is described the determination and masking of metals in a most imaginative way by manifold combinations of formation and fission of kinetically labile metal complexes. (The determination of non-metals, *e.g.* fluorine, should, however, be considered critically.) The literature up to the end of 1963 is cited in 1437 references, arranged alphabetically in groups according to the year of their appearance.

In its new expanded form this book has become the standard work for complexometric titrations. It is a valuable adviser for analytical practice and is exciting reading for all who are interested in the theoretical foundations of chemistry in aqueous solutions.

*F. Seel* [NB 463/316 IE]

**Boron-Nitrogen Compounds.** Vol. VI of the Series "Anorganische und allgemeine Chemie in Einzeldarstellungen". By *K. Niedenzu* and *J. W. Dawson*. Springer-Verlag, Berlin-Heidelberg-New York 1965. 1st Edit., viii + 176 pp., numerous figs., linen 27.– DM (about $ 7.–).

Several books have recently appeared on the chemistry of boron. The present one concerns boron-nitrogen compounds, which have been extensively studied during the last 10 years or so, and to which the authors have made numerous contributions. Six chapters are devoted to amine-boranes (borazanes), aminoboranes (borazenes), borazoles, BNC heterocycles, and boron nitrides. Additionally there is a short section on $^{11}$B nuclear magnetic resonance. Numerous tables

and recipes for the preparation of important starting materials complete the text. A useful author index (12 pp.) is to be contrasted with too short a subject index (5 pp.).

This readable book undoubtedly fulfils its object, as an introduction into the chemistry of boron-nitrogen compounds, and it provides stimulation for further development thereof. However, the chemistry of the borazoles and BNC heterocycles, *e.g.* the borazarenes deserves more detailed treatment, and so do the results obtained in the laboratories of *W. M. Michailow* and *V. I. Zacharkin*. It is mainly the work of the last five years that is discussed. The reviewer does not always agree with the authors' views, and study of the book makes it clear that more quantitative work is needed in order to provide a firm thermodynamic, kinetic, and structural basis for further discussions and to place the present plausible working hypotheses on a firmer basis.

*H. Nöth* [NB 465/318 IE]

**Die Bestandteile der Lebensmittel** (The Constituents of Foodstuffs). Volume I of the Series "Handbuch der Lebensmittelchemie" (Handbook of Foodstuffs Chemistry). Edited by *J. Schormüller*. Springer-Verlag, Berlin-Heidelberg-New York 1965. 1st Edit., xxviii + 1288 pp., 136 figs., linen DM 298.– (about $ 75.–). Subscription price DM 238.40 (about $ 60.–).

After 32 years the first volume of the new edition of the Handbuch der Lebensmittelchemie (Handbook of Foodstuffs Chemistry) has appeared, on the constituents of foodstuffs. This long interval has had the inevitable consequence that only the form of the old book is preserved, the text having been largely rewritten, yet strict control by the editor has ensured that the total number of pages is somewhat less than in the previous edition.

For treatment of the 24 chapters of this volume experts in specialized fields have been enlisted as well as specialists in general foodstuffs chemistry. References to the literature are given at the end of each chapter, and some of the authors have included references up to 1964.

Chapter 1 treats the history of food science from prehistory to the 20th century. This review is certainly comprehensive, including control and research, and has some very telling illustrations. In the next chapter *O. Högl* expounds the objectives of foodstuffs science. The most important aim is to disclose and evaluate the composition of foods; the recognition and removal of injurious components are recorded in further sections of this chapter, and in a very short space but quite comprehensively a further section treats the importance of water as a food constituent, including its place in fresh and preserved foods. Additionally *H. Langendorf* discusses inorganic cations and anions which are essential for the organism, sometimes in large quantities and sometimes in traces; their function in metabolism is also noted; and five tables give information about the content of essential ions in the most important foods.

The chapter on amino acids, peptides, and other nitrogen compounds seems to the reviewer to be too detailed: not only the chemical properties and physiological importance, but also the occurrence of rare amino acids, are reported, even for products that are not foods. The same applies to the discussion of peptides, but the treatment of proteins is better related to the main theme. There is, however, no reference to the manifold changes undergone by methionine or the unpleasant smell and taste that can result from its decomposition products.

The chapter on fats, lipids, waxes, and resins provides a short but very valuable review. The most important saturated and unsaturated fatty acids are described, and also glycerides, phosphatides, sphingolipids, and other possible secondary ingredients. It should, however, be noted that γ-sitosterol (pp. 338 and 345) has meanwhile been recognized as a 1:1 mixture of β-sitosterol and campesterol. Finally the author describes the natural and technological changes undergone by fats.

The isolation and composition of essential oils is treated by *K. Herrmann*. The most important mono- and sesqui-terpenes are mentioned, as well as other constituents such as acids, esters, ketones, and sulfur compounds that determine the taste.

In the chapter on carbohydrates and glycosides *Almut Klemer* describes the chemistry and analysis of sugars, and also sugar esters, amino sugars, pectins, algal products, and carbohydrate-protein compounds. The chapter concludes with seven tables giving the most important constants of these compounds. The authoress reports also on *O*-, *N*-, and *S*-glycosides. A few inaccuracies have crept in concerning saponins: α-amyrin is derived from ursane, and β-amyrin from oleanane (p. 527); aescin is an oleanane derivative, its structure having been determined in 1963 (p. 529); the triterpene acid of ursane type is named ursolic acid (pp. 530 and 1284).

*H. Endres* discusses the most important tannins. Unfortunately, except for passing mention of the catechins of tea and coffee beans, this chapter contains no reference to foodstuffs; but the omission is rectified to some extent in the next chapter where *K. Herrmann* treats plant phenolics in foodstuffs.

The following chapter, by *E. Beyer*, describes the isolation, constitution, and detection of natural dyes, in particular carotenoids, quinones, flavanoids, anthocyanins, and some porphyrins. It is expanded by *R. Hamm* in a good review of the chemistry of haemoglobin and myoglobin. The chapter on carboxylic acids, esters, carbonyl compounds, and alcohols shows a welcome orientation towards the requirements of foodstuffs chemistry. However, the formulae of the two optically active tartaric acids (p. 778) do not agree with the latest information: the formula described as D-(+)-tartaric acid is that of L-(+)-tartaric acid, and that described as L-(−)-tartaric acid is D-(−)-tartaric acid.

*K. Myrbäck* makes a valuable contribution to the general field of enzymes. It is supplemented by *H. Mohler*'s description of the importance of enzymes in foodstuffs technology and in the formation of aromatic ingredients, also by *H. Sommer*'s report on commercially prepared enzymes and their use in manufacture and analysis of foodstuffs. The chapter on vitamins deals first with their stabilization and with procedures for their analysis; it then treats the individual vitamins in alphabetical order, including their mode of action. There is, however, no mention of the artefact nature of cyanocobalamin in the discussion of vitamin $B_{12}$ or of the present-day preference of vitamin $D_3$ over vitamin $D_2$. The chapter on chemical additives treats preservatives very thoroughly, including their properties, uses, and modes of action. The discussion of dyes for foodstuffs records both the old use of saffrom and curcuma, and the toxic effects of certain azo dyes. There follows a list of permitted dyes in accordance with the data of the Farbstoffkommission of the Deutsche Forschungsgemeinschaft.

In the last chapter *S. W. Souci* and *E. Mergenthaler* report on all other chemical additives, such as antioxidants, synergists and complex-formers, color improvers and bleaching agents, thickening and gelling agents, surface-active materials and materials having a physical effect, coatings, insecticides, and herbicides. The list is comprehensive and provides a good orientation on the properties of the individual compounds. The book ends with a subject index running to 65 pages.

The publishers have produced the book to their usual high standard. The printing is almost free from error, and the formulae cannot be misinterpreted (with very few exceptions, *e.g.* gossypol, p. 351). The editor and the publishers are to be congratulated on a noteworthy achievement.

*C. H. Brieskorn* [NB 462/315 IE]

**Selected Papers on Molecular Genetics.** A Collection of Reprints with Introductory Material. Vol. 1 of the Series "Perspectives in Modern Biology – A Series of Reprint Collections". By *J. H. Taylor*. Academic Press Inc., New York 1965. 1st Edit., xii + 650 pp., bound $ 9.–, paper back $ 5.95.

In few parts of biochemistry has development been as lively during recent decades as in genetics with all its far-reaching

implications. It would be only too easy for those who take no direct part in this work to lose sight of the broad lines of the development, only too easy for interest in questions that are currently in the forefront to diminish attention to other problems. It was therefore a good idea to recall to memory the milestones of progress by republishing selected papers from the years 1913–1963 in their original form. It is, of course, not to be expected that a complete picture can be reconstructed from 46 publications. The editor was himself aware of this difficulty and has therefore written introductory prefaces to the five sections of the book (Biochemical Genetics, The Nature of Genetic Material, DNA Structure and Replication, Genetic Recombination, The Function of Genetic Material), these prefaces showing the relation between the papers that are reproduced and giving references to papers that have not been included.

Clearly no selection can be made entirely without arbitrariness. The editor has been at pains to find that paper – or at least a very early report – which has opened the door to each development: truly no light undertaking! Nevertheless, after reading this book, one is tempted to think, in periphrasis of a well-known phrase, that "la biochemie de l'hérédité est une science anglo-saxonne" – corresponds to the facts in many but not quite all respects.

Yet the book is to be recommended, in particular to the student seeking an introduction into biochemical genetics.

*H. Grünewald* [NB 450/303 IE]

**Biochemistry of Phenolic Compounds.** Edited by *J. B. Harborne*. Academic Press, London-New York 1964. 1st Edit. X + 618pp., 1 plate, several illustrations, 30 tables, £ 6.6.0d.

A combination of several factors, such as the improvement of physical methods of extraction, the isolation and elucidation of complex organic substances, the revival by *Birch* of *Collie*'s acetate theory, the introduction of labelling with $^{14}C$, and the development of enzymology and microbiology, has led in the past 20 years to an enormous growth of interest in phenolic compounds of natural origin. It is now recognized that the phenols and their derivatives are not insignificant end products of the natural processes, but sometimes play an important part in the animal or plant metabolism. There was therefore a real need for a review of the biochemistry of natural phenols.

The present book contains 14 chapters written by 17 experts of world-wide renown. The subjects discussed include: the structures and reactions of natural phenols (*Thomson*, 29 pp.), methods used for the isolation and identification of phenols from biological material (*Seikel*, 39 pp.), the occurrence of phenolic aglycones (*Harborne* and *Simmonds*, 45 pp.) and glycosides (*Harborne*, 36 pp.), the genetics of phenols (*Alston*, 30 pp.) and their metabolism in animals (*Williams*, 40 pp.) and plants (*Towers* 40 pp.), the biosynthesis of phenolic compounds (*Neish*, 50 pp.) and of lignin and the tannins (*Brown*, 33 pp.), the enzymology (*Conn*, 31 pp.) and physiology (*Siegelmann*, 16 pp.) of the biosynthesis of phenols, the physiology and pharmacology of phenols in animals (*Ramwell*, *Sherratt*, and *Leonard*, 48 pp.) and plants (*Cruikshank* and *Perrin*, 27 pp.), and finally the taste of phenol glycosides in citrus fruits (*Horowitz*, 24 pp.).

The literature up to the end of June 1962 has been taken into account in most cases. More than 2000 references and 2200 names in the index testify to the value of this book as a reference work. Almost 900 structural formulae, some 1150 entries in the subject index, and 950 names in the excellent class index will be very useful in searches for information. The scope of the book is possibly rather narrow. Many purely chemical model experiments in connection with biochemical problems would have merited some mention, and a detailed, separate chapter on phenolic alkaloids would have been welcome. No mention is made of the giberellins.

In its present form, however, the book must be recommended to the phytochemist, the taxonomist, and the plant physiologist, and in short, to all biochemists who are concerned with phenolic natural products. *J. M. Harkin* [NB 445/280 IE]

**The Oligosaccharides.** By *J. Staněk*, *H. Černý*, and *J. Pacák*. Academic Press, New York-London, and Publishing House of The Czechoslovak Academy of Science, Prague 1965. 1st Edit., 567 pp., numerous tables, linen $ 21.–.

"The Monosaccharides" [1] by *Staněk* and his collaborators, published in 1963, has now been followed by the second part of the comprehensive monograph, also in English. As is stated in the preface, this is not merely a translation of the Czechoslovak edition that appeared in 1962, but has been partly rewritten, with incorporation of publications up to the middle of 1964.

All who are interested in oligosaccharides, whether as chemists, biochemists, or biologists, will be glad that the authors have undertaken the tedious task of a general oversight of the oligosaccharide material that has accumulated over the years and have brought order into the myriad of results. The number of references – nearly 4500 – shows how thoroughly they have gone to work.

Division into many short chapters with their own lists of references greatly clarifies the text, and the very numerous formulae are a further help. Comprehensive tabulation of oligosaccharide classes, arranged according to molecular size, type of linkage, and type of derivative, made it possible to keep the text short and precise. Particularly noteworthy are a comprehensive table of oligosaccharides of natural origin and a collection of the oligosaccharides that have been obtained by enzymic degration and synthesis. Chemical syntheses and reactions of oligosaccharides and formation of derivatives of this class of compound are treated exhaustively, as are oligosaccharides with a basic or acidic function and even such a recondite class of compounds as the glycosylinositols. Moreover, several chapters are devoted to chromatographic and electrophoretic methods of analysis and separation.

However, the section on enzymatic synthesis could have been rather more detailed, for the benefit of the reader particularly interested in this field. The kinetics of interaction of enzymes and oligosaccharides are not mentioned, and it is only the kinetic study of these complex reactions that throws light on the simultaneous synthesis, hydrolysis, and resynthesis of the various combinations of reactants. Further, the titles "Transglycosylation of maltose, isomaltose, lactose, etc." are unhappily chosen; it would have been better to collect these sections under the titles "Transglucosylation, transgalactosylation, etc." The sections on the use of physical methods such as X-ray analysis and infrared spectroscopy for structure determination of oligosaccharides are also rather too short. However, these matters and a few erroneous references can be corrected in a new edition which will certainly be necessary within a few years.

Finally it can be stated that this book will be a welcome help to chemists and biologists. Together with "The Monosaccharides" it can be included among the most valuable reference works for carbohydrate chemistry.

*J. Lehmann* [NB 455/308 IE]

**Advances in Physical Organic Chemistry.** Vol. 2. Edited by *V. Gold*. Academic Press. London-New York 1964. 1st Edit., xii + 288 pp., numerous illustr., £ 3.3.– (ca. $ 8.80).

The second volume of this series contains four sections: 1. *C. J. Collins*, Isotopes and Organic Reaction Mechanisms (84 pp.), 2. *W. E. Whalley*, Use of Volumes of Activation for Determining Isotope Reaction Mechanisms (65 pp.), 3. *H. Zollinger*, Hydrogen Isotope Effects in Aromatic Substitution (33 pp. , 4. *A. P. Wolf*, The Reaction of Energetic Tritium and Carbon Atoms with Organic Compounds (87 pp.). The first contribution describes in particular the less usual applications of isotopes, *e.g.* the use of compounds with two or more labels, the combination of isotope and kinetic experiments, and of isotope and stereochemical experiments. Fi-

[1] Cf. Angew. Chem. 77, 687 (1965); Angew. Chem. internat. Edit. 4, 723 (1965).

nally, kinetic isotope effects are discussed very critically, mainly from the experimental standpoint.

In the second contribution the experimental methods and theory are discussed in relation to a few types of reaction, and then the potentialities of the method are outlined. However, in this report little attention is paid to knowledge of reaction mechanism that was derived by other methods and recorded in the most recent literature. In the third section a narrower complex of questions is treated, in this case exhaustively. In the fourth contribution *A. P. Wolf* aimed at writing less a review article than a (most successful) introduction to a field that is highly interesting from a mechanistic point of view and in which few "experts" have hitherto worked.

The editor has been particularly successful in obtaining as contributors men who are leaders in their fields. They have been equal to the demands made on them.

*H. Simon* [NB 454/307 IE]

**A New German/English Dictionary for Chemists.** By *H. H. Neville, N. C. Johnston,* and *G. V. Boyd.* Blackie & Son Ltd., London-Glasgow 1964. 1st Edit., xviii + 330 pp., £ 2.15.0 (about $ 10.–).

**Elsevier's Dictionary of Industrial Chemistry in Six Languages:** English,American/French/Spanish/Italian/Dutch/German. Compiled and arranged by *A. F. Dorian.* Vol. 1: A–O and Vol. 2: P–Z. Elsevier Publishing Comp., Amsterdam-London-New York 1964. 1st Edit., 1220 pp., DM 130.– (about $ 33.–).

The first of the two works to be reviewed here is intended as a German-English dictionary for chemists "with little knowledge of German". It is adapted wholly to the needs of a user to whom English is the mother tongue or almost as familiar. Thus, for instance, the various English equivalents of the same German word are not differentiated; since such differences are known to an Anglo-Saxon that is justified in the authors' view, but it will be regarded as a serious deficiency by the user who does not come from an English-speaking country. Occasionally one gets the impression that the authors themselves have only "little knowledge of German", as, for in stance, when the first three of the four translations given for "abfüllen" – "to empty, to draw off, to decant, to bottle" do not correspond to the German word at all, but rather to ausgießen, abziehen, and abgießen, respectively; or when "Nachlaß" is ascribed the translations relaxation, remission, diminution, reduction", of which the first three mean Nachlassen. Apart from this, the choice of the about 20000 German entries can be considered successful.

The last remark can unfortunately not be applied to the six-language "Dictionary of Industrial Chemistry". Many-language dictionaries have their own problems and are so seldom satisfactory that it is difficult to understand why such lexicons continue to appear. In the present case the difficulties begin with the fact that a two-volume work of 1220 pages contains only 8426 entries. It cannot be considered that the vocabulary of "industrial chemistry" is even approximately exhausted thereby. Necessarily the choice has remained arbitrary. One might wish to know what an opacifier, a dialyser, or a centrifual pump is in one of the six languages, but must then turn to some other dictionary. The reviewer does not find that "enjoyable" (to use a word from the Preface). Some compensation for the small number of entries is provided by short explanations given with each entry. In this way the two volumes acquire the character of a reference work as well as that of a dictionary. *H. Grünewald* [NB 449/302 IE]

**Nobel Lectures, Physiology or Medicine** 1922–1941. Elsevier Publish. Comp., Amsterdam 1965. 1st Edit., xii + 548 pp., Dutch fl. 240.– (ca. $ 66.–) (3 vol.).

This middle volume[1] of the collection of Nobel lectures on physiological or medical subjects contains much that has already become history or a firm ingredient of our textbooks. Precisely that lends it a particular interest, because the laudations and the lectures of the prize winners lead us back to the early days, to the time when, for instance, the effect of insulin therapy on diabetes mellitus was not self-evident (the prize for the discovery of insulin was awarded to *Banting* and *Macleod* in 1923), or to a time when we did not know that typhus was carried from the sick to the healthy by lice and so were delivered helpless to an epidemic. It was in 1928 that the Frenchman *Charles Nicolle* received the Nobel prize for tracking down the route of typhus infection in Tunisian hospitals and prisons. In his Nobel lecture he said: "If in 1914 we had been unaware of the mode of transmission of typhus, and if infected lice had been imported into Europe, the war would not have ended by a bloody victory but in an unparalleled catastrophe, the most terrible in human history."

The history of science during the first half of the twentieth century is to be found in a nitshell among the Nobel lectures of this period; and it were hardly possible to relive this development more directly than by reading the lectures collected in this book. The volume is therefore most warmly recommended to all scientists (not only to physiologists or doctors), and particularly to the younger among us.

*H. Grünewald* [NB 448/301 IE]

[1] Review of 3rd volume: Angew. Chem. *77*, 632 (1965); Angew. Chem. internat. Edit. *4*, 617 (1965).

**Rodd's Chemistry of Carbon Compounds.** Edited by *S. Coffey.* Vol. I, Part A: General Introduction, Hydrocarbons, Halogen Derivatives. Elsevier Publishing Comp., Amsterdam-London-New York 1964. 2nd Edit., xix + 569 pp., numerous figs. and tables. Volume price Dutch fl. 80.– (about £ 8.0.0).

The first edition of this new version of Richter's "Chemie der Kohlenstoffverbindungen" established itself during the last decade as a valuable source for rapid, preliminary literature searches.

Now, only two years after appearance of the last volume of that work, we have the first three parts of the second edition. The new edition of this encyclopaedic work – itself a valiant effort in view of the rapid development of organic chemistry – is considerably larger than the first. Volume I, previously in two parts, is now issued in seven single volumes. It is questionable whether such a systematic treatment of organic chemistry, whose compilation necessarily takes several years, can in the future compete with the numerous up-to-date monographs and reviews.

The arrangement of subject matter in the new edition does not differ materially from that in the old. The present Part I, A (19 authors) is again divided into general and special chapters. Twelve short sections, some completely rewritten, include: theoretical organic chemistry (acid-base theory, *H. D. Springall*; stereochemistry, *I. G. M. Campbell*; reaction mechanism, *D. V. Banthorpe*; free radicals and homolytic reactions, *D. H. Hey* and *W. A. Waters*; wave mechanics, *W. Byers-Brown*) and methods (quantitative analysis, *R. Belcher*; physical properties, *H. D. Springall*; crystallography, *A. F. Wells*; spectroscopy, *I. E. Page*; labeled compounds, *H. R. V. Arnstein*). Although the literature is covered up to 1960 (partly up to 1963) the coverage of these important fields in barely 350 pages is unsatisfactory and gives only superficial informations; this applies especially to photochemistry (1 page), and ESR ($1^1/_2$ pages), NMR (2 pages), and mass spectrometry ($^1/_2$ page).

In the three following special chapters syntheses, properties, and reactions of the alkanes, alkenes, alkynes, and their halogen derivatives are handled briefly and clearly. Numerous references (up to 1962) and some short mechanistic indications make this part of the volume a welcome reference book which, if one is not looking for the completeness of Beilstein, will provide information rapidly on the most important new results in organic chemistry.

It is to be hoped that the individual volumes of the second edition will appear in rapid succession, for the "New Rodd" will doubtless be a valuable and much used reference work in every library. *K. Hafner* [NB 470a/323 IE]

**Rodd's Chemistry of Carbon Compounds,** Edited by *S. Coffey* Vol. I, Part B: Monohydric Alcohols, their Ethers and Esters, Sulphur Analogues, Nitrogen Derivatives, Organometallic Compounds. xvi + 313 pp., numerous figs. and tables. DM 56.– (about $ 11.–); Part C: Monocarbonyl Derivatives of Aliphatic Hydrocarbons, Analogues and Derivatives. xvi + 432 pp., numerous figs. and tables, DM 83.50 (about $ 20.50). Elsevier Publishing Comp., Amsterdam 1965, 2nd Edit.

The two most recent Parts B and C of Volume I concern simple functional derivatives of aliphatic hydrocarbons. Almost all the chapters contrast with those in the first edition in the fullness of information provided.

Part I, B comprises monohydric alcohols, their ethers and their esters with mineral acids, aliphatic sulfur and nitrogen compounds, and aliphatic organometallic compounds including transition-metal complexes of alkenes and alkynes. There are four sections giving clear accounts of their respective classes, but confined to synthesis, reactions and properties; the authors are *I. G. Buchanon, N. A. Hughes, G. A. Swan, H. Goldwhite, C. B. Milue,* and *A. N. Wright.*

Special attention should be paid to the much enlarged description (110 pp.; 40 pp. in the first edition) of organometallic compounds, whose importance has increased so greatly in recent decades. It is preceded by a short introduction into the theory of the metal-carbon bond. However, the detailed description of individual compounds often contains no reference to their preparative values (tertiary phosphines, ylides, Wittig reaction; olefin-nickel complexes, cyclooligomerization of dienes; *etc.*).

Part I, C concerns aliphatic monocarbonyl compounds (aldehydes and ketones) and their derivatives and oxidation products (carboxylic acids). The chapters on monocarboxylic acids and carbonic acid (174 pp. in the first edition) have been subdivided by the new authors (*M. F. Ansell, R. H. Gigg,* and *R. Howe*) into three large sections (300 pp.): monocarboxylic acids and their derivatives; carbon monoxide (metal carbonyls) isocyanides, and fulminic acid; carbonic acid derivatives. Although as in other chapters of these Parts there has been no attempt a theoretical explanation of the reactions, the clear presentation of the individual classes of compound will be of value to all those studying this field, even if, occasionally, important recent results (particularly those in the German literature) are not mentioned (*e.g.* reactions of isocyanides; acid amide acetals).

Both these Parts contain carefully compiled subject indexes and numerous references to original papers, reviews, and collected works (*e.g.* Houben-Weyl), the literature being partly covered up to 1963; they will be an essential reference book for every organic-chemical laboratory. *K. Hafner* [NB 470b/324 IE]

**Rubidium and Caesium.** By *F. M. Perelman.* Vol. 2 of the International Series of Monographs on Nuclear Energy, Division VIII, Materials. Pergamon Press 1965. 1st Engl. Edit., 144 pp., 17 illustr., 41 tables, linen, £3.–.– (*ca.* $ 7.40).

Since the appearance of the first (Russian) edition (1941) of *Perelman*'s monograph, caesium (besides other applications) has achieved greater technical importance in connection with the direct conversion of energy (heat/electricity). Further uses appear possible also in connection with propulsion in space by ion-beam engines. The 2nd edition, presented in English, has been reworked throughout; the additions needed have doubled the size.

Five sections treat the discovery and occurrence of rubidium and caesium (7 pp.), the properties of the two metals and their compounds (49 pp.), aqueous and non-aqueous systems (15 pp.), their analytical chemistry (27 pp.), the production of concentrates of the two elements from their ores (15 pp.), and finally their preparation in metallic form (15 pp.). Collections of data in tables and graphic presentations assist a survey of the material although, particularly in the section on "Properties", many numerical data remain scattered through the text and are thus not easily recoverable.

The book will provide welcome help to those who want a rapid introduction to rubidium and caesium or need to find the original papers concerning detail that specially interests them. 346 References are given to the literature up to 1949. 105 Further references for the period 1960–1964 are arranged according to subjects. The book contains few misprints, and the translation has introduced some incertainties.

*F. Endter* [NB 458/311 IE]

**Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry.** By *P. Crabbé.* Holden-Day, San Francisco-London-Amsterdam 1965. 1st Edit., xv + 378 pp., numerous figs. and tables, $ 12.95.

Although they were known already in the previous century, it is only recently that the two complementary methods of optical rotatory dispersion (ORD) and circular dichroism (CD) have found their way into the laboratories of organic chemists and biochemists. Whereas *Djerassi*'s classical book (1960) was based mainly on measurements by a single school, some 1000 publications have appeared in the meantime, and from many laboratories. A general review and introduction into this field was thus an urgent necessity, and *Crabbé* has provided this in a didactically excellent manner. Although the author has not attempted comprehensive coverage of the literature, all the important work published up to the end of 1964 is cited; and more than that, for many papers are included that were available only as manuscripts when the book went to the press. This monograph then like all the volumes in the Holden-Day series "Physical Techniques in Chemistry", is completely up to date.

A short introduction into theory and nomenclature, and a brief explanation of the principles involved in the measurements, are followed by a general review of the range of application of ORD and CD and their relative advantages and disadvantages. Next the chromophoric systems in compounds of low molecular weight are discussed, ketones naturally requiring most space here. A short review of the applications to polypeptides, proteins, and nucleic acids closes the descriptive section. An appendix contains a computer program for calculation of rotational strengths and thermodynamic data from low-temperature measurements of CD, and there is a bibliography which includes also papers that could not be discussed in detail in the special sections.

The text is made more readily intelligible by many carefully prepared diagrams, and the formulae are supplemented by stereoprojections where necessary. Misprints are very rare. The wealth of material presented and, above all, the skill with which it is presented, make "Crabbé" equally valuable for beginners and experts. This monograph is indispensible for all concerned with the use of ORD or CD in organic chemistry, and the author and publisher are to be congratulated on this outstanding aschievement.

*G. Snatzke* [NB 452/305 IE]

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# New Methods in Preparative Organic Chemistry VI[*]

## Ring Closures with Carbon Monoxide

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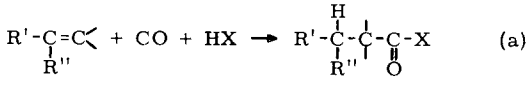
*Carbon monoxide undergoes catalytic reactions with unsaturated compounds to give heterocyclic carbonyl compounds. This cyclization has led to new syntheses of imides, lactams, lactones, phthalimidines, indazolones, and tetrahydroquinazolines.*

### A. Introduction

Around the middle of the 1920's, carbon monoxide started to become an important reactant for organic syntheses. It was used in the Fischer-Tropsch synthesis [1] for the production of synthetic gasoline and later for the synthesis of methanol with hydrogen [2,3], for *Roelen*'s oxo synthesis [4], and for Reppe syntheses [5]. These uses were followed by *Koch*'s carboxylic acid synthesis [6], which is being used to an increasing extent in industry.

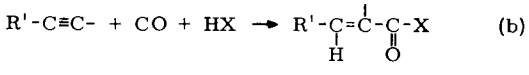
With a few exceptions, the reactions of carbon monoxide with organic compounds can be classified as three-component reactions and two-component insertion reactions.

The three-component reactions are those with unsaturated hydrocarbons and compounds containing reactive hydrogen atoms to form carbonyl compounds as indicated by Equations (a) and (b).



(a)

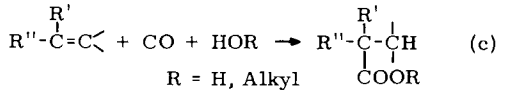
X = $OR^{[7]}$, $NHR^{[8]}$, $SR^{[9]}$, $H^{[4]}$



(b)

X = $OR^{[10]}$, $NHR^{[10]}$, $SR^{[10]}$

When this reaction is catalysed by transition-metal carbonyls, the carbon monoxide preferentially adds to the end of the carbon chain. If, on the other hand, olefins [6] or reactive cycloaliphatic compounds [11] are treated under mild conditions (room temperature and pressures below 100 atm) with carbon monoxide and water or alcohols in the presence of inorganic acids such as sulfuric acid, phosphoric acid, or $H_3PO_4/BF_3$, the reaction leads exclusively to secondary or tertiary carboxylic acids or their esters [see Equation (c)].



(c)

R = H, Alkyl

In two-component reactions [Equations (d) to (f)], a molecule of carbon monoxide is inserted into an existing bond.

[*] The papers in the preceding series have been published in three volumes by Verlag Chemie, Weinheim/Bergstr.; English edition: Academic Press, New York-London. Volumes IV and V are in preparation.

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[3] *K. Winnacker* and *E. Weingärtner*: Chemische Technologie. Carl Hanser Verlag, München 1952, p. 776.

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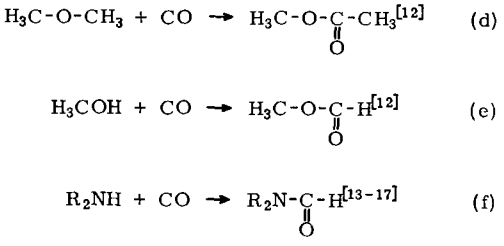
The mechanisms of both types of reactions have been studied in detail by numerous research groups. The reader is referred to a number of publications, which have also been of great assistance in the interpretation of the ring closures described below[18–29].



(d)



(e)

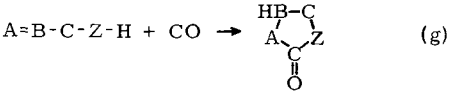


(f)

## B. General Remarks on Ring Closure with Carbon Monoxide

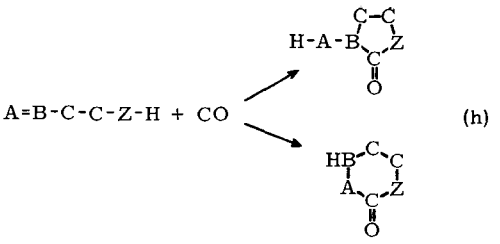
The present review deals with a third type of reaction of carbon monoxide, *viz.* two-component reactions leading to ring closure.

Unsaturated compounds containing a reactive hydrogen atom in a position that favors ring closure react with carbon monoxide in the presence of catalysts to give cyclic carbonyl compounds. If the starting compound is a four-atom chain, the product is a five-membered ring, as illustrated in Equation (g). If the chain in the starting



(g)

compound is five or more atoms long, six-membered rings may be formed as well as five-membered rings [see Scheme (h)].



(h)

For example, carbon monoxide reacts with unsaturated amides to give imides [30–33], with unsaturated amines [34] to give lactams [35], with unsaturated alcohols to give lactones [36], with Schiff bases [24, 37, 38], aromatic ketoximes [39], phenylhydrazones [28, 40], semicarbazones [41], azines [41], and nitriles [42] to give phthalimidines, and with azobenzenes [24, 43, 44] to give indazolones or 2,4-dioxo-1,2,3,4-tetrahydroquinazolines.

These reactions proceed at 170 to 280 °C under pressure (100 to 300 atm). The best catalysts are cobalt carbonyls [33, 35, 36, 38]; rhodium [36, 44] and iron carbonyls [38] also are active; however, nickel carbonyls [33, 38], which are active in Reppe syntheses, are inactive in this case. Some of the reactions can also be carried out with stoichiometric quantities of cobalt or rhodium carbonyls at normal pressure in the absence of free carbon monoxide [45]. Suitable solvents include benzene, toluene and inert hydrocarbons [36, 38]; tetrahydrofuran or dioxane may be used where the starting materials or the products are highly polar.

## C. Special Reactions

### 1. Imides from Unsaturated Amides [30–33]

Acrylamide *(1)* reacts with carbon monoxide to give succinimide *(2)* in 82% yield. *N*-Substituted acrylamides *(3)* are converted into the corresponding *N*-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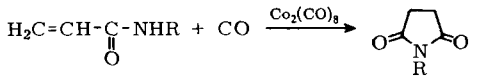


*(1)*, R = H *(2)*, R = H
*(3)*, R ≠ H *(4)*, R ≠ H

Table 1. Syntheses of *N*-substituted succinimides *(4)* from *N*-monosubstituted acrylamides *(3)* and carbon monoxide in the presence of $Co_2(CO)_8$.

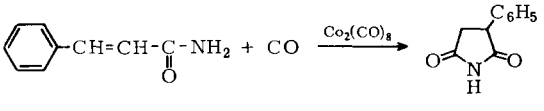
| | Substituent R in *(3)* | Reaction product *(4)* | Yield [%] | Ref. |
|---|---|---|---|---|
| *(a)* | Methyl | *N*-Methylsuccinimide | 94 | [33] |
| *(b)* | Butyl | *N*-Butylsuccinimide | 72 | [33] |
| *(c)* | Isobutyl | *N*-Isobutylsuccinimide | 80 | [33] |
| *(d)* | Hexyl | *N*-Hexylsuccinimide | 77 | [33] |
| *(e)* | Dodecyl | *N*-Dodecylsuccinimide | 85 | [30,33] |
| *(f)* | Ethoxycarbonyl-methyl | Ethyl succinimido--*N*-acetate | 70 | [33] |
| *(g)* | Phenyl | *N*-Phenylsuccinimide | 64 | [33] |
| *(h)* | *p*-Chlorophenyl | *N*-(*p*-Chlorophenyl)-succinimide | 65 | [33] |
| *(i)* | 2,6-Dichloro-phenyl | *N*-(2,6-Dichlorophenyl)-succinimide | 44 | [33] |
| *(j)* | Benzyl | *N*-Benzylsuccinimide | 92 | [33] |
| *(k)* | Allyl | *N*-Allylsuccinimide | 55 | [35] |

substituted succinimides *(4)* (see Table 1). When the starting materials contain halogenated aromatic groups, no dehalogenation takes place. Similarly, methacrylamides and *N*-substituted methacrylamides *(5)* give α-methylsuccinimides *(6)* (see Table 2).

Table 2. Reaction of methacrylamide and *N*-substituted methacrylamides *(5)* with carbon monoxide in the presence of $Co_2(CO)_8$ [33].

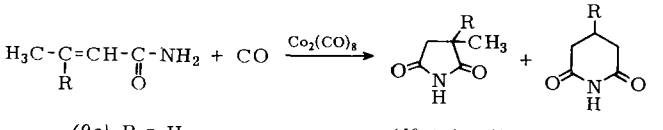
| *N*-Substituent in *(5)* | | Reaction product *(6)* | Yield [%] |
|---|---|---|---|
| *(a)* | H | α-Methylsuccinimide | 68 |
| *(b)* | Methyl | *N*-Methyl-α-methylsuccinimide | 70 |
| *(c)* | n-Butyl | *N*-n-Butyl-α-methylsuccinimide | 74 |
| *(d)* | Benzyl | *N*-Benzyl-α-methylsuccinimide | 76 |

β-Arylated acrylamides also react to give α-substituted succinimides. Thus α-phenylsuccinimide *(8)* is obtained from cinnamamide *(7)*.



*(7)* *(8)*

The reaction of β-alkylacrylamides leads not only to α-alkylsuccinimides, but also to glutarimides. For example, crotonamide *(9a)* reacts to form a mixture of α-methylsuccinimide *(10a)* and glutarimide *(11a)*, and β,β-dimethylacrylamide *(9b)* gives only β-methylglutarimide *(11b)*.

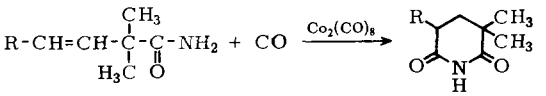


*(9a)*, R = H *(10a)*, (68%) *(11a)*, (19%)
*(9b)*, R = $CH_3$ *(11b)*, (67%)

The six-membered rings are formed by isomerization of intermediate complexes of olefinic starting material and the catalyst. Similar isomerizations were observed in other reactions with carbon monoxide in the presence of transition metal carbonyls [25,46–57] (see Section D).

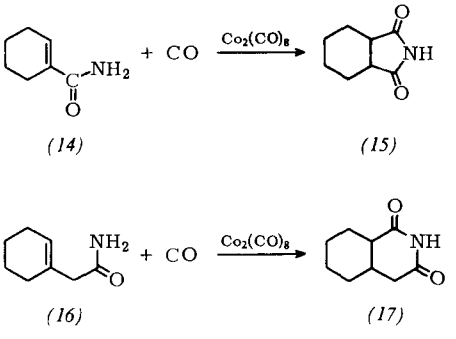
The exclusive formation of the six-membered cyclic imide from β,β-dimethylacrylamide has a parallel in the oxo synthesis. *Keulemans* reported that no quaternary carbon atoms are formed during hydroformylations in the presence of cobalt catalysts [58]. Thus the hydroformylation of isobutene gives almost exclusively isopentanol, with only small quantities of neopentanol [59]; 2,6-dimethyl-5,6-dihydro-4*H*-pyran gives only 3-formyl products, whereas 5,6-dihydro-4*H*-pyran gives mainly 2-formyl products [60].

β,γ-Unsaturated amides such as *(12)* also react in accordance with the above scheme to give glutarimides *(13)*. Unsaturated alicyclic amides *(14)* and *(16)* yield



*(12a)*, R = H *(13a)*, (58%)
*(12b)*, R = $CH_3$ *(13b)*, (64%)

five-membered *(15)* or six-membered *(17)* bicyclic imides, depending on the position of the double bond. As expected, unsaturated *N*,*N*-dialkylamides and aromatic amides, such as benzamide, do not react in accordance with this scheme.



*(14)* *(15)*

*(16)* *(17)*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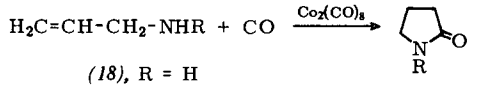
## 2. Lactams from Unsaturated Amines [35]

Allylamine *(18)* reacts with carbon monoxide to give 2-pyrrolidone [*(20)*, R = H]. The *N*-alkylallylamines



*(18)*, R = H
*(19)*, R ≠ H *(20)*

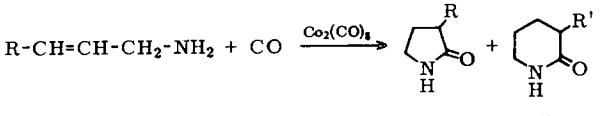
*(19)* [34], which are readily accessible from allyl chloride and primary amines or from allylamine and alkyl chlorides, react to form *N*-alkyl-2-pyrrolidones *(20)* (R ≠ H).

Table 3. Reactions of *N*-monosubstituted allylamines *(19)* with carbon monoxide in the presence of $Co_2(CO)_8$.

| | Substituent R in *(19)* | Reaction product *(20)* | Yield [%] | Ref. |
|---|---|---|---|---|
| *(a)* | Methyl | *N*-Methylpyrrolid-2-one | 78 | [35] |
| *(b)* | Ethyl | *N*-Ethylpyrrolid-2-one | 61 | [35] |
| *(c)* | Isobutyl | *N*-Isobutylpyrrolid-2-one | 61 | [35] |
| *(d)* | Octyl | *N*-Octylpyrrolid-2-one | 58 | [35] |
| *(e)* | Dodecyl | *N*-Dodecylpyrrolid-2-one | 47 | [35] |
| *(f)* | Phenyl | *N*-Phenylpyrrolid-2-one | 26 | [30] |

The carbonylation of diallylamine $HN(CH_2-CH=CH_2)_2$ leads to a mixture of *N*-allyl-2-pyrrolidone, *N*-propenyl-2-pyrrolidone, and 2-pyrrolidone. The principal product may be any one of the three lactams, depending on the reaction conditions. The migration of the double bond again is probably due to isomerization promoted by the metal carbonyl catalysts. The formation of 2-pyrrolidone, which becomes appreciable only at high temperatures, is accompanied by formation of propene. Under these conditions, the C–N bond evidently undergoes hydrogenolytic cleavage with hydrogen transfer.

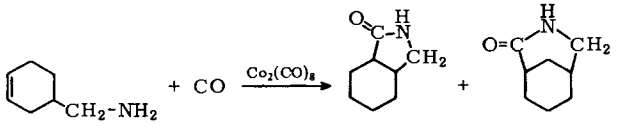
Carbonylation of *N*-alkylated β-methylallylamines yields 1-alkyl-4-methyl-2-pyrrolidones. γ-Alkylallylamines*(21)* give mixtures of 3-alkyl-2-pyrrolidones *(22)* and 2-piperidones *(23)*. As in the synthesis of imides, the



*(21)*, R = $CH_2R'$ *(22)* *(23)*

formation of six-membered lactam rings is attributed to the isomerization of intermediate complexes of the catalyst and the starting material.

Isomerizations also occur during the carbonylation of unsaturated alicyclic amines; for example, the carbonylation of (3-cyclohexenylmethyl)amine *(24)* leads to the bicyclic lactams *(25)* and *(26)*.

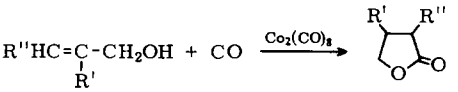


*(24)* *(25)* *(26)*

*N*-Alkenylformamides are formed only in small quantities in all the above reactions.

## 3. Lactones from Unsaturated Alcohols

Lactones *(28)* can be obtained by the reaction of primary unsaturated alcohols *(27)* with carbon monoxide. However, this is often accompanied by an un-

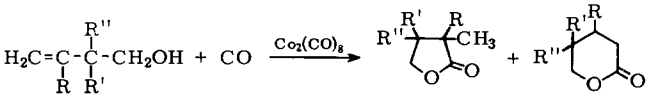


*(27a)*, R' = R'' = H *(28)*
*(27b)*, R' = $CH_3$, R'' = H
*(27c)*, R' = H, R'' = $CH_3$

desirable side-reaction (i), namely the carbonyl-catalysed isomerization of the unsaturated alcohols to saturated aldehydes. Thus allyl alcohol *(27a)*, β-methallyl alcohol *(27b)*, and crotyl alcohol *(27c)* give only about 2% of the γ-lactones, while about 50% of the starting compounds isomerize to the aldehydes. These undergo further reactions such as the aldol condensation or the Tischtschenko reaction, or polymerize at higher temperatures.

$$H_2C=CH-CH_2OH \rightarrow [CH_3-CH=CHOH] \rightarrow CH_3-CH_2-CHO \quad (i)$$

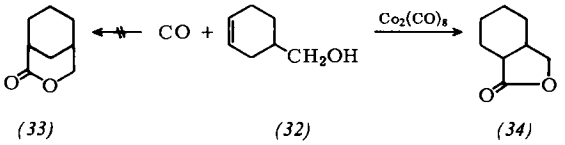
Higher yields of the lactones are obtained from unsaturated alcohols *(29)* that cannot undergo isomerizations of this type owing to the presence of substituents in position 2. As in the carbonylation of unsaturated



| | | |
|---|---|---|
| *(29a)*, R = H, R' = R'' = $CH_3$ | *(30a)*, (51%) | *(31a)*, (14%) |
| *(29b)*, R = R' = R'' = $CH_3$ | *(30b)*, (3%) | *(31b)*, (25%) |
| *(29c)*, R = H, R' = $CH_3$, R'' = $C_2H_5$ | *(30c)*, (40%) | *(31c)*, (13%) |

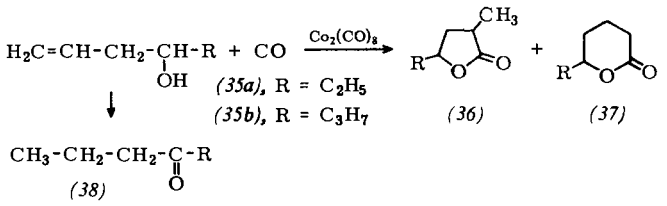
amines, formation of the six-membered ring is favored by an alkyl substituent in position 3.

Unsaturated alicyclic alcohols also give lactones. The reaction of 3-cyclohexenylmethanol *(32)* leads not to the expected bicyclic δ-lactone *(33)* but to the isomeric bicyclic γ-lactone *(34)*, probably again by isomerization of an intermediate cobalt complex.



*(33)* *(32)* *(34)*

γ-Unsaturated secondary alcohols *(35)* also form lactones *(36)* and *(37)*, but only in small yields, since the main reaction is isomerization to the ketones *(38)*.

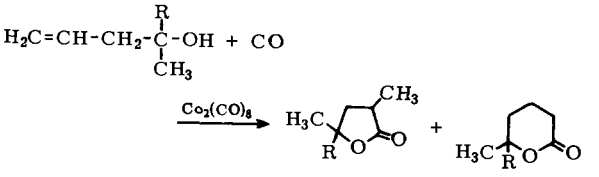


*(35a)*, R = $C_2H_5$
*(35b)*, R = $C_3H_7$

*(36)* *(37)*

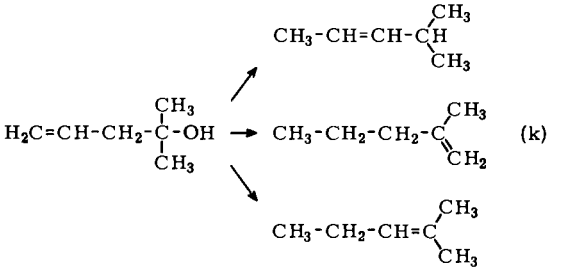
*(38)*

Since γ-unsaturated tertiary alcohols *(39)* cannot isomerize to carbonyl compounds, they generally give better yields of lactones.



| | | |
|---|---|---|
| *(39a)*, R = $CH_3$ | (10%) | (2%) |
| *(39b)*, R = $C_2H_5$ | (29%) | (6%) |
| *(39c)*, R = i-$C_4H_9$ | (10%) | (2%) |

The carbonylation of γ-unsaturated tertiary alcohols is accompanied by another side-reaction (k) leading to the formation of large quantities of mono-olefin. This can be

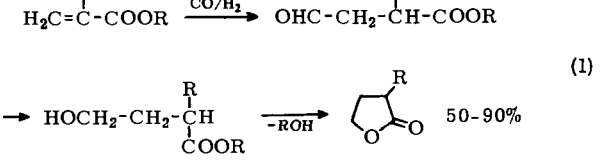


(k)

explained by elimination of water from the γ-unsaturated tertiary alcohols and hydrogenation of the resulting dienes by hydrogen transfer. The nature of the oxidation products formed in the hydrogen transfer has not been established. A related reaction was described by *Nicholson* and *Shaw*[61], who obtained propene when an aqueous solution of allyl alcohol was heated in the presence of catalytic amounts of $RuCl_3$. In this case the hydrogen was obtained by oxidation of allyl alcohol to acrolein.

[61] *J. K. Nicholson* and *B. L. Shaw*, Proc. chem. Soc. (London) *1963*, 282.

Many of the lactones that are difficult to obtain by the method described here can be prepared in good yields by a single-stage reaction (l) from esters of unsaturated carboxylic acids, carbon monoxide, and hydrogen[62,63].

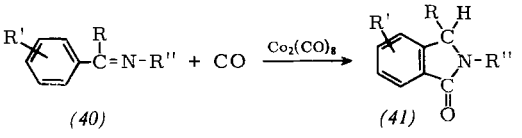


(l)

### 4. Phthalimidines from Schiff Bases[24,37,38] or Aromatic Nitriles[42]

The ring-closure reaction is not confined to compounds containing a C=C double bond, and the atom represented by Z in Equations (g) and (h) need not be a heteroatom.For example,Schiff bases,in which the unsaturated bond is a C=N double bond and Z is a carbon atom, react with carbon monoxide to give high yields of phthalimidines.

*N*-Benzylidenaniline *(40a)* gives 2-phenylphthalimidine *(41a)* in 84% yield. *N*-Benzylidenanilines with *o,p*-directing substituents also undergo this reaction. If, on the other hand, the starting compound contains a nitro group, the reaction fails. It appears that the nitro group is reduced, and the product then undergoes further reactions. Lower yields are obtained if the aromatic ring of the benzylidene group in *N*-benzylidenaniline carries an *o,p*-directing substituent such as a hydroxy or methoxy group in the *o*-position [see (n) in Table 4]. Schiff bases *(42)* of aliphatic amines also give phthalimidines, such as *(41q)* and *(41r)*.



*(40)* *(41)*

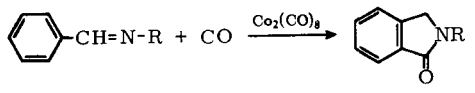
Table 4. Phthalimidines *(41)* obtained from Schiff bases *(40)* and carbon monoxide in the presence of $Co_2(CO)_8$.

| | Substituents in *(40)* R′ | R″ | R | Substituents in *(41)* | Yield [%] | Ref. |
|---|---|---|---|---|---|---|
| *(a)* | H | $C_6H_5$ | H | 2-$C_6H_5$ | 84 | [37] |
| *(b)* | H | *p*-$H_3CO$—$C_6H_4$ | H | 2-*p*-$H_3CO$—$C_6H_4$ | 86 | [38] |
| *(c)* | H | *p*-HO—$C_6H_4$ | H | 2-*p*-HO—$C_6H_4$ | 65 | [38] |
| *(d)* | H | *p*-Cl—$C_6H_4$ | H | 2-*p*-Cl—$C_6H_4$ | 75 | [38] |
| *(d)* | H | *p*-Cl—$C_6H_4$ | H | 2-*p*-Cl—$C_6H_4$ | 75 | [38] |
| *(e)* | H | *p*-$(C_2H_5)_2N$—$C_6H_4$ | H | 2-*p*-$(C_2H_5)_2N$—$C_6H_4$ | — | [37] |
| *(f)* | H | 1-Naphthyl | H | 2-(1-Naphthyl) | 55 | [37] |
| *(g)* | *p*-$(CH_3)_2N$ | $C_6H_5$ | H | 2-$C_6H_5$, 6-$(CH_3)_2N$ | 82 | [37,38] |
| *(h)* | *p*-HO | $C_6H_5$ | H | 2-$C_6H_5$, 6-HO | 77 | [38] |
| *(i)* | *p*-$H_3CO$ | $C_6H_5$ | H | 2-$C_6H_5$, 6-$H_3CO$ | 86 | [37] |
| *(j)* | *p*-Cl | $C_6H_5$ | H | 2-$C_6H_5$, 6-Cl | 45 | [37] |
| *(k)* | *m*-$(CH_3)_2N$ | $C_6H_5$ | H | 2-$C_6H_5$, 7-$(CH_3)_2N$ | 87 | [64] |
| *(l)* | H | $C_6H_5$ | $CH_3$ | 2-$C_6H_5$, 3-$CH_3$ | 61 | [37,38] |
| *(m)* | H | $C_6H_5$ | $C_6H_5$ | 2-$C_6H_5$, 3-$C_6H_5$ | 97 | [37,38] |
| *(n)* | *o*-$H_3CO$ | $C_6H_5$ | H | 2-$C_6H_5$, 4-$H_3CO$ | 18 | [38] |
| *(o)* | *m*-$H_3CO$ | $C_6H_5$ | H | 2-$C_6H_5$, 5-$H_3CO$ | 5 | [38] |
| *(p)* | *m*-HO | $C_6H_9$ | H | 2-$C_6H_5$, 7-HO | 77 | [64] |

[62] *J. Falbe* and *F. Korte*, Angew. Chem. *74*, 900 (1962), Angew. Chem. internat. Edit. *1*, 657 (1962).

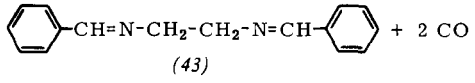
[63] *J. Falbe*, *N. Huppes*, and *F. Korte*, Chem.Ber. *97*, 863 (1964).

[64] *S. Murahashi* and *S. Horiie*, Annu. Rep. sci. Works, Fac. Sci., Osaka Univ. *7*, 89 (1959).

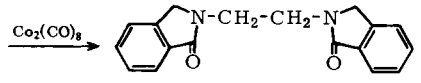


*(42q)*, R = $CH_3$ *(41q)*, (79%)
*(42r)*, R = $CH_2$-$C_6H_5$ *(41r)*, (82%)

Compounds containing two phthalimidine groups can also be prepared in this way; thus *N,N'*-dibenzylidenethylenediamine *(43)* gives *N,N'*-ethylenediphthalimidine *(44)*.

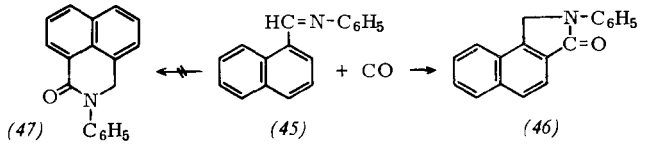


*(43)*



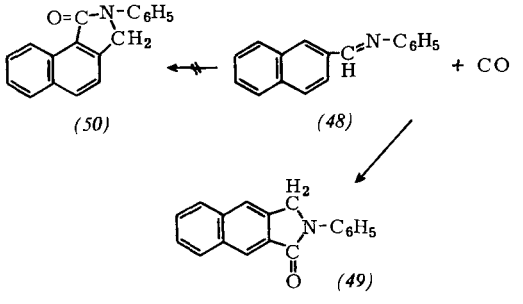
*(44)*, (49%)

Schiff bases from naphthaldehydes react in a similar manner. The reaction of 1-naphthaldehyde anil *(45)* leads to *N*-phenylbenzo[*e*]phthalimidine *(46)*; compound *(47)* was not observed among the products.



*(47)* *(45)* *(46)*

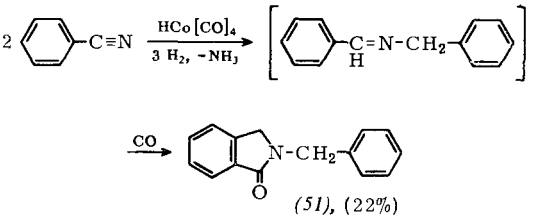
2-Naphthaldehyde anil *(48)* gives, not *N*-phenylbenzo[*g*]phthalimidine *(50)*, but only *N*-phenylbenzo[*f*]phthalimidine *(49)*. On the basis of the charge distribution, cyclization would be expected in position 1.



*(50)* *(48)* *(49)*

However, Stuart-Briegleb molecular models show that ring closure in this position is subject to strong steric hindrance, whereas ring closure in position 3 is unhindered.

The synthesis of *N*-benzylphthalimidine *(51)* by reaction of benzonitrile with carbon monoxide or synthesis gas in the presence of cobalt carbonyls may be regarded as a special case of the reaction with Schiff bases. It is known that nitriles can give Schiff bases as intermediates on hydrogenation [65]. From the products obtained in the carbonylation of nitriles, and from the fact that higher yields are obtained with synthesis gas than with pure carbon monoxide [29], as well as from the observation that the best yields are obtained when 1 mole of benzylamine is added per mole of benzonitrile [29], it is very probable that the formation of the phthalimidine in this case again proceeds *via* the Schiff base.

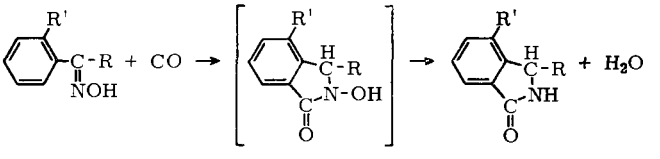


*(51)*, (22%)

[65] *E. N. Zilbermann, A. A. Kalugin*, and *E. M. Perepletchikova*, Zh. obshch. Khim. *1962*, 900, Chem. Abstr. *58*, 1337 (1963).

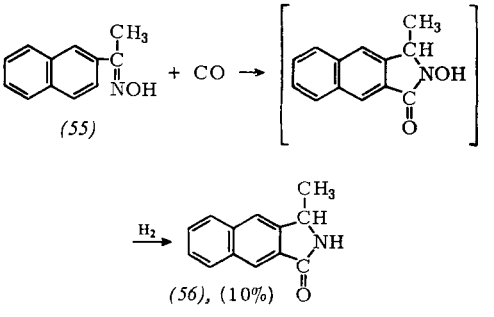
### 5. Phthalimidines from Aromatic Ketoximes [39], Phenylhydrazones [28,40], Semicarbazones [41], and Azines [41]

Aromatic ketoximes such as *(52)* react with a $CO/H_2$ mixture (98.5:1.5) to give phthalimidines. The initial products are probably *N*-hydroxyphthalimidines *(53)*, which are then hydrogenated to phthalimidines *(54)*. Reactions with alkyl aryl ketoximes such as *(52c)* and *(52d)* are less selective than reactions with diaryl



*(52a)*, R = $C_6H_5$, R' = H *(53)* *(54a)*, R = $C_6H_5$, R' = H, (80%)
*(52b)*, R = $C_6H_5$, R' = COOH *(54b)*, R = $C_6H_5$, R' = H, (86%)
*(52c)*, R = $CH_3$, R' = H *(54c)*, R = $CH_3$, R' = H
*(52d)*, R = $CH_2$-$C_6H_5$, R' = H *(54d)*, R = $CH_2$-$C_6H_5$, R' = H

ketoximes. Thus methyl 2-naphthyl ketoxime *(55)* gives the phthalimidine *(56)*, together with other products.



*(55)*

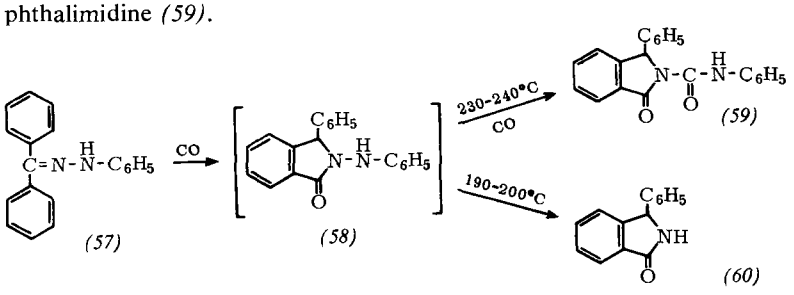


*(56)*, (10%)

As in the case of 2-naphthaldehyde anil, ring closure again takes place in position 3 because of steric hindrance. Attempts to prepare the *N*-hydroxy- or *N*-methoxy-methylphthalimidines were unsuccessful [39]; the products in every case were simply phthalimidines. The N–O bond appears to be very susceptible to hydrogenolysis by the hydrogen present (ratio CO:$H_2$ = 98.5:1.5).

Phenylhydrazones of aromatic ketones (see Table 5) also undergo ring closure with carbon monoxide [28,40]; however, the expected *N*-phenylaminophthalimidines, *e.g. (58)* from *(57)*, cannot be isolated. As in the

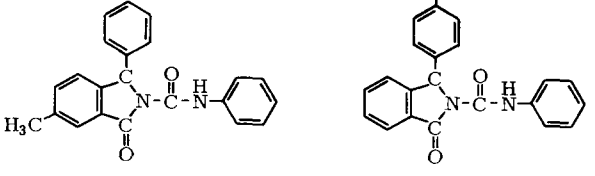
experiments with aromatic oximes, the N–N bond suffers hydrogenolysis at 190 to 200 °C. At higher temperatures, the hydrogenolysis gives way to the insertion of carbon monoxide into the N–N bond, leading to formation of *N*-(*N'*-phenylcarbamoyl)-phthalimidine *(59)*.



*(57)* *(58)* *(59)* *(60)*

Table 5. Carbonylation of phenylhydrazones of aromatic ketones in the presence of $Co_2(CO)_8$ [40].

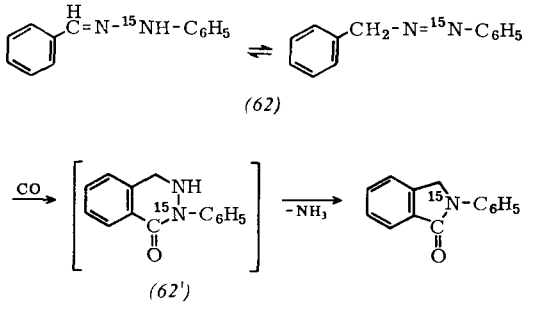
| Ketone | Reaction product | T [°C] | Yield [%] |
|---|---|---|---|
| Benzophenone | 3-Phenylphthalimidine *(60)* | 190–200 | 20 |
| Benzophenone | 3-Phenyl-(*N'*-phenylcarbamoyl)-phthalimidine | 210–220 | 12 |
| | 3-Phenylphthalimidine | | 50 |
| Benzophenone | 3-Phenyl-(*N'*-phenylcarbamoyl)-phthalimidine | 230–240 | 70 |
| 4-Methyl-benzophenone | *N'*-phenylcarbamoyl-3-(*p*-tolyl)phthalimidine *(61')* | 230 | 20 |
| | 6-Methyl-3-phenyl-(*N'*-phenyl-carbamoyl)phthalimidine *(61)* | | 20 |
| Acetophenone | 3-Methyl-(*N'*-phenylcarbamoyl)-phthalimidine | 230 | |
| | 3-Methyl-*N*-phenyl-phthalimidine | | |



*(61)*, (20%) *(61')*, (20%)

4-Methylbenzophenone phenylhydrazone gives two isomeric reaction products *(61)* and *(61')* [28]. Thus ring closure does not take place exclusively on the substituted ring, as in the case with Schiff bases and with the azo compounds described below, but proceeds to an equal extent on the unsubstituted ring.

Phenylhydrazones of aromatic aldehydes also give phthalimidines (cf. Table 6) [28,40]. With the use of compounds labelled with $^{15}N$ [*e.g. (62)*] it was shown that the nitrogen originally attached directly to the phenyl group of the phenylhydrazone is retained in the indazolone.



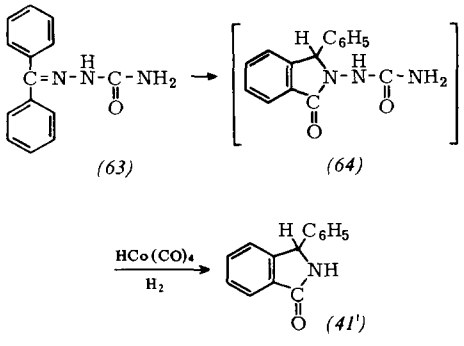
*(62)* *(62')*

Whereas the C=N double bond in the phenylhydrazones of aromatic ketones reacts in accordance with its original position, owing to conjugation with the two aromatic rings, the phenylhydrazones of aromatic aldehydes, like those of aliphatic aldehydes and ketones [66], exist partly in the tautomeric azo form. The phenylhydrazones of aromatic aldehydes evidently react in the azo form with carbon monoxide. However, the expected six-membered heterocycles, *e.g. (62')*, are not obtained; one nitrogen atom is eliminated as ammonia as a result of hydrogen transfer from the starting material or from the solvent.

Table 6. Carbonylation of phenylhydrazones of aromatic aldehydes in the presence of $Co_2(CO)_8$ [28].

| Phenylhydrazone | Reaction product | T [°C] | Yield [%] |
|---|---|---|---|
| Benzaldehyde phenyl-hydrazone | *N*-Phenylphthalimidine | 230–240 | 50 |
| Benzaldehyde (*m*-Tolyl)-hydrazone | *N*-(*m*-Tolyl)phthal-imidine | 230 | 20 |
| 1-Naphthaldehyde phenylhydrazon | 2-Phenylbenzo[*e*]-isoindol-1-one | 230–235 | |

Semicarbazones of aromatic ketones also react to form phthalimidines [41]. Once again, the expected *N*-ureidophthalimidines, *e.g. (64)*, cannot be isolated, evidently



*(63)* *(64)* *(41')*

because of hydrogenolysis. However, carbonylation probably does not take place exclusively on the unchanged semicarbazone, since benzophenone semicarbazones such as *(63)* decompose above their melting points to give benzophenone azines such as *(65)* [67]; according to *Rosenthal* [41] these react with carbon monoxide to give high yields of phthalimidines such as *(41')*. The formation of benzhydryl semicarbazones

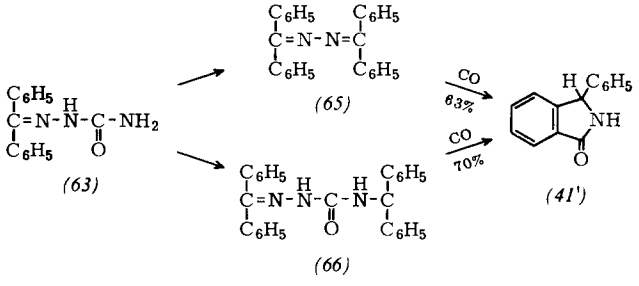
[66] *R. O'Connor*, J. org. Chemistry *26*, 4375 (1961).

[67] *W. Borsche* and *C. Merkwitz*, Ber. dtsch. chem. Ges. *37*, 3180 (1904).

Table 8. Products obtained by reaction of azobenzenes with carbon monoxide at temperatures above 200 °C in the presence of $Co_2(CO)_8$.

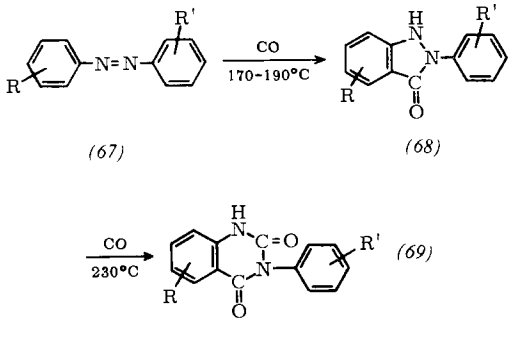
| | (67) with R | R' | Substituted 2,4-dioxo-1,2,3,4-tetrahydroquinazolines (69) | Yield [%] | Ref. |
|---|---|---|---|---|---|
| (a) | H | H | 3-Phenyl- | 65 | [44] |
| (b) | p-$CH_3$ | H | 6-Methyl-3-phenyl- | 36 | [44] |
| (c) | p-Cl | H | 6-Chloro-2-phenyl- | 45 | [43] |
| (d) | p-$(CH_3)_2N$ | H | 6-Dimethylamino-3-phenyl- | 18 | [44] |
| (e) | m-$CH_3$ | H | 7-Methyl-3-phenyl- | 26 | [44] |
| (f) | p-$CH_3$ | p-$CH_3$—$C_6H_4$ | 6-Methyl-3-(p-toluyl)- | 40 | [44] |
| (g) | p-Cl | p-Cl—$C_6H_4$ | 6-Chloro-3-(p-chlorophenyl)- | 17 | [44] |
| (h) | p-$CH_3$ | p-$CH_3O$—$C_6H_4$ | 6-Methoxy-3-(p-methoxyphenyl)- | 28 | [44] |

[(66) in this case] has also been observed; these react further to phenylphthalimidines in high yields [41].




### 6. Indazolones and 2,4-Dioxo-1,2,3,4-tetrahydroquinazolines from Azobenzenes [43,44]

Aromatic azo compounds react with carbon monoxide to form indazolones. At higher temperatures, further reaction of the indazolones leads to insertion of CO to form 2,4-dioxo-1,2,3,4-tetrahydroquinazolines. Thus the reaction of azobenzenes *(67)* between 170 and 190 °C yields 2-phenylindazolones *(68)* (cf. Table 7), which react with further CO at 220 to 230 °C to form 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazolines *(69)*. Azobenzenes containing *o,p*-directing substituents react in a




similar manner. If only one aromatic ring is substituted, cyclization always takes place on the substituted ring. Azobenzenes containing *m*-directing substituents do not

Table 7. Reaction of azobenzenes with carbon monoxide in the presence of $Co_2(CO)_8$.

| | (67) with R (R' = H) | Reaction product (68) | Yield [%] | Ref. |
|---|---|---|---|---|
| (a) | H | 2-Phenylindazolone | 55 | [43,44] |
| (b) | p-$CH_3$ | 5-Methyl-2-phenylindazolone | 35 | [44] |
| (c) | p-Cl | 5-Chloro-2-phenylindazolone | 24 | [44] |
| (d) | p-$(CH_3)_2N$ | 5-Dimethylamino-2-phenylindazolone | 80 | [44] |

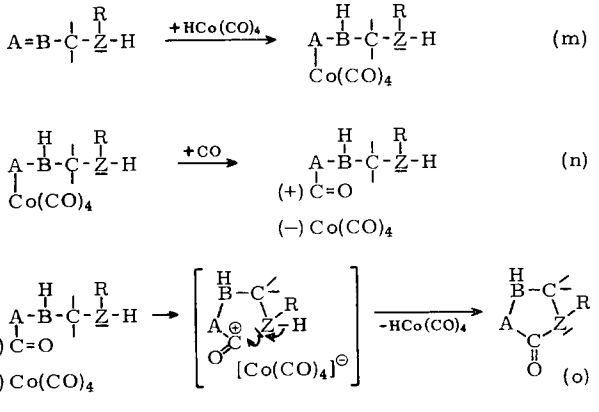
cyclize [38]. (An explanation for this is given in Section D).

The reaction of the indazolones *(68)* by CO insertion may be regarded as analogous to the formation of *N,N'*-dibenzylurea from hydrazobenzene and carbon monoxide [24]. The 2,4-dioxo-1,2,3,4-tetrahydroquinazolines *(69)* can be obtained in a single-stage reaction if the azobenzenes are allowed to react at temperatures above 200 °C [43,44] (see Table 8).

## D. The Mechanism of Ring Closure

It is reasonable to conclude, from the reactions described above, that the true catalysts are not the transition metal carbonyls, but the corresponding hydrogen metal carbonyls. On the one hand, the only metal carbonyls that are active as catalysts are those that can form hydrogen metal carbonyls, *e.g.* cobalt, rhodium, and iron [33,35,36,38], whereas nickel [33,38], for example, is inactive. Secondly, it is known that cobalt, rhodium, and iron carbonyls are able to abstract hydrogen from alcohols, amines, and even the much less reactive cycloparaffins under the reaction conditions used, to form hydrogen metal carbonyls [26,28,38,68]. Moreover, it has been shown that amides of unsaturated acids react with stoichiometric amounts of cobalt hydrogen tetracarbonyl, even at −30 to −20 °C, with ring closure to form imides; with $Co_2(CO)_8$, on the other hand, no reaction occurs under these conditions [45].

The three-step mechanism (m)–(n)–(o) agrees with the experimental results. The first step is the addition of the metal hydrogen carbonyl to the double bond of the starting compound (m).

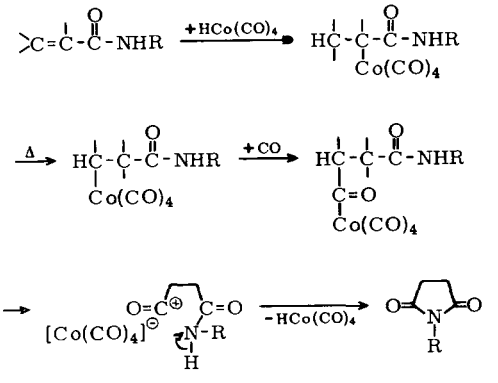



[68] *W. Hieber*, Angew. Chem. *55*, 7 (1942).

Although hydrogen tetracarbonylcobaltate gives a strongly acidic reaction in aqueous media [69–74], the hydrogen possesses hydride character in the gaseous substance [75–78]. The nature of the catalyst therefore also depends on the solvent. *Heck* and *Breslow* have already pointed out that the nature of the addition of the hydrogen carbonylmetallate is also largely dependent on the electron configuration of the substrate [25]. In the examples described, the hydrogen carbonylmetallates probably react preferentially in the hydride form. This explains the fact that their addition to the double bond of unsaturated amines and alcohols leads mainly to compounds with terminal metal.

The addition of hydrogen carbonylmetallates to Schiff bases, oximes, azo compounds, phenylhydrazones, semicarbazones, and azines can be explained on the basis of polar structures. If the electron density on the C atom of the C=N double bond in the Schiff bases is increased by a methyl substituent,the yields of cyclization products decrease, whereas the highest yields are obtained when the electron density is lowered by a phenyl substituent.

In unsaturated carboxamides, on the other hand, the electron-attracting carbamoyl group causes the hydride ion to be added to the β-carbon atom. The metal should therefore become attached in the α-position [top line in Equation (p)], as in unsaturated esters, which react at



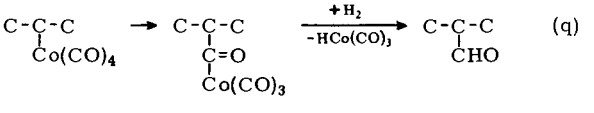
(p)

low temperatures (50 to 70 °C) to give products with Co attached in the α-position [25,63,79]; these products react with CO and then with hydrogen or alcohols to give the corresponding α-formyl esters of the carboxylic acid or diesters of malonic acid. At higher temperatures (110 to 150 °C), however, the reactions of the same starting materials lead to β-substituted esters of the carboxylic acids [62,63]. Compounds with longer chains give products containing even ω-substituted compounds, formed by isomerization of the intermediate cobalt compounds and migration of the metal substituent towards the end of the chain. An analogy to these results is the isomerization of alkylboron [80–85], alkylsilicon [86–88], and alkylaluminum compounds [89].

In compounds with longer chains the double bond can migrate already before the actual carbonylation. Various mechanisms [46–57,89a,89b] have been suggested for these isomerizations, including migration of an allyl hydrogen.

However, the alkyl-metal compound resulting from the addition of the hydrogen carbonylmetallate remains hypothetical. No such alkylcobalt compound has ever been detected with certainty in the addition of hydrogen tetracarbonylcobaltate to unsaturated compounds [25,27].

In the study of the hydroformylation mechanism, it has also been suggested that alkyltetracarbonylcobalt compounds may rearrange to acyltricarbonylcobalt compounds without taking up CO from the gas phase [25] [see Eq. (q)]. In the presence of hydrogen or alcohols, this should lead to the formation of $HCo(CO)_3$, which either catalyses the process as such, or takes up gaseous CO to re-form hydrogen tetracarbonylcobaltate [25,27].



(q)

Though this or a similar mechanism is not impossible, it is more likely, in view of the high CO pressures used, that the reaction proceeds *via* the hydrogen tetracarbonylcobaltate.

The last step in the reaction is the ring closure (with simultaneous regeneration of the hydrogen carbonylmetallate), the excess of electrons on the atom Z causing a nucleophilic attack on the acyl cation, while the hydrogen attached to Z is transferred as a proton to the $[Co(CO)_4]^{\ominus}$ anion.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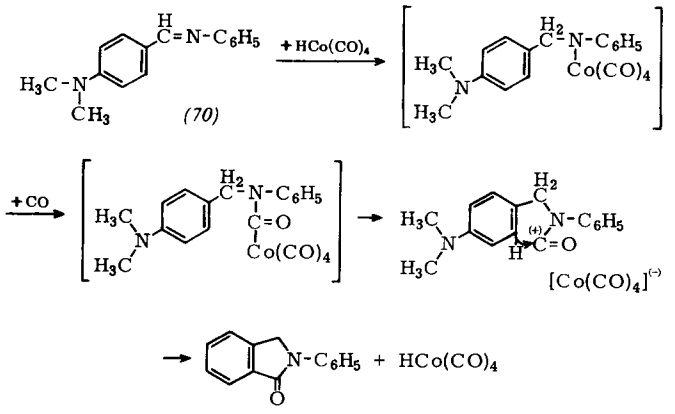
[89a] *H. Höver, H. Mergard*, and *F. Korte*, Liebigs Ann. Chem. *685*, 89 (1965).

[89b] *F. Korte* and *H. Höver*, Tetrahedron *1965*, 1287.

It is easy to see from the experimental results how the ring closure is affected by the electron density on the atom Z. For example, better yields are obtained with methylallylamine or *N*-methylacrylamide than with the phenyl homologues [33, 35].

Similarly, higher yields are obtained from the Schiff bases [*e.g. (70)*] derived from *p*- or *m*-dimethylaminobenzaldehyde and from *p*- or *m*-methoxybenzaldehyde, or the analogous azo compounds [38], than from the unsubstituted compounds; this is due to the inductive effect of the substituents and the resulting increased electron density in the aromatic system.



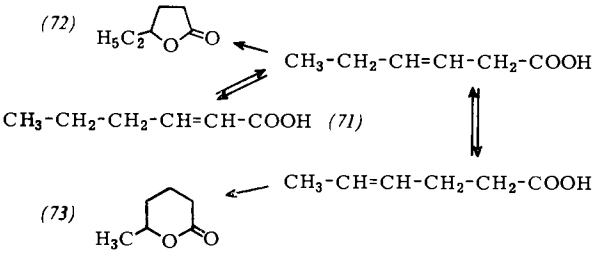
Only one result appears not to fit the proposed mechanism *viz.* the reaction of the Schiff base of 2-naphthaldehyde [38]. In this case the ring closure takes place, not on C-1, as expected, but on C-3; however, the special steric effects involved here have already been mentioned (Section C. 4).

A mechanism proposed by *Horiie* and *Murahashi* [24] for the carbonylation of Schiff bases and azo compounds, and later by *Rosenthal* [28] for the carbonylation of phenylhydrazones, has been shown to be incorrect. $Co_2(CO)_8$ was thought to react with the lone electron pair on the nitrogen atom to form a π-compound; insertion of CO then leads to an unsaturated Co-acyl compound containing 4-coordinate nitrogen, which subsequently undergoes ring closure in a multi-center reaction, the aromatic hydrogen in the *o*-position being simultaneously transferred to the C=N or C=C double bond. However, *Rosenthal*, and *Gervay* [29] later showed that in the reaction of nitriles with CO, $H_2$, and $D_2$, cyclization is not accompanied by simultaneous transfer of the *o*-hydrogen to the double bond.

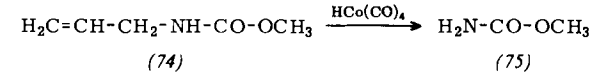
## E. Limitations of the Ring-Closure Reaction

A number of compounds having the structural formulae A=B–C–Z–H and A=B–C–C–Z–H do not react in accordance with Schemes (g) or (h). Thus unsaturated thiols give only traces of thiolactones, the principal products being polymers [90]. This is not surprising, since unsaturated thiols are well known for their thermal instability [91]. Moreover, thiols undergo a number of other reactions with carbon monoxide [92], and sulfur compounds also form complexes with the carbonyl catalyst [93–101a].

Acrylic acid and methacrylic acid polymerize under the conditions required for ring closure [90]; long-chain unsaturated acids such as *(71)* isomerize, and lactones such as *(72)* and *(73)* are then formed by intramolecular addition of the carboxyl groups to the double bond.



Unsaturated sulfonamides are recovered unchanged at the temperatures normally used for the ring closure, and decompose at temperatures above 300 °C [90]. Allylureas undergo thermal decomposition to give a large number of products [45]. Allylurethanes such as *(74)* react with hydrogenolysis of the C–N bond to form carbamates *(75)* and a number of unidentified products [45].



The reaction of aromatic aldoximes does not proceed in the same manner as that of the ketoximes, but leads by a Beckmann rearrangement to carboxamides. *Murahashi* [38] reported that this Beckmann rearrangement in the presence of hydrogen carbonylmetallates is confined to aromatic aldoximes, whereas aliphatic aldoximes are hydrogenated. It was later shown, however, that aliphatic aldoximes also undergo the Beckmann rearrangement. Thus the reaction of butyraldehyde oxime led to 38 % of butyramide and 23 % of 2-propyl-3,5-diethylpyridine [102].

Diethyl allylmalonate, ethyl allylacetoacetate, and ethyl allylcyanoacetate do not give cyclic ketones; the reactions of these compounds lead only to migration of the double bond and to hydrogenation by hydrogen transfer [90]. Whereas the failure of the reaction with unsaturated thiols, acids, urethanes, ureas, and aldoximes must be attributed to side-reactions, with the three allyl compounds mentioned above it is due rather to the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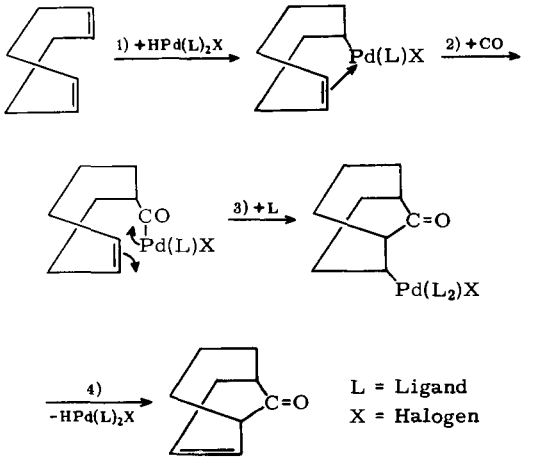
decrease in the electron density on the atom Z [see Equation (m)], with the result that the nucleophilic attack on the cobaltacylium cation is no longer possible.

## F. Appendix

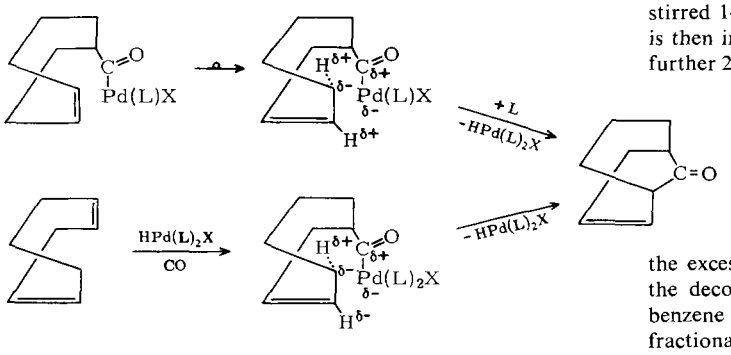
A few months after completion of this paper, *Brewis* and *Hughes*[103] described a related reaction.

1,5-Cyclooctadiene reacts in tetrahydrofuran at 180 °C and a CO pressure of 1000 atm in the presence of 1 % of diiodobis-(tributylphosphine)palladium(II) to give bicyclo[3.3.1]non-2-en-9-one in 40–45 % yield; 1,3-cyclooctadiene is also obtained in 45–50 % yield.

The authors propose the reaction sequence 1)–4). Steps 1) and 2) of this scheme correspond to the ring-closure mecha-




nism suggested in our own work. The formation of 1,3-cyclooctadiene shows the occurrence of isomerization, and it seems possible that instead of steps 3) and 4), the reaction proceeds by the mechanism indicated by Equations (m) to (o) (Section D) in accordance with step 5).




## G. Experimental Procedures

*Succinimide (2) from Acrylamide*[33]

Acrylamide (760 g, stabilized with 7 g of hydroquinone) and 60 g of $Co_2(CO)_8$ are dissolved in 5 *l* of tetrahydrofuran and heated to 200 °C over a period of 1 h in a magnetically stirred 10-*l* autoclave under 160 atm of CO. When the temperature reaches 200 °C, the CO pressure is increased to 300 atm and the mixture is stirred for a further 2 h. When the system has cooled to room temperature, the excess of CO is blown off; the mixture is refluxed for 1 h in a 10-*l* flask and nitrogen is constantly bubbled through to remove residual CO and to destroy the cobalt catalyst. The decomposition products of the catalyst are filtered off, the solvent is removed by distillation, and the crude product is fractionated in vacuum. Yield: 864 g (82 %); b.p.122–127 °C/0.6 mm Hg; m.p.125 °C.

*N-Methylsuccinimide (4a) from N-Methylacrylamide*[33]

A solution of 54 g of *N*-methylacrylamide in 250 g of thiophene-free benzene is carbonylated in the presence of 7.5 g of $Co_2(CO)_8$ in a magnetically stirred autoclave at 200 °C and under a CO pressure of 300 atm. After 4 h, the mixture is cooled to room temperature and the excess of carbon monoxide is blown off. The reaction mixture is then refluxed for 1 h in a current of nitrogen to ensure complete decomposition of the cobalt catalyst, and the decomposition products are filtered off. Benzene is distilled off in vacuum, and the crude product is distilled over a column. Yield: 67.5 g (94 %); b.p. 90–100 °C/1–2 mm Hg; m.p. 68–69 °C.

*2-Pyrrolidone from Allylamine*[35]

A solution of 50 g of allylamine and 2.9 g of $Co_2(CO)_8$ in 250 ml of benzene is heated to 280 °C under 150 atm of CO in a magnetically stirred 0.5-*l* autoclave. The CO pressure is increased to 300 atm, and the mixture is stirred for a further 2 h. When the system has cooled to room temperature, the excess CO is blown off. The mixture is refluxed for 30 min in a stream of nitrogen to destroy the cobalt catalyst, and benzene and unchanged allylamine are distilled off. The allylamine content of the benzene solution determined by gas chromatography corresponds to a conversion of 87 %. Distillation of the crude product yields 39 g of 2-pyrrolidone (52 %); m.p. 120–122 °C.

*N-Methyl-2-pyrrolidone from N-Methylallylamine*[35]

A mixture of 100 g of *N*-methylallylamine, 33 g of $Co_2(CO)_8$, and 500 g of benzene is heated to 250 °C in a magnetically stirred 1-*l* autoclave under 150 atm of CO. The CO pressure is then increased to 300 atm and the mixture is stirred for a further 2 h. When the system has cooled to room temperature, the excess of CO is blown off; the products resulting from the decomposition of the catalyst are filtered off, and the benzene is removed by distillation. The crude product is fractionated in vacuum. Yield: 109 g (78 %); b.p. 76–78 °C/10 mm Hg; $n_D^{20} = 1.4690$. 4 g (3 %) of *N*-methyl-*N*-allylformamide is obtained as a by-product.

*α,β,β-Trimethyl-γ-butyrolactone (30a) and γ,γ-Dimethyl-δ-valerolactone (31a) from 2,2-Dimethyl-3-buten-1-ol*[36]

A solution of 30 g of 2,2-dimethyl-3-buten-1-ol and 3.5 g of $Co_2(CO)_8$ in 130 ml of benzene is heated to 250 °C in a magnetically stirred autoclave under 150 atm of CO; the CO pressure is then increased to 300 atm. Samples are taken at 30 minute intervals by means of a steel capillary tube dipping into the liquid phase, and analysed by gas chromatography. When the starting material can no longer be detected in the sample, the autoclave is cooled to room temperature and the excess of CO is blown off. The reaction mixture is refluxed for 1 h in a current of nitrogen to decompose the catalyst,

[103] *S. Brewis* and *P. R. Hughes*, Chem. Commun. *1966*, 6.

and the decomposition products are filtered off. The benzene is removed by distillation, and the crude product left is vacuum distilled (b.p. 75–125 °C/10 mm Hg). Gas-chromatographic analysis shows that this fraction (29 g) contains α,β,β-trimethyl-γ-butyrolactone (51 % yield) and 18 % of γ,γ-dimethyl-δ-valerolactone (14 % yield). These lactones can be separated by preparative gas chromatography through Apiezon L on Chromosorb R (42/60 mesh).

*2-Phenylphthalimidine (41a) from Benzylidenaniline* [37]

A solution of 20 g of benzylidenaniline and 1.0 g of $Co_2(CO)_8$ in 100 g of benzene are heated for 1 h at 325 °C with constant stirring in a silvered 0.4-*l* autoclave under 200 atm of CO. The system is cooled to room temperature. Filtration of the product (total weight 111.5 g) yields 17.5 g of solid 2-phenylphthalimidine; a further 1.7 g is obtained by concentration of the benzene solution. Yield: 19.2 g (83 %); m.p. 163–164 °C.

*N-Phenylphthalimidine (41a) from Benzaldehyde Phenylhydrazone* [28]

Benzaldehyde phenylhydrazone (8 g) in benzene is carbonylated in a 0.28-*l* rocking autoclave for 2.2 h at 230 to 240 °C and under 250 atm of CO in the presence of $Co_2(CO)_8$. The decrease in pressure at 20 °C is 6.3 atm. When the reaction is complete, 1 g of a blue-black organocobalt complex is filtered off, and the catalyst is destroyed by heating to 70 °C. The solution is filtered once more, and the solvent is distilled off in vacuum. The residue is recrystallized twice from ethanol; the product is 4.2 g (50 %) of *N*-phenylphthalimidine (m.p. 166.5–167.5 °C).

*3-Phenylphthalimidine (54a) from Benzophenone Oxime* [39]

A $CO/H_2$ mixture (98.5:1.5) is introduced at a pressure of 145 atm into a glass-lined autoclave containing 14.1 g (0.07 mole) of benzophenone oxime, 7 g (0.02 mole) of $Co_2(CO)_8$, and 25 ml of thiophene-free benzene. When the autoclave is heated to 250 °C, the pressure increases to 285 atm. After 6 h, the system is cooled to room temperature. The cobalt catalyst is destroyed by refluxing (70 to 80 °C), and the benzene is distilled off in vacuum. The solid residue is extracted three times with 100 ml portions of ether. When the ether is distilled off, it leaves 2 g of a green syrupy substance, the melting point of which is about −10 °C. The ether-insoluble residue is extracted with hot chloroform, and gives 11.6 g (80 %) of 3-phenylphthalimidine. After recrystallization from ethanol, the product melts at 218–220 °C.

*3-Phenyl-2-(N'-phenylcarbamoyl)phthalimidine (59) from Benzophenone Phenylhydrazone* [40]

A solution of 7 g (0.023 mole) of benzophenone phenylhydrazone and 2 g (0.006 mole) of $Co_2(CO)_8$ in 50 ml of anhydrous benzene is subjected to a CO pressure of 140 atm. The solution is heated at 230 to 240 °C for 190 min, with constant stirring. The autoclave is allowed to cool (*e.g.* overnight), and the excess of gas is then blown off. The product consists of a dark brown solution and 6 g (71 %) of a yellow solid. When recrystallized twice from 75 % acetic acid, the solid gives 3-phenyl-(*N'*-phenylcarbamoyl)phthalimidine (white needles, m.p. 211–214 °C).

*2-Phenylindazolone (68a) from Azobenzene* [44]

A solution of 5 g of azobenzene and 1 g of $Co_2(CO)_8$ in 25 ml of benzene is heated in a 0.1-*l* stainless-steel autoclave to 180–190 °C under a CO pressure of 150 atm. The autoclave is shaken for 4 h and then cooled to room temperature. Approximately 3 g of a solid product precipitates from the benzene solution. After the catalyst has been decomposed and the benzene removed, 1.5 g of azobenzene is recovered. The solid product is treated with 5 % aqueous NaOH and the solution filtered. The component insoluble in NaOH consists mainly of diphenylurea (0.65 g, 16 %; m.p. 240 °C) and a little of the lactone of 2-(3-hydroxyindazol-2-yl)benzoic acid (m.p. 296 °C). The alkaline solution is acidified with HCl or $H_2SO_4$ or by the introduction of $CO_2$. The white crystalline product that precipitates is collected and recrystallized from alcohol. The alcohol-insoluble quinazolone (0.8 g, 17.5 %) remains behind. From the alcoholic solution 2.8 g (49.1 %) of 2-phenyl-indazolone crystallize as colorless needles (m.p. 204 °C).

*3-Phenyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (69a) from Azobenzene* [44]

A mixture of 5 g of azobenzene, 2 g of $Co_2(CO)_8$, and 45 ml of benzene is heated for 30 min at 220–230 °C under 150 atm of CO. When the solution is cooled to room temperature, 5.2 g of a crystalline substance precipitates; this precipitate is filtered off. The filtrate is refluxed on a water bath to decompose the catalyst. The inorganic components are filtered off; the solution then contains 0.1 g of the lactone of 2-(3-hydroxyindazol-2-yl)benzoic acid. The crystals are treated with 5 % aqueous NaOH, in which 0.7 g (12.1 %) of the solid is insoluble (diphenylurea). The soluble material can be reprecipitated from the solution by acidification with $CO_2$, HCl, or $H_2SO_4$. The white crystalline product obtained in this way is 3-phenyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (m.p. 275 °C).

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# New Methods in Preparative Organic Chemistry VI[*]

## Syntheses of Thiocarboxamides

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*Methods for the preparation of thiocarboxamides are described with special reference to progress achieved in the last few years. The discussion is arranged according to the eight most important reaction types.*

1. Reaction of nitriles with hydrogen sulfide and thiols
2. Reaction of imidic acid derivatives with hydrogen sulfide and thiols
3. Sulfurization of amides
4. Addition of nucleophiles to isothiocyanates
5. The Willgerodt-Kindler reaction
6. Thioacylation of amines
7. Cleavage of heterocycles
8. Rearrangement of the benzenesulfonates of ketoximes
9. Procedures

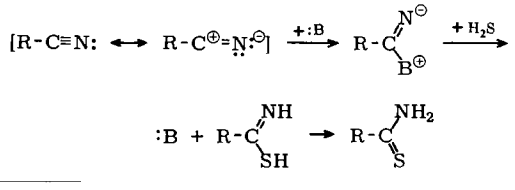
The chemistry of thiocarboxamides has been developing rapidly for some 25 years. The compounds have many technical applications, *e.g.* as vulcanization promoters [1–3], as metal deactivators in petrochemistry [4], in pest control [5–7a], and as pharmacologically important substances [8–14]. The reader is referred to the reviews [15–18] for surveys of the earlier literature.

Departure from the division according to reaction types is occasionally made to refer to the preparation of individual thiocarboxamides when it seems appropriate in view of the nature of a reaction. The review is generally confined to syntheses in which a thioamide is formed or is directly involved. Thioureas and thiourethanes are not discussed.

### 1. Reaction of Nitriles with Hydrogen Sulfide and Thiols

The synthesis of thiocarboxamides from nitriles is one of the first known. *Völckel* [19] treated nitriles with hydrogen sulfide as early as 1841. The reaction requires high hydrogen sulfide concentrations; it is catalysed by bases, and is generally favored by the exclusion of water [20–20c].

Water-soluble sulfides or polysulfides can be used instead of hydrogen sulfide [20d]. The base-catalysed addition of hydrogen sulfide to nitriles could proceed in accordance with Equation (a).



(a)

[*] The papers in the preceding series have been published in three volumes by Verlag Chemie, Weinheim/Bergstr., English edition: Academic Press, New York – London. Volumes IV and V are in preparation.

[1] US-Pat. 2875202 (Feb. 24th, 1959), Cyanamid, inventors: *F. A. V. Sullivan* and *S. A. J. Westerback*, Chem. Abstr. *53*, 14, 122 (1959).

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[20] *K. Kindler*, Liebigs Ann. Chem. *431*, 187 (1923).

[20a] East German Pat. 34198 (Dec. 5th, 1965), inventors: *D. Eilhauer*, *W. Hoefling*, *G. Reckling*, and *F. Andreas*; Chem. Abstr. *63*, 13222 (1965).

[20b] Brit. Pat. 980997 (Jan. 20th, 1965), Roumanian Ministry for Petro- and chem. Industry, Chem. Abstr. *63*, 13221 (1965).

[20c] French Pat. 1352839 (Jan. 13th, 1964), Leuna-Werke.

[20d] Austrian Pat. 241461 (July 26th, 1965), Richter, Gedeon, Vegyeszeti Gyar R. T., inventors: *O. Fuchs*, *V. Senkariak*, *A. Nemes*, *A. Lazar*, and *T. Somogyi*.

Suitable catalysts, apart from ammonia, include aliphatic amines, pyridine, alkoxides, and potassium hydrogen sulfide[20–21a]. *Fairfull*, *Lowe*, and *Peak*[22] obtained very good yields by addition of hydrogen sulfide with hydrogen sulfide. *O*-Ethyl thioacetate *(5)* was identified by gas chromatography and mass spectrometry.

Some examples of thiocarboxamides prepared in accordance with Equation (a) are given in Table 1.

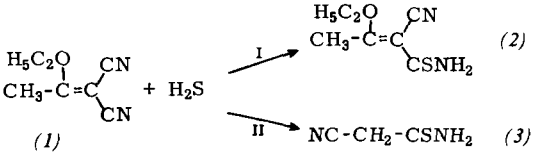
Table 1. Thiocarboxamides from nitriles and hydrogen sulfide, according to Equation (a).

| Compd. | Thiocarboxamide | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|
| *(6)* | 3-$C_2H_5O$–$C_6H_4$–$CSNH_2$ | 75–77 | 100 | [28] |
| *(7)* | 1,4-$(CSNH_2)_2$–$C_6H_4$ | 263 | 94 | [29] |
| *(8)* | 4-$CH_3SO_2$–$C_6H_4$–$CSNH_2$ | 205–206 | 100 | [30] |
| *(9)* | 2-Cl–$C_6H_4$–$CSNH_2$ | 57 | 100 | [22] |
| *(10)* | $CF_3$–$CSNH_2$ | 42–43 | 37 | [31] |
| *(11)* | $H_2NCS$–$(CF_2)_2$–$CSNH_2$ | 112–114 | 40 | [32] |
| *(12)* | $C_6H_5$–$CH_2O$–CO–$CH_2$–$CSNH_2$ | 70–71 | 80 | [32a] |
| *(13)* | $(C_2H_5)_2C(CSNH_2)_2$ | 195 | 93 | [33] |
| *(14)* | $C_6H_5$–NH–N=C(CN)–$CSNH_2$ | 211–213 | 88 | [33a] |
| *(15)* | $(CH_3)_2N$–CH=C(CN)–$CSNH_2$ | 200–203 | 72 | [34] |
| *(16)* [a] | $H_2NCS$–$C_6H_4$–$O(CH_2)_x$–O–$C_6H_4$–$CSNH_2$ | – | 92–98 | [35] |
| *(17)* [b] | RCO–NH–CS–NH–$C_6H_4$–$CSNH_2$ | – | 87–98 | [36, 36a] |

[a] x = 3 to 10; [b] from the nitrile RCO–NH–CS–NH–$C_6H_4$–CN with R = $C_6H_5$, *p*-Cl–$C_6H_4$, *p*-$CH_3O$–$C_6H_4$, *p*-n-$C_4H_9O$–$C_6H_4$.

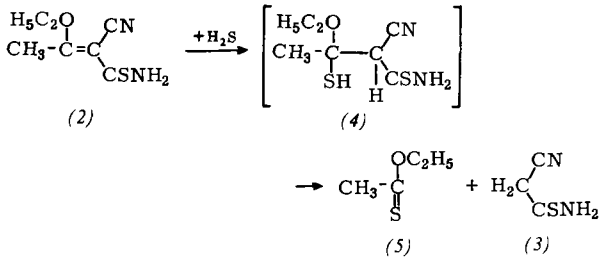
to aromatic nitriles in the presence of pyridine and triethylamine. *Kindler* measured the rates of reaction of several aromatic nitriles with hydrogen sulfide in the presence of sodium alkoxide[23].

Aliphatic nitriles often react very slowly and give poor yields unless the reaction is carried out at elevated temperatures and pressures[24–26a]. Aliphatic nitriles with several substituents exhibit interesting behavior[27]. 1-Ethoxyethylidenemalonodinitrile *(1)* can react with hydrogen sulfide to give different products, depending on the solvent. The product obtained in benzene (route I) is 2-cyano-3-ethoxythiocrotonamide *(2)*, whereas that obtained in ethanol (route II) is cyanothioacetamide *(3)*.



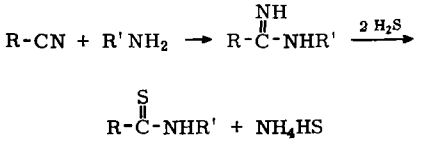
*(1)* *(2)* *(3)*

*McCall*'s explanation for this difference is that the same product *(2)* is initially formed in both solvents. This product is insoluble in benzene and precipitates; in hot ethanol, on the other hand, small quantities dissolve and react further



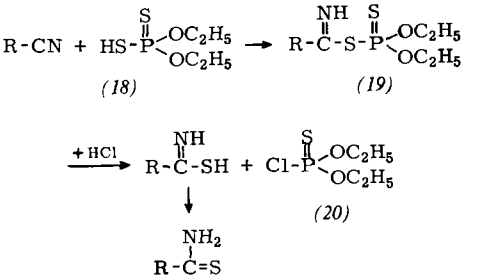
*(2)* *(4)* *(5)* *(3)*

This method was extended by *Kindler*[20] and *Hanford*[37] to permit the preparation of *N*-substituted thiocarboxamides by addition of hydrogen sulfide to nitriles in the presence of primary amines [Equation (b)].



(b)

Very good results are obtained by the addition of *O,O'*-diethyl dithiophosphate *(18)* (readily obtainable from ethanol and phosphorus pentasulfide) to nitriles[38]. The S–P bond in the adduct *(19)* is cleaved by hydrogen chloride.



*(18)* *(19)* *(20)*

[21] *U. Schmidt*, Chem. Ber. *92*, 1171 (1959).

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[26] *M. Erne* and *H. Erlenmeyer*, Helv. chim. Acta *31*, 652 (1952).

[26a] *K. A. Jensen*, *H. R. Baccaro*, and *O. Buchardt*, Acta chem. scand. *17*, 163 (1963).

[27] *M. A. McCall*, J. org. Chemistry *27*, 2433 (1962).

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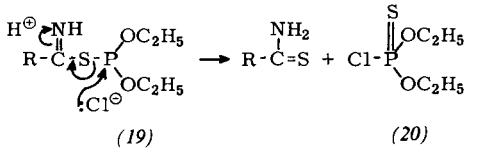
The cleavage of the S–P bond possibly is introduced by attack of the proton on the imino group[39]. This would explain the fact that acyl cyanides cannot be converted into α-oxothiocarboxamides by this method, as our own experiments have shown, since withdrawal of electrons by the α-keto group opposes the attack of the proton on the imino group. If this were the first step of the reaction, the scheme proposed in[38] could be modified in such a way that the thiocarboxamide is formed directly from *(19)*.



*(19)* *(20)*

Some thiocarboxamides can be prepared in very good yields in this way, as can be seen from Table 2. $CD_3$–$CSNH_2$ prepared by this method from $CD_3CN$ (D-content 99%) still contains 89% D attached to carbon[40a].

Table 2. Thiocarboxamides from nitriles and *O,O'*-diethyl dithiophosphate *(18)*.

| Compd. | Thiocarboxamide | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|
| *(21)* | $CH_3$–$CSNH_2$ | 107.5–108.5 | 84 | [38] |
| *(22)* | $C_6H_5$–$CSNH_2$ | 115–116 | 90 | [38] |
| *(23)* | $C_6H_5CH_2$–$CSNH_2$ | 97.8–98 | 82 | [38] |
| *(24)* | $ClCH_2$–$CSNH_2$ | 78–79 | 80 | [38] |
| *(25)* | $Cl_3C$–$CSNH_2$ | 98–100 | 80 | [38] |
| *(26)* | $C_2H_5O$–CO–$CH_2$–$CSNH_2$ | 30–31 | 54 | [40] |
| *(27)* | $CH_3OCH_2$–$CSNH_2$ | 63–64 | 29 | [40] |
| *(28)* | 2,6-Cl,F–$C_6H_3$–$CSNH_2$ | – | 42 | [5] |
| *(29)* | 2,6-Cl,I–$C_6H_3$–$CSNH_2$ | 136–137 | 71 | [5] |
| *(30)* | 2,4-$Cl_2$–$C_6H_3$–$CSNH_2$ | 95–96 | 73 | [5] |
| *(31)* | 2,6-Cl($C_6H_5S$)–$C_6H_3$–$CSNH_2$ | 180–181 | 20 | [5] |

Preparation with the aid of *(18)* is at present the only method for the synthesis of chlorothioacetamide *(24)*, since the addition of hydrogen sulfide to chloroacetonitrile *(32)* leads first to a sulfide *(33)*, which then reacts further to the bis-thioamide *(34)*.

$$2\ ClCH_2CN + H_2S + 2\ NH_3 \longrightarrow S(CH_2CN)_2 + 2\ NH_4Cl$$

*(32)* *(33)*

$$S(CH_2CN)_2 + 2\ H_2S \longrightarrow H_2N\text{-}\underset{\underset{S}{\|}}{C}\text{-}CH_2\text{-}S\text{-}CH_2\text{-}\underset{\underset{S}{\|}}{C}\text{-}NH_2$$

*(33)* *(34)*

The reaction of nitriles with thioacetamide *(21)* instead of hydrogen sulfide has gained some importance; the thiocarboxamides are probably formed in accordance with Equation (c)[41–41b].

$$R\text{-}CN + CH_3\text{-}CSNH_2 \rightleftharpoons R\text{-}\underset{\underset{NH}{\|}}{C}\text{-}S\text{-}\underset{\underset{NH}{\|}}{C}\text{-}CH_3 \quad (c)$$

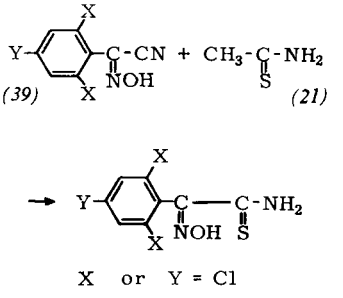
*(21)*

$$\rightleftharpoons R\text{-}\underset{\underset{S}{\|}}{C}\text{-}NH_2 + CH_3CN$$

The formation of the thiocarboxamide is favored by removal of acetonitrile from the equilibrium. The advantage of this method is that it can be used for the preparation of thiocarboxamides from nitriles and reducible substances. Some examples are given in Table 3. Halogenated α-cyanobenzaldoximes such as *(39)* can be converted into the α-thiocarbamoylbenzaldoximes by this method[7].

Table 3. Thiocarboxamides from nitriles and thioacetamide *(21)*, in accordance with Equation (c).

| Compd. | Thiocarboxamide | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|
| *(35)* | *p*-$NO_2$–$C_6H_4$–$CSNH_2$ | 158.5–159.5 | 83 | [41] |
| *(36)* | *p*-$CH_3O$–$C_6H_4$–$CSNH_2$ | 148.5–149.5 | 87 | [41] |
| *(37)* | $CH_2(CSNH_2)_2$ | 211–212 | 63 | [41] |
| *(38)* | $H_2NCS$–$(CH_2)_4$–$CSNH_2$ | 178.5–179.5 (decomp.) | 78 | [41] |



*(39)* *(21)*

X or Y = Cl

On the other hand, for the reaction with hydrogen sulfide of nitriles containing hydroxyl groups, the OH groups must first be protected by acylation[42,43]. Keto groups such as that in *(40)* are readily converted into thioxo groups in acidic solution[44].

$$R\text{–}CO\text{–}CH_2\text{–}CONHR' + H_2S \xrightarrow{HCl}$$

*(40)* $R\text{–}CS\text{–}CH_2\text{–}CONHR + H_2O$

This reaction had previously been applied by *Mitra*[45] to acetoacetic ester.

The base-catalysed conversion of ketones into thiones by treatment with hydrogen sulfide was developed by *Mayer et al.* into a useful preparative method[46]. *Asinger* and *Gentz*[47] made the interesting observation that the previously unknown primary α-oxothiocarboxamides *(41)* are formed from acyl cyanides and hydrogen sulfide in ether in the presence of triethylamine. Some examples are given in Table 4.


[38] German Published Pat. Appl. 1111172 (Feb. 1st, 1962), Farbenfabriken Bayer, inventors: *H.-G. Schicke* and *G. Schrader*; Chem. Zbl. *1963*, 291.

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[40] *W. Walter* and *K.-D. Bode*, unpublished.

[40a] *W. Walter* and *H. P. Kubersky*, unpublished.

[41] *E. C. Taylor* and *J. A. Zoltewicz*, J. Amer. chem. Soc. *82*, 2656 (1960).

[41a] Jap. Pat. 6684/64 (May 7th, 1964), Yamanouchi Pharm. Co.

[41b] US-Pat. 3158623 (Nov. 24th, 1964), Abbott Laboratories, inventors: *A. M. von Esch* and *W. R. Shermann*, Chem. Abstr. *62*, 4008 (1965).

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[43] *J. F. Olin* and *T. B. Johnson*, Recueil Trav. chim. Pays-Bas *50*, 72 (1931).

[44] *J. Goerdeler* and *W. Mittler*, Chem. Ber. *96*, 944 (1963).

[45] *S. K. Mitra*, J. Indian chem. Soc. *10*, 491 (1933), Chem. Abstr. *28*, 1330 (1934).

[46] *R. Mayer, G. Hiller, M. Nitzschke*, and *J. Jentzsch*, Angew. Chem. *75*, 1011 (1963); Angew. Chem. internat. Edit. *2*, 370 (1963).

Table 4. α-Oxothiocarboxamides of the type R–CO–CS–$NH_2$ *(41)*

| Compd. | R | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|
| *(41a)* | $(CH_3)_3C-CH_2$ | 76 | 94 | [47] |
| *(41b)* | $(CH_3)_2CH-CH_2$ | 35 | 84 | [47] |
| *(41c)* | $(CH_3)_3C$ | 85.5–87 | 35 | [40] |
| *(41d)* | $C_6H_5$ | 97 | 94 | [47a] |
| *(41e)* | $p$-$CH_3O-C_6H_4$ | 93 | 75 | [40] |
| *(41f)* | $CH_3-(CH_2)_2$ | 56–57 | 5.4 | [47b] |

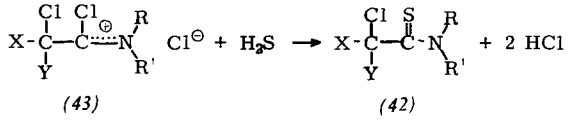
A possible reason for the different courses of the reactions observed by *Mayer* and by *Asinger* is that, owing to the polarization of the nitrile as shown in Equation (a), the carbonyl group cannot attain its normal polarization, so that the nitrile C-atom becomes the strongest electrophilic center in the molecule.

## 2. Reaction of Imidic Acid Derivatives with Hydrogen Sulfide and Thiols

The reaction of imidoyl chlorides with hydrogen sulfide was described almost simultaneously by *Bernthsen* [48], *Leo* [49], and *Wallach* [50].

$$R-C(NR)Cl + H_2S \rightarrow R-CS-NHR + HCl$$

This method has led to the preparation of many thiocarboxamides that could not previously be prepared. Thus *Speziale* and *Smith* [51] obtained a number of new α-chlorothioacetamides *(42)* by reaction of the immonium chloride *(43)* with hydrogen sulfide. Some examples are given in Table 5.

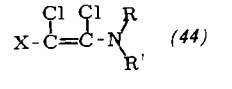


*(43)* *(42)*

Table 5. α-Chlorothioacetamides of the type *(42)* from the immonium chlorides *(43)* [51].

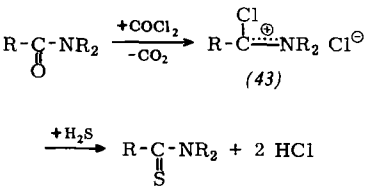
| Compd. | X | Y | R | R′ | M.p. [°C] | Yield [%] |
|---|---|---|---|---|---|---|
| *(42a)* | H | H | $C_6H_5$ | $C_6H_5$ | 140–147 (decomp.) | 88 |
| *(42b)* | H | H | $CH_3$ | $C_6H_5$ | 38–39.5 | 34 |
| *(42c)* | H | Cl | $CH_3$ | $C_6H_5$ | 103 | 60 |
| *(42d)* | H | Cl | $C_2H_5$ | $C_2H_5$ | *oil* | 73 |
| *(42e)* | Cl | Cl | $CH_3$ | $C_6H_5$ | 71–72 | 63 |
| *(42f)* | Cl | Cl | $C_2H_5$ | $C_2H_5$ | oil | 56 |

The immonium chlorides *(43)* were obtained by addition of hydrogen chloride to 1,2-dichloro- *(44a)* and 1,2,2-trichlorovinylamines *(44b)*.



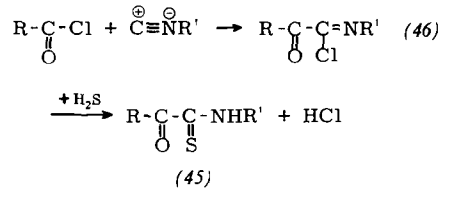
*(44)*

The immonium chlorides leading to the trichlorothioacetamides are obtained by addition of chlorine to *(44a)* or *(44b)*. *N,N*-disubstituted carboxamides and phosgene also give immonium chlorides *(43)*, which then react in the usual manner [52].



*(43)*

The *N*-substituted α-oxothiocarboxamides *(45)*, which could not previously be prepared, have been obtained by a similar method [53] (see Table 6) [*].

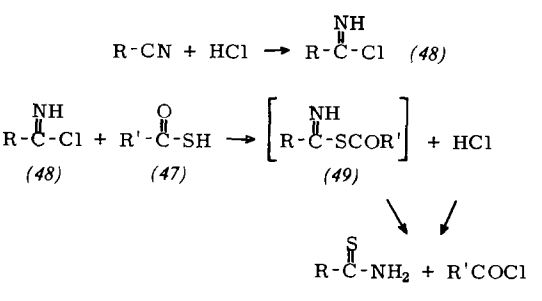


*(45)*

Table 6. *N*-Substituted α-oxothiocarboxamides *(45)* from *(46)*.

| Compd. | R | R′ | M.p. [°C] (B.p. [°C/mm Hg]) | Yield [%] | Ref. |
|---|---|---|---|---|---|
| *(45a)* | $p$-$NO_2-C_6H_4$ | $(CH_3)_2CH$ | 76–78 | 87 | [53] |
| *(45b)* | $CH_3$ | $(CH_3)_2CH$ | (104/11) | 85 | [53] |
| *(45c)* | $C_6H_5$ | $CH_3$ | (140/0.07) | 45 | [40] |
| *(45d)* | $CH(_3)_2CH$ | $(CH_3)_2CH$ | (40–41/11) | 75 | [40] |
| *(45e)* | $CH_3$ | $CH_3$ | (52/2) | 97 | [40] |
| *(45f)* | $p$-$NO_2-C_6H_4$ | c-$C_6H_{11}$ | 106–108 | 74 | [40] |

In *Ishikawa*'s method [54], nitriles are treated with thiocarboxylic *S*-acids *(47)* in the presence of hydrogen chloride. The initial product appears to be the imidoyl chloride *(48)*, which reacts with the thiocarboxylic acid *(47)*.



When thioacetic *S*-acid [*(47)*, R′ = $CH_3$] is used, an *N*-acetylthioamide may occur as a by-product, probably as a result of acetyl migration in *(19)* [55,56]. However, this rearrangement is avoided if the reaction is carried out at room temperature.


[47] *F. Asinger* and *F. Gentz*, Angew. Chem. *75*, 577 (1963); Angew. Chem. internat. Edit. *2*, 397 (1963).

[47a] *F. Asinger, W. Schäfer*, and *A. Saus*, Mh. Chem. *96*, 1278 (1965).

[47b] *F. Asinger* and *F. Gentz*, Mh. Chem. *96*, 1474 (1965).

[48] *A. Bernthsen*, Ber. dtsch. chem. Ges. *10*, 1238 (1877).

[49] *H. Leo*, Ber. dtsch. chem. Ges. *10*, 2133 (1877).

[50] *O. Wallach* and *H. Leo*, Ber. dtsch. chem. Ges. *9*, 1216 (1876).

[51] *A. J. Speziale* and *L. R. Smith*, J. org. Chemistry *28*, 3492 (1963).

[52] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Chem. Ber. *96*, 2671 (1963).

[53] *W. Walter* and *K.-D. Bode*, Angew. Chem. *74*, 694 (1962); Angew. Chem. internat. Edit. *2*, 510 (1962).

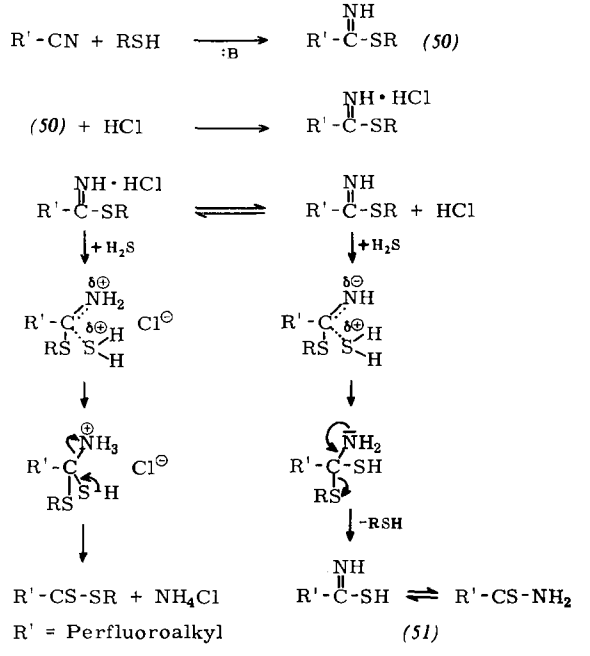
[54] *S. Ishikawa*, Sci. Papers Inst. physic. chem. Res. (Tokyo) *7*, 293 (1927), Chem. Abstr. *22*, 1343 (1928).


[*] Note added in proof: Oxo-α-dichloro compounds R–CO–$CCl_2$-R′ react with sulfur and primary amines to give monosubstituted α-oxothiocarboxamides in yields of 30–100%: *F. Asinger, A. Saus, H. Offermanns*, and *H.-D. Hahn*, Liebigs Ann. Chem. *691*, 92 (1966).

Amidines, also being imidic acid derivatives, give thiocarboxamides with hydrogen sulfide [48,57–60]. This reaction supports the proposed reaction scheme (a) for the base-catalysed addition of hydrogen sulfide to nitriles. If B is ammonia or an amine, the nitriles are first converted into amidines, which then add on hydrogen sulfide to form a thiocarboxamide. Amidines react with carbon disulfide at 100 °C to give thiocarboxamides [61–63].

$$R\text{–}C(NH)\text{–}NH_2 + CS_2 \rightarrow R\text{–}CS\text{–}NH_2 + HSCN$$

An interesting variant was discovered by *Brown* and *Pater* [64]. By addition of mercaptans to cyanoperfluoroalkanes, they obtained perfluoroalkylcarboximidic esters *(50)*, which react with hydrogen sulfide in acidic media to give perfluoroalkylthiocarboxamides *(51)*, together with dithio esters.




Finally, mention may be made of the esters of imidic acids, which also form thiocarboxamides on reaction with hydrogen sulfide. This method has not yet attained much importance, since imidic esters are generally prepared from the nitriles, which can themselves react with hydrogen sulfide. An interesting example, however, is the particularly useful laboratory preparation of dithiooxamide *(52)* from the ester *(53)*, which is easily accessible from cyanogen chloride and ethanol, and which reacts with hydrogen sulfide to give *(52)* in 90% yield [65].

$$C_2H_5O\text{–}C(=NH)\text{–}C(=NH)\text{–}OC_2H_5 \xrightarrow{+H_2S} H_2N\text{–}C(=S)\text{–}C(=S)\text{–}NH_2 + 2\ C_2H_5OH$$

*(53)* *(52)*

Substituted dithiooxamides are readily obtainable from *(52)* and amines, as is shown in Section 6.

### 3. Sulfurization of Amides

The replacement of the oxygen in carboxamides by sulfur is a general method for the preparation of thiocarboxamides, since it also permits the synthesis of *N*-monosubstituted and N-disubstituted compounds from the readily obtainable amides. The most useful reagent for this replacement is phosphorus pentasulfide, which reacts in accordance with Equation (d) [*].

$$10\ R\text{–}CO\text{–}NH_2 + P_4S_{10} \rightarrow 10\ R\text{–}CS\text{–}NH_2 + P_4O_{10} \qquad (d)$$

This method was first used by *A. W. Hofmann* [66]. Other sulfurizing agents are discussed at length in [15–18]. Little use is made of these nowadays; in special cases, *e.g.* in the synthesis of thiocaprolactam, carbon disulfide [67] and carboxylic *S*-acids have proved useful. The latter appear to add specifically to *cis*-amides [68]. Low yields are obtained on fusion of amides with phosphorus pentasulfide [69]. Better results are obtained in dry, inert solvents with sufficiently high boiling points. The reaction time is then reduced, and undesirable side reactions, such as the reaction of the phosphorus pentoxide produced with unsubstituted thiocarboxamides, are avoided.

Methods have been devised for sulfurization in benzene, toluene, xylene, tetrahydrofuran, dioxane, and diethylene glycol diethyl ether [70–75]. The sulfurization of liquid amides is also possible in an excess of the amide as solvent [76, 77].

[55] *H. Behringer, L. Hauser*, and *K. Kohl*, Chem. Ber. *92*, 910 (1959).

[56] *H. Behringer* and *D. Weber*, Liebigs Ann. Chem. *682*, 197 (1965).

[57] *A. Bernthsen*, Liebigs Ann. Chem. *192*, 39 (1878).

[58] Ger. Pat. 1168897 (April 30th, 1964), BASF, inventors: *H. Weidinger* and *H. Eilingsfeld*.

[59] *D. Vorländer*, Ber. dtsch. chem. Ges. *24*, 803 (1891).

[60] *H. M. Woodburn, W. Patek*, and *E. L. Graminski*, J. org. Chemistry *23*, 319 (1958).

[61] *A. Bernthsen*, Liebigs Ann. Chem. *184*, 290 (1877).

[62] *A. Bernthsen*, Liebigs Ann. Chem. *197*, 341 (1879).

[63] *A. Bernthsen* and *H. Trompetter*, Ber. dtsch. chem. Ges. *11*, 1756 (1878).

[64] *H. C. Brown* and *R. Pater*, J. org. Chemistry *27*, 2858 (1962).

[65] Ger. Pat. 868908 (March 2nd, 1953), BASF, inventor: *E. Urbschat*.

[*] Note added in proof: Sulfurization of amides with phosphorus pentasulfide gives better yields in the presence of potassium thiophosphate: Jap. Pat. 9002/65 (May 11th, 1965); Zaidan Hogin Seisan Kaihatsu Kagaku Kenyusho.

[66] *A. W. Hofmann*, Ber. dtsch. chem. Ges. *11*, 340 (1878).

[67] *J. Prochazka*, Chem. Techn. *7*, 19 (1955).

[68] German Published Patent Appl. B 19761/12p (March 28th, 1952), BASF, inventors: *H. Behringer* and *G. F. Grunwald*; *F. Kleekamm*, Dissertation, Universität München, 1954.

[69] *A. Spilker*, Ber. dtsch. chem. Ges. *22*, 2767 (1869).

[70] *L. R. Cerecedo* and *J. G. Tolpin*, J. Amer. chem. Soc. *59*, 1660 (1937).

[71] Danish Pat. 57825 (May 3rd, 1939), I.G. Farben, Chem. Zbl. *1940*, II, 2960.

[72] *S. Gabriel*, Ber. dtsch. chem. Ges. *49*, 1110 (1916).

[73] US-Pat. 2682558 (June 29th, 1954), Du Pont, inventor: *W. R. Schmitz*, Chem. Abstr. *49*, 9029 (1955).

[74] Canad. Pat. 392513 (Nov. 12th, 1940), Winthrop Chemical Co., inventors: *K. Westphal* and *H. Andersag*, Chem. Abstr. *35*, 1413 (1941).

[75] *H. Behringer, M. Ruff*, and *R. Wiedemann*, Chem. Ber. *97*, 1732 (1964).

[76] *A. G. Pesina*, Zh. obshch. Khim. *9*, 804 (1939), Chem. Abstr. *34*, 425 (1940).

[77] *R. Willstätter* and *T. Wirth*, Ber. dtsch. chem. Ges. *42*, 1911 (1909).

A considerable improvement is obtained, however, by the use of pyridine[78,79]. In our experience, the pure thiocarboxamides are obtained in high yields in this solvent. Some examples are given in Table 7.

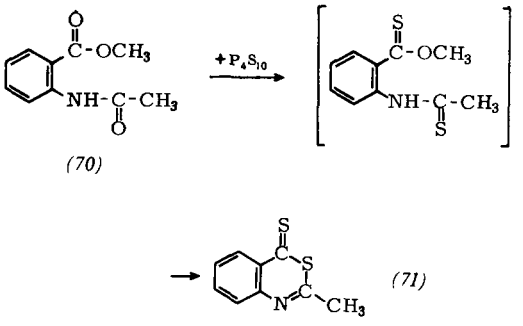
Table 7. Thiocarboxamides by sulfurization of amides with phosphorus pentasulfide in pyridine, in accordance with Equation (d).

| Compd. | Thiocarboxamide | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|
| *(54)* | $C_6H_5$–CH=CH–$CSNH_2$ | 142 | 56 | [80] |
| *(55)* | $C_6H_5$–CH=CH–$CSNHCH_3$ | 119 | 93 | [80] |
| *(56)* | $C_6H_5$–CH=CH–$CSNHC_6H_5$ | 128 | 59 | [80] |
| *(57)* | $C_6H_5$–CH=CH–$CSN(C_2H_5)_2$ | 54–55 | 59 | [80] |
| *(58)* | $C_6H_5$–CH=CH–$CSN(C_6H_5)_2$ | 231 | 33 | [80] |
| *(59)* | 2-Furyl-CH=CH–$CSNHCH_3$ | 102–103 | 90 | [80a] |
| *(60)* | $C_6H_5$–$CSNHC_6H_5$ | 101–102 | 73 | [79] |
| *(61)* | $CH_3$–$CSNHC_6H_5$ | 115–116 | 67 | [78] |
| *(62)* | $C_2H_5O$–CO–$CSN(CH_3)_2$ | 46–47 | 42 | [81] |
| *(63)* | $C_2H_5O$–CO–$CSNH_2$ | 58–60 | 58 | [81] |
| *(64)* | $Br^{\ominus}H_3\overset{\oplus}{N}$–$CH_2$–$CSNH_2$ | 158–159 | | [82] |
| *(65)* [a] | $Br^{\ominus}H_3\overset{\oplus}{N}$–$CH_2$–$CSNHC_6H_{13}$ | 220–221 | | [82] |
| *(66)* [a] | $Br^{\ominus}H_3\overset{\oplus}{N}$–$CH_2$–CS–piperidino | 175–176 | | [82] |
| *(67)* [a] | $Br^{\ominus}CH_3$–$CH(\overset{\oplus}{N}H_3)$–$CSNHC_2H_5$ | 207–208 | 83 | [82] |
| *(68)* [a] | $Br^{\ominus}H_3\overset{\oplus}{N}$–$CH_2$–$CH_2$–$CSNHC_6H_5$ | 171–172 | | [82] |
| *(69)* | 2-Furyl-$CSNHC_6H_5$ | 107–108 | 86 | [82a] |

[a] The compound was protected by benzyloxylation before sulfurization.

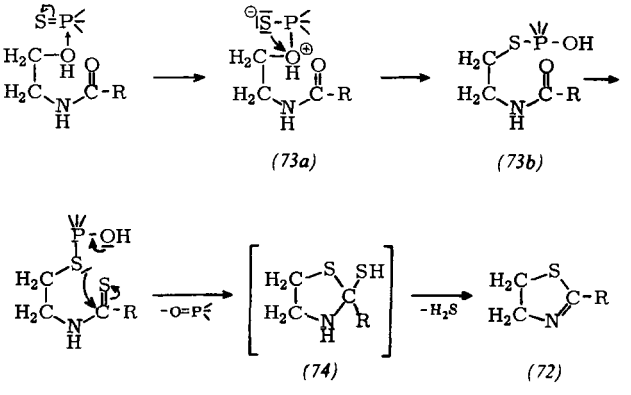
As in the preparation of thiocarboxamides from nitriles, the yields in the sulfurization of aromatic amines depend on the substituents. For example, 3- and 4-nitrobenzanilides give very good yields in the sulfurization, whereas the yields obtained with the corresponding aminobenzanilides are only moderate[83]. Unsubstituted amides often give very poor yields, because of further reaction to give nitriles, as mentioned above; in this case, however, the thiocarboxamides can often be obtained by the addition of hydrogen sulfide to the nitriles. The best yields are always obtained for *N*-monosubstituted thiocarboxamides. This reaction cannot be used with thermally unstable amides. Hydroxyl groups must be protected by acetylation before sulfurization[84,84a].

Ester groups generally are not attacked, as is shown by the sulfurization of the ethoxycarbonylthioformamides *(62)* and *(63)*[81,85]. An interesting exception to this rule was observed by *Legrand*[86] in the sulfurization of methyl *N*-acetylanthranilate *(70)*, in which sulfur is introduced into both the amide group and the ester group; the product cyclizes to give 2-methyl-4*H*-3,1-benzothiazine-4-thione *(71)*.



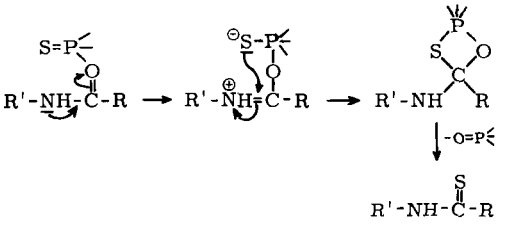
*(70)* *(71)*

Sulfurization of *N*-substituted amides with functional groups β to the nitrogen leads to 2-thiazolines *(72)*[87]. *Roggero* and *Metzger*[88] assume that the reaction proceeds by way of the intermediates *(73a)* and *(73b)*. The sulfurization of the amide group is followed by formation of *(74)*, which reacts further to form the thiazoline *(72)*.



*(73a)* *(73b)* *(74)* *(72)*

*Long* and *Tulley*[89] have proposed a similar scheme for the sulfurization of amides:



However, this mechanism has not yet been proved, since no intermediates have so far been isolated. The first attempts to elucidate the reaction mechanism were made by *Kindler*[20]; during the reaction of phosphorus pentachloride with *N*,*N*-dimethylbenzamide in cold carbon disulfide, this author isolated an oil, from which the amide is re-formed by hydrolysis, but which gives the thiocarboxamide when heated in an inert solvent. Thus the compound unites both reactants.

During an attempt to obtain 2-hydroxythiobenzamide by treatment of salicylamide in pyridine with phosphorus pentasulfide, we obtained a compound differing substantially from the desired product. It does not give the phenol color reaction with $FeCl_3$ solution, but after oxidation with hydro-

[78] Jap. Pat. 1710 (March 30th, 1951), Oriental Photo Ind., inventor: *K. Kikuchi*, Chem. Abstr. *47*, 4908 (1953).

[79] *E. Klingsberg* and *D. Papa*, J. Amer. chem. Soc. *73*, 4988 (1951).

[80] *N. Pravdić* and *V. Hahn*, Croat. chem. Acta *34*, 85 (1962), Chem. Abstr. *57*, 12377 (1962).

[80a] *N. Pravdić* and *V. Hahn*, Croat. chem. Acta *37*, 55 (1965).

[81] *W. Walter* and *K.-D. Bode*, Liebigs Ann. Chem. *660*, 74 (1962).

[82] *K. Jakopčić* and *V. Hahn*, Naturwissenschaften *51*, 482 (1964).

[82a] *V. Hahn*, *Ž. Stojanac*, *O. Ščedrov*, *N. Pravdić-Sladovic*, *S. Tomašić*, and *D. Emer*, Croat. chem. Acta *29*, 319 (1957).

[83] *H. Rivier* and *J. Zeltner*, Helv. chim. Acta *20*, 691 (1937).

[84] *G. Wagner* and *D. Singer*, Z. Chem. *2*, 306 (1962).

[84a] *M. Jančevska*, *K. Jakopčic*, and *V. Hahn*, Croat. chem. Acta *37*, 67 (1965).

[85] *A. Reissert*, Ber. dtsch. chem. Ges. *37*, 3708 (1904).

[86] *L. Legrand*, Bull. Soc. chim. France, *1960*, 337.

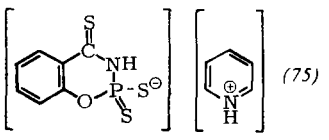
[87] *S. Tatsuoka*, *S. Rin*, and *K. Hirata*, Annu. Rep. Takeda Res. Lab. *9*, 17 (1950), Chem. Abstr. *46*, 2489 (1952).

[88] *J. Roggero* and *J. Metzger*, Bull. Soc. chim. France *1963*, 2553.

[89] *A. G. Long* and *A. Tulley*, J. chem. Soc. (London) *1964*, 1190.

gen peroxide it gives an olive-green color with $FeCl_3$, indicating the presence of a thiocarboxamide grouping[90]. This substance is only sparingly soluble in many organic solvents, but dissolves readily in hot water, dimethylformamide, and dimethyl sulfoxide. After the addition of hydrochloric acid, the compound decomposes when heated. Treatment of the decomposition product with picric acid gives a picrate with a melting point similar to that of pyridine; however, the pyridine cannot be removed by vacuum distillation. Reaction with ammonium molybdate solution shows that the substance contains phosphorus.

These observations, together with the elemental analysis, can be explained by the formation of an intermediate *(75)*.



*(75)*

This assumption is supported by the mass spectrum of the substance, which is shown schematically in Fig. 1.

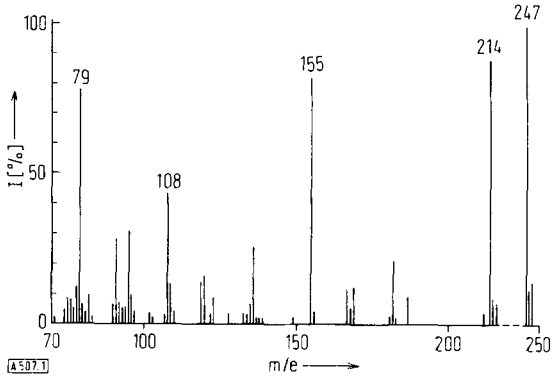
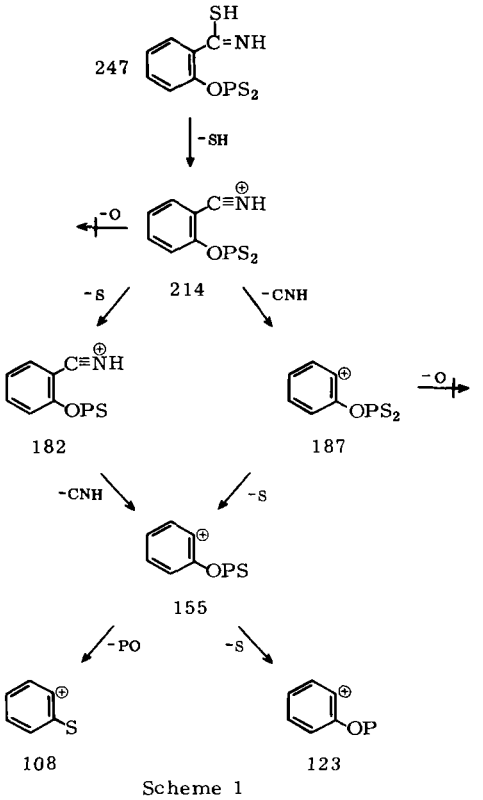



Fig. 1. Mass spectrum of substance *(75)*.




Scheme 1

[90] *W. Walter*, Liebigs Ann. Chem. *633*, 35 (1960).

The following decomposition sequence (Scheme 1) was constructed on the basis of the mass numbers: It must be assumed that the compound *(75)* first loses pyridine, with the result that the heterocyclic ring is opened. The compound formed in this way is assigned the mass number 274, so that further decomposition starts at this point.

The fragments corresponding to mass numbers 123 and 108 decompose further, with loss of OP and S, respectively, to form a fragment having the mass number 76. Other significant lines in the spectrum of Fig. 1 are that at mass number 95, due to the fragment $PS_2$, and that at mass number 79, due to pyridine. It can be concluded from these findings, and particularly from the presence of a line at mass number 123, that *(75)* contains a C–O–P linkage. The reaction therefore involves an intermediate such as *(73a)*, which may be stabilized by salt formation with pyridine. However, the line at mass number 108 also shows that the sulfurization has proceeded further under the conditions of measurement. Finally, further proof of the presence of a C–O–P linkage is provided by the infrared spectrum, in which an absorption band characteristic of this linkage appears at 1190 $cm^{-1}$ [92a].

## 4. Addition of Nucleophiles to Isothiocyanates

### a) Organometallic Compounds

Isothiocyanates react with Grignard compounds; subsequent hydrolysis under mild conditions leads to thiocarboxamides *(76)*.

$$RMgBr + R'NCS \rightarrow R{-}C(NR'){-}SMgBr \xrightarrow{H_2O} R{-}CS{-}NHR' + MgOHBr$$

*(76)*

This method was first used by *Sachs* and *Loevy*[91]. *Worrall*[92] later used it to prepare a large number of *N*-substituted thiovaleramides. In spite of the high yields and the relatively simple procedure, few publications deal with this reaction. A number of thiocarboxamides obtained by this method are given in Table 8 (in many of the earlier papers yields are not given).

Table 8. Thiocarboxamides *(76)* by addition of isothiocyanates to Grignard compounds.

| Compd. | R | R' | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|---|
| *(76a)* | n-$C_4H_9$ | *p*-$CH_3$-$C_6H_4$ | 69–70 | 100 | [92] |
| *(76b)* | n-$C_4H_9$ | *p*-$CH_3O$-$C_6H_4$ | 62–63 | | [92] |
| *(76c)* | n-$C_4H_9$ | *p*-Cl-$C_6H_4$ | 107.5–102 | | [92] |
| *(76d)* | n-$C_4H_9$ | *p*-Br–$C_6H_4$ | 112 | | [92] |
| *(76e)* | n-$C_4H_9$ | α-Naphthyl | 79–80 | | [92] |
| *(60)* | $C_6H_5$ | $C_6H_5$ | 101.5–102 | 65,88 | [19,94] |
| *(76f)* | $C_2H_5$ | $C_6H_5$ | 67–67.5 | | [91] |
| *(76g)* | $CH_3$ | *p*-Cl–$C_6H_4$ | 143 | | [93] |
| *(76h)* | Piperidino-$CH_2$-*o*-$C_6H_4$ | $C_6H_5$–$CH_2$ | 149–150 | 60 | [95] |
| *(76i)* | Piperidino-$CH_2$-*o*-$C_6H_4$ | α-Naphthyl | — | 40 | [95] |
| *(76j)* | *N*-Pyrrolidinyl-$CH_2$-*o*-$C_6H_4$ | $C_6H_5CH_2$ | 126 | 40 | [95] |

[91] *F. Sachs* and *H. Loevy*, Ber. dtsch. chem. Ges. *36*, 585 (1903).

[92] *D. E. Worrall*, J. Amer. chem. Soc. *47*, 2974 (1925).

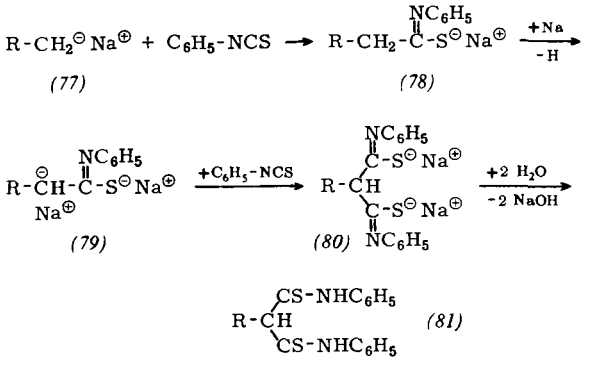
[92a] *W. Otting*: Spektrale Zuordnungstafel der Infrarot-Absorptionsbanden. Springer, Heidelberg 1963.

[93] *F. Sachs* and *H. Loevy*, Ber. dtsch. chem. Ges. *37*, 874 (1904).

[94] *G. Alliger*, *G. E. P. Smith*, *E. L. Carr*, and *H. P. Stevens*, J. org. Chemistry *14*, 962 (1949).

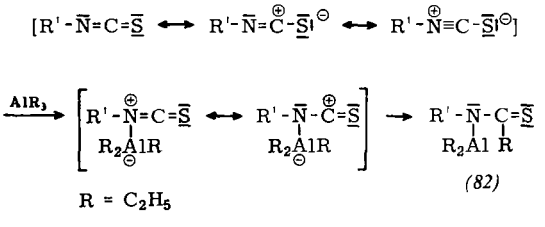
[95] *N. B. Mehta* and *J. Zupicich-Strelitz*, J. org. Chemistry *27*, 4412 (1962).

The reaction of alkylsodium compounds *(77)* with phenyl isothiocyanate leads to bifunctional thiocarboxamides *(81)* [96–99].

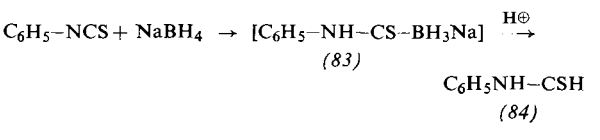


Thiobenzanilide *(60)* is obtained in a similar manner from phenyl-lithium and phenyl isothiocyanate [100].

*Reinheckel* and *Jahnke* [101] obtained a series of thiopropionamides by addition of $Al(C_2H_5)_3$ and $(C_2H_5)_{1.35}AlCl_{1.65}$ to aliphatic and aromatic isothiocyanates; these authors suggest the following mechanism [101a]:

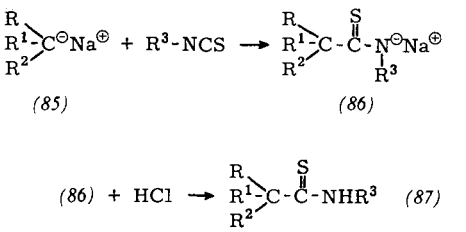


On hydrolysis of *(82)* with dilute acid, the thiocarboxamide is obtained in yields of 58 to 96%. An interesting reaction is that of phenyl isothiocyanate with sodium borohydride, which leads to the formation of thioformanilide *(84)* [102, 102a].



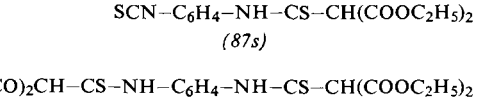
### b) CH Acids

The reaction of isothiocyanates with CH acids has become an important means of obtaining thiocarboxamides in very good yields. The CH acids are used in the form of their alkali-metal salts, as shown in Equation (e). Some examples are given in Table 9.

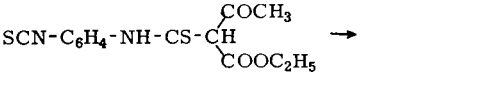


(e)

Sodiomalonic ester reacts with *p*-phenylene diisothiocyanate in anhydrous ethanol to give the sodium salts of the mono- and di-adducts; acidification of these yields diethyl *N*-(*p*-isothiocyanatophenyl)thiocarbomoylmalonate *(87s)* and diethyl *N,N'*-(*p*-phenylene)bis(thiocarbamoylmalonate) *(87t)*.



Sodioacetoacetic ester, on the other hand, gives only the mono-adduct, which decomposes in ethanol at room temperature to give ethyl acetate and ethyl *N*-(*p*-isothiocyanatophenyl)thiocarbamoylacetate *(87u)*. Ethyl *N*-arylmalonomonothioamides are readily obtainable in this way [113c].



The reaction of sodioacetylacetone with aryl isothiocyanates in absolute ethanol leads to *N,N'*-diaryldithiomalonodiamides [113d]. *Borisevich*, *Grabenko*, and *Pelkis* even obtained acetyldithiomalonodianilides *(87v)* by reaction of the sodium salts of acetylthioacetanilides with phenyl isothiocyanate [113e].

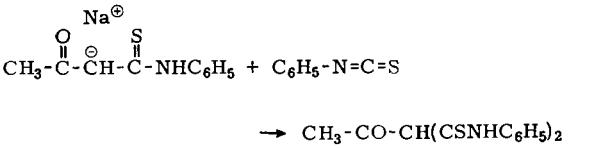



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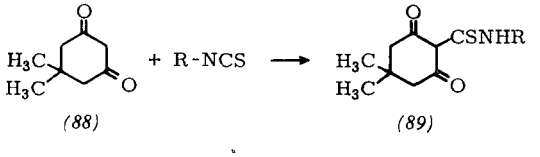
Table 9. Thiocarboxamides *(87)* by addition of CH acids *(85)* to isothiocyanates.

| Compd. | R | $R^1$ | $R^2$ | $R^3$ | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|---|---|---|
| *(87a)* | $H_2NCO$ | CN | H | $C_6H_5$ | 186–187 (decomp.) | 64 | [103] |
| *(87b)* | $H_2NCO$ | $H_2NCO$ | H | $C_6H_5$ | 193 (decomp.) | 37 | [103] |
| *(87c)* | $H_2NCO$ | $C_2H_5CO_2$ | H | $C_6H_5$ | 135–136 (decomp.) | 88 | [103] |
| *(87d)* | $H_2NCO$ | $CH_3CO$ | H | $C_6H_5$ | 159 (decomp.) | 75 | [103] |
| *(87e)* | $H_2NCO$ | $C_6H_5CO$ | H | $C_6H_5$ | 140 (decomp.) | 48 | [103] |
| *(87f)* | $C_2H_5CO_2$ | $C_2H_5CO_2$ | H | $C_2H_5$ | 51–52 | 60–80 | [40, 104–106] |
| *(87g)* | $C_2H_5CO_2$ | $C_2H_5CO_2$ | H | $C_6H_5$ | 60–60.5 | 84 | [113a] |
| *(87h)* | $C_2H_5CO_2$ | CN | H | $C_6H_5$ | 118–119 | 75 | [40, 107, 108] |
| *(87i)* | $CH_3CO$ | $CH_3CO$ | H | $C_6H_5$ | 107–108 | 70–80 | [40, 109, 110] |
| *(87j)* | $CH_3CO$ | $C_2H_5CO_2$ | H | $C_6H_5$ | 82–83 | 55 | [111] |
| *(87k)* | $H_3C-C(NH)$ | $CH_3CO$ | H | $C_6H_5$ | 163 (decomp.) | 61 | [112] |
| *(87l)* | $H_3C-C(NH)$ | $C_6H_5CO$ | H | $C_6H_5CO$ | 160 (decomp.) | 77 | [112] |
| *(87m)* | $H_3C-C(NH)$ | CN | H | $p$-$NO_2-C_6H_4$ | 218–221 | 78 | [112] |
| *(87n)* | $C_2H_5CO_2$ | $H_2N-C(OC_2H_5)$ | | $p$-$NO_2-C_6H_4$ | 148 (decomp.) | 85 | [103] |
| *(87o)* | $C_2H_5CO_2$ | $(H_2N)_2C$ | | $p$-$NO_2-C_6H_4$ | 166–168 (decomp.) | 78 | [103] |
| *(87p)* | $C_2H_5CO_2$ | $H_3C-C(NH_2)$ | | $C_6H_5CO_2$ | ≈130 (decomp.) | 60 | [113] |
| *(87q)* | $H_2NCO$ | $C_6H_5-C(NH_2)$ | | $p$-$NO_2-C_6H_4$ | decomp. > 200 | 63 | [113] |
| *(87r)* | $CH_3CO$ | $CH_3NH-CH$ | | $C_6H_5$ | 138–139 | 71 | [113b] |

Cyclic CH acids have also been used. *Bullock* and *Abraham* [114] prepared various substituted pyrrolethiocarboxanilides, some in very high yields. The addition of isothiocyanates to dimedone *(88)* in acetonitrile proceeds in yields of about 60% in the presence of a little alkali [115], whereas no reaction occurs in ethanol with phenyl isothiocyanate [113a].



*(88)* *(89)*

*(89a)* R = $C_6H_5$
*(89b)* R = $p$-Cl–$C_6H_4$
*(89c)* R = $p$-$NO_2$–$C_6H_4$
*(89d)* R = α-Naphthyl [115a]

Alkali-metal cyanides react with isothiocyanates to give *N*-substituted cyanothioformamides *(90)*, which form *N*-substituted dithiooxamides on reaction with hydrogen sulfide [116]. Sodium cyanide gives poorer yields than potassium cyanide [for examples of *(90)*, see Table 10].

$$KCN + R-NCS \rightarrow \underset{(90)}{R-NH-CS-CN} \xrightarrow{H_2S} \underset{(91)}{R-NH-CS-CS-NH_2}$$

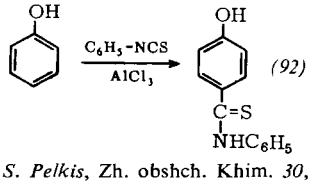
*Grabenko* and *Pelkis* treated alkoxyphenyl isothiocyanates with sodium or acetone cyanohydrin and obtained good yields of alkoxycyanothioformamides, which they converted into the alkoxyphenyldithiooxamides with hydrogen sulfide [117]. Some of the cyanothioformamides prepared in this way are listed in Table 10.

Table 10. Cyanothioformamides *(90)* by addition of isothiocyanates to cyanides.

| Compd. | R | M.p. [°C] | Yield [%] | Ref. |
|---|---|---|---|---|
| *(90a)* | $C_6H_5$ | 82 | 82 | [116] |
| *(90b)* | $p$-$CH_3O-C_6H_4$ | 123 | 79 | [116] |
| *(90c)* | $p$-Cl–$C_6H_4$ | 124–125 | 89 | [116] |
| *(90d)* | $p$-Br–$C_6H_4$ | 134–135 | 88 | [116] |
| *(90e)* | 2,3-$(CH_3)_2C_6H_3$ | oil | 75 | [116] |
| *(90f)* | $C_6H_5-CH_2$ | oil | 83 | [116] |
| *(90g)* | $p$-n-$C_4H_9O-C_6H_4$ | 85–86 | 98 | [117] |
| *(90h)* | $p$-$CH_3O-C_6H_4$ | 118–119 | 96 | [117] |
| *(90i)* | $p$-$C_2H_5O-C_6H_4$ | 111–112 | 65 | [117] |
| *(90j)* | $o$-$C_2H_5O-C_6H_4$ [a] | 70–72 | 65 | [117] |
| *(90k)* | $o$-n-$C_3H_7O-C_6H_4$ [a] | 59–60 | 91 | [117] |
| *(90l)* | $p$-i-$C_3H_7O-C_6H_4$ [a] | 58–60 | 91 | [117] |
| *(90m)* | $CH_3$ | 38 | 25 | [40] |
| *(90n)* | $C_2H_5$ | 54 | 61 | [40] |
| *(90o)* | 3,5-$(NO_2)_2$-4-[$(CH_3)_2N$]-$C_6H_2$ | 99.5–100.5 | 50 | [40] |

[a] From acetone cyanohydrin and isothiocyanate.

Isothiocyanates react with phenols and phenol ethers in the presence of aluminum chloride [118–121]; the products obtained from the phenols are not thionourethanes but thiocarboxamides *(92)*.



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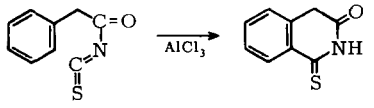
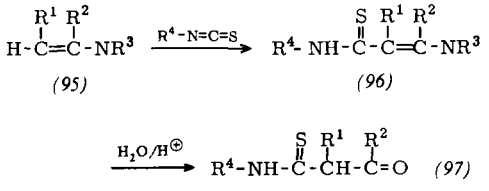
In analogy with the phenol ethers, phenyl ethyl sulfide was converted into a thiocarboxamide by treatment with phenyl isothiocyanate[122]. Aromatic hydrocarbons react under identical conditions[123]. In this way *Smith* and *Kan*[124] obtained homomonothiophthalimides such as *(94)* in yields of 40 to 70% by an intramolecular reaction of phenacetyl isothiocyanates such as *(93)*.



*(93)* *(94)*

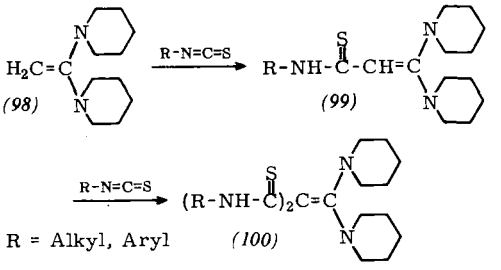
c) Enamines

Enamines of the type *(95)* react with aryl isothiocyanates to form β-aminoalkenethiocarboxamides *(96)*, which can be readily hydrolysed to β-oxothiocarboxamides *(97)*[125–126a].



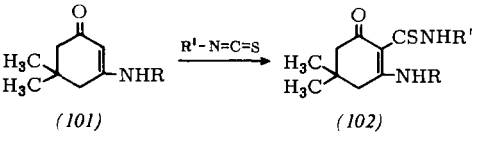
*(95)* *(96)* *(97)*

Some examples of β-aminoalkenethiocarboxamides *(96)* (which were prepared for the first time by this method) and β-oxothiocarboxamides *(97)* are given in Table 11.



*(98)* *(99)* *(100)*

*Goerdeler* and *Keuser*[115] obtained thiocarboxamides *(102)* in good yields by addition of tautomeric enamines of the type *(101)* to aryl isothiocyanates.



*(101)* *(102)*

Compounds containing a $\Delta^1$-triazoline ring, which can be prepared from cyclopentene and aryl azides, react with isothiocyanates only after thermal elimination of nitrogen to form cyclopentenylamines has taken place; the product is a thiocarboxamide (yields 50–99%)[127a, 127b].

Moreover, secondary enamines such as the esters of β-methylaminocrotonic acid can add to aryl and acyl isothiocyanates[113b]. Some examples are given in Table 9 [*(87j)–(87l), (87r)*].

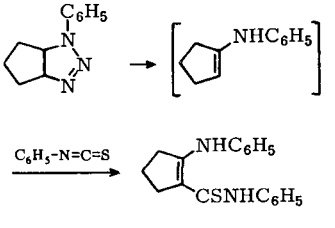


Table 11. Thiocarboxamides *(96)* and *(97)* by addition of isothiocyanates to enamines and hydrolysis.

| Compd. | $R^1$ | $R^2$ | $NR^3$ | $R^4$ | *(96)* Yield [%] | M.p. [°C] | *97)* Yield [%] | M.p. [°C] | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| *a* | H | $C_6H_5$ | Mor. [a] | $C_6H_5$ | 77 | 157–158 | 94 | 80–83 | [125] |
| *b* | H | $C_6H_5$ | Mor. | $COC_6H_5$ | 75 | 161–164 | 87 | 140–142 | [125] |
| *c* | $C_2H_5$ | H | Pyrr. [b] | $C_6H_5$ | 52 | 106–109 (decomp.) | — | — | [125] |
| *d* | $-(CH_2)_3-$ | | Mor. | $C_6H_5$ | 86 | 115–119 (decomp.) | 72 | 96–97 | [125] |
| *e* | $-(CH_2)_3-$ | | — | $COC_6H_5$ | — | — | 66 | 91.5-92.5 | [125] |
| *f* | $-(CH_2)_4-$ | | Mor. | $C_6H_5$ | 83 | 125–129 | 62 | 84–89 (decomp.) | [125] |
| *g* | $-(CH_2)_4-$ | | Mor. | $COC_6H_5$ | 83 | | — | — | [125] |
| *h* | $-(CH_2)_4-$ | | — | $p$-$CH_3$-$C_6H_4$ | — | — | 76 | 97 | [126] |
| *i* | $-(CH_2)_5-$ | | Mor. | $C_6H_5$ | 83 | 119 | 73 | 93.5 | [126] |
| *j* | $-(CH_2)_5-$ | | Mor. | $p$-$CH_3$-$C_6H_4$ | 78 | 121–122 | — | — | [126] |

[a] Mor. = Morpholino. [b] Pyrr. = Pyrrolidinyl.

Enamines such as *(98)* add on two molecules of alkyl or aryl isothiocyanates[127].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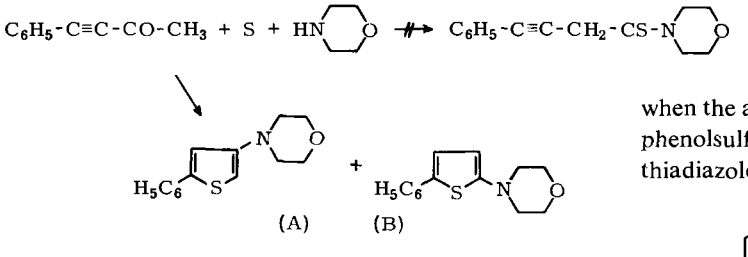
## 5. The Willgerodt-Kindler Reaction

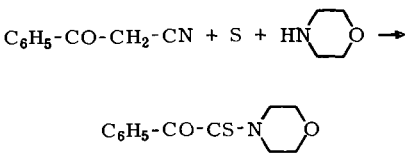
*Willgerodt* found that when aromatic-aliphatic ketones are heated with ammonium polysulfide to 150–200 °C under pressure, amides of aliphatic-aromatic carboxylic acids with the same number of carbon atoms are formed. The Willgerodt reaction [128] consists in the reduction of the keto group to a methylene group, accompanied by oxidation of the chain end by the sulfur. *Kindler* [20] improved the method by the use of primary or secondary amines and sulfur at high temperature. The course of this reaction is not yet certain [129,130]. Since there are several reviews [129–131] of the Willgerodt-Kindler reaction, only the most recent relevant papers will be discussed here.

According to *Asinger* [131], it appears impossible that the Willgerodt-Kindler reaction proceeds by a single mechanism, particularly since not only aromatic-aliphatic ketones, but *inter alia* also aromatic hydrocarbons [132], aromatic aldehydes [133], unsaturated aliphatic compounds [134], diazoketones [135], Schiff bases [136], and even amines themselves, react with sulfur [137]. The most important step is thought to be the initial thiolation and geminal dithiolation, which was also observed by *R. Mayer* [46] in the reaction of ketones with hydrogen sulfide in basic solution.

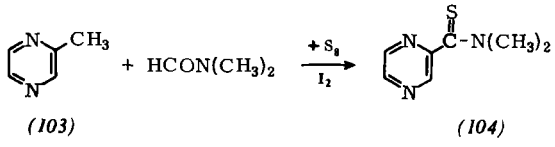
It has recently been shown that the reaction with acetylenic ketones leads not to the thiocarboxamides, as was previously believed, but to isomeric thiophene derivatives [138]. The isomers (A) and (B) are formed in the proportions 9:1.



Similar behavior was observed by *Asinger* and *A. Mayer* in the reaction of aliphatic-aromatic ketones [138a]. Diketones are reduced to monoketones, which then give thiocarboxamides [138b]. α-Cyanoketones give α-oxothiocarboxamides, with loss of a carbon atom [138c].



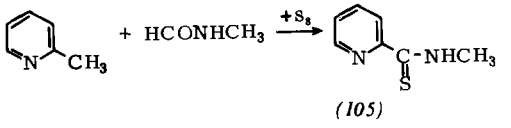
It is possible in principle to carry out the reaction at a much lower temperature by the use of a different solvent [131,139,140]. Another possibility is illustrated by the preparation of *N,N*-dimethylpyrazinethiocarboxamide *(104)* from methylpyrazine *(103)*, dimethylformamide, and sulfur in the presence of iodine. The iodine lowers the viscosity of the sulfur, and so permits the use of a lower reaction temperature. However, the yield is only about 14%, since the monomethylthiocarboxamide and other by-products are also formed [141].



*(103)* *(104)*

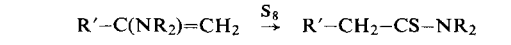
This synthesis is similar to the preparation of *N*-methylpyridine-2-thiocarboxamide *(105)* from α-picoline, sulfur, and methylformamide [142]. The yield in this case is about 50%.

Quinaldine can be converted in the same way into quinaldine-2-thiocarboxamides. However, the reaction fails when the amine component is anthranilic acid, *o*-aminophenolsulfanilic acid, 2-aminothiazole, 2-amino-1,3,4-thiadiazole, and 2-aminopyridine [142a].



*(105)*

A useful variant of the Willgerodt-Kindler reaction is the reaction of enamines with sulfur at room temperature in polar solvents such as dimethylformamide; thiocarboxamides are formed in yields of about 75% [143].



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[131] *F. Asinger*, *W. Schäfer*, *K. Halcour*, *A. Saus*, and *H. Triem*, Angew. Chem. *75*, 1050 (1963); Angew. Chem. internat. Edit. *3*, 19 (1964), and literature cited there.

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[133] *R. Guépet*, *R. Piganiol*, *A. Carayon-Gentil*, and *P. Chabrier*, Bull. Soc. chim. France *1965*, 224.

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[137] *W. J. Horton* and *J. van den Berghe*, J. Amer. chem. Soc. *70*, 2425 (1948).

[138] *T. Bacchetti*, *A. Alemagna*, and *B. Danieli*, Tetrahedron Letters *1965*, 2001.

[138a] *F. Asinger* and *A. Mayer*, Angew. Chem. *77*, 812 (1965); Angew. Chem. internat. Edit. *4*, 788 (1965).

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[138c] *G. Purrello*, Gazz. chim. ital. *95*, 1089 (1965).

[139] *A. Carayon-Gentil*, *M. Minot*, and *P. Chabrier*, Bull. Soc. chim. France *1964*, 1420.

[140] *L. F. Fieser* and *G. W. Kilmer*, J. Amer. chem. Soc. *62*, 1354 (1940).

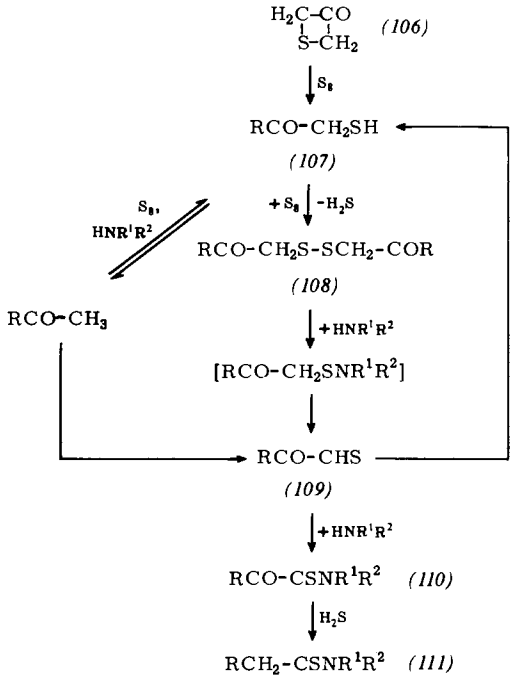
[141] *T. Taguchi* and *K. Yoshihira*, Chem. pharmac. Bull. (Tokyo) *11*, 1354 (1940).

[142] German Pat. 1149356 (May 30th, 1963), Farbenfabriken Bayer, inventors: *W. Schäfer* and *R. Wegler*.

[142a] *O. N. Čupachin*, *Z. V. Puškareva*, *Z. J. Kokoško*, and *M. J. Podgornaja*, Zh. org. Khim. *1*, 772 (1965).

[143] *R. Mayer* and *J. Wehl*, Angew. Chem. *76*, 861 (1964); Angew. Chem. internat. Edit. *3*, 705 (1964).

As a result of studies on the reaction of thietan-3-one *(106)* with secondary amines, *Funk* and *R. Mayer*[144] recently proposed the reaction sequence shown in Scheme 2 for the Willgerodt-Kindler reaction.




Scheme 2. R = $CH_3$

According to this scheme, the reaction begins with the formation of the α-mercaptoketone *(107)*. This step requires vigorous conditions and is rate-determining. The formation of the disulfide *(108)* proceeds very readily. This compound is then converted, *via* the oxosulfenamide, into the oxothioaldehyde *(109)*, which undergoes a Cannizzaro disproportionation, the products in the presence of the amine being *(110)* and *(107)*. The α-oxothiocarboxamide *(110)* is then reduced to the thiocarboxamide *(111)*. A Cannizzaro reaction is thus regarded as the central event. However, this assumption is unnecessary for the reaction with ammonia, since *Asinger*, *Schäfer*, *Baumgarte*, and *Müting*[145] showed that unsubstituted oxosulfenamides *(112)* are dehydrogenated by sulfur at room temperature to give α-oxothiocarboxamides *(113)* (Equation f); for the mechanism see[145a].

$$\underset{(112)}{RCOCH_2-S-NH_2} \xrightarrow{+S} \underset{(113)}{RCOCS-NH_2} + H_2S \qquad (f)$$

This provides further confirmation of *R. Mayer*'s thesis that "this complex and variable reaction cannot be described by a single mechanism"[144].

## 6. Thioacylation of Amines

Thiocarboxamides can be prepared by thioacylation of amines with a wide variety of thioacylating agents. *Staudinger* and *Siegwart*[146] obtained thiobenzanilide *(60)* by reaction of thiobenzoyl chloride with aniline.

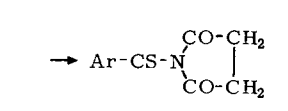
However, this method is of no importance, in view of the difficulty of preparing thioacyl chlorides (see[147]). Thiocarboxamides have also been obtained directly from dithiocarboxylic acids[148,149] and their salts[94, 150–154a] by reaction with aliphatic and aromatic amines. Sodium cyanodithioformate, which can be prepared from carbon disulfide and sodium cyanide, reacts with dimethylamine or diethylamine to form cyano-*N*,*N*-dialkylthioformamide[154b].

Esters of thiocarboxylic acids also act as thioacylating agents[152,155–156b]. Owing to their instability, however, these compounds are not generally suitable. Nevertheless, *R. Mayer* and *Orgis*[157] recently obtained thioformamide (which had previously been relatively difficult to prepare) in yields of more than 90% by reaction of ethyl *O*-thioformate with ammonia.

*Reynaud*, *Moreau* and *Samana*[157a] also obtained good results with this method in the preparation of monosubstituted and disubstituted aliphatic and aromatic thiocarboxamides. In some cases the reaction of the ester of the *O*-thiocarboxylic acid with substituted magnesium anilide bromides was found particularly useful[157a, 157b].

$$RO-C_6H_4-CS-OC_2H_5 + BrMgNH-C_6H_4-OR' \rightarrow RO-C_6H_4-CS-NH-C_6H_4-OR' + C_2H_5OMgBr$$

*Goerdeler* and *Horstmann*[157c] obtained high yields of thioacylimides, *e.g.* thioacylsuccinimides, by acylation of unsubstituted aromatic thiocarboxamides with dicarbonyl dichlorides, *e.g.* succinyl dichloride.




[144] *K. F. Funk* and *R. Mayer*, J. prakt. Chem. [4], *21*, 65 (1963).

[145] *F. Asinger*, *W. Schäfer*, *G. Baumgarte*, and *P. F. Müting*, Liebigs Ann. Chem. *661*, 95 (1963).

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[149] *H. Wuyts* and *L. Ch. Kuang*, Bull. Soc. chim. Belgique *42*, 153 (1933).

[150] US-Pat. 2647144 (July 28th, 1953), Firestone, inventor: *G. E. P. Smith*, Chem. Abstr. *48*, 7637 (1954).

[151] *H. B. König*, W. *Siefken*, and *H. A. Offe*, Chem. Ber. *87*, 825 (1954).

[152] *A.A.Goldberg* and *W. Kelly*, J. chem.Soc.(London) *1948*, 1919.

[153] *A. R. Todd*, *F. Bergel*, *Karimullah*, and *R. Keller*, J. chem. Soc. (London) *1937*, 361.

[154] *Y. Sakurada*, Bull. chem. Soc. (Japan) *2*, 307 (1927), Chem. Zbl. *1928*, I, 683.

[154a] Polish Pat. 48359 (June 10th, 1964), Warszawskie Zaklady Fotochemiczme, inventors: *M. Malawski*, *H. Mogilnicki*, and *W. Czerska*, Chem. Abstr. *62*, 7698 (1965).

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[155] *P. Reynaud* and *C. Moreau*, Bull. Soc.chim. France *1964*, 2999.

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[156b] Hungarian Pat. 151818 (Jan. 23rd, 1965), Gyogyszeriparikutato Intezet, inventors: *O. Fuchs* and *A. Nemes*, Chem. Abstr. *62*, 13129 (1965).

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[157a] *P. Reynaud*, *R. C. Moreau*, and *J.-P. Samana*, Bull. Soc. chim. France *1965*, 3623.

[157b] *P. Reynaud*, *R. C. Moreau*, and *J.-P. Samana*, Bull. Soc. chim. France *1965*, 3628.

[157c] *J. Goerdeler* and *H. Horstmann*, Chem. Ber. *93*, 671 (1960).

These products are very useful as thioacylating agents (yields between 60 and 95%).

According to *Walter* and *Maerten*[158], substituted thioformamides *(114)* can be obtained in good yields by the reaction of chloroform, amines, and hydrogen sulfide in alkaline solution. It is thought that the chloroform first undergoes α-elimination to form dichlorocarbene, which then reacts in accordance with Equation (g).

$$CCl_2 + R^1R^2NH + 2\,SH^{\ominus} \rightarrow R^1R^2N{-}CS{-}H + H_2S + 2\,Cl^{\ominus} \quad (g)$$

*(114)*

A number of thioformamides prepared by this method are listed in Table 12.

Table 12. Substituted thioformamides *(114)* by thioformylation of amines.

| Compd. | $R^1$ | $R^2$ | B.p. [°C/mm Hg] | Yield [%] |
|---|---|---|---|---|
| *(114a)* | H | $n\text{-}C_4H_9$ | 91–92/0.12 | 48 |
| *(114b)* | H | $c\text{-}C_6H_{11}$ | 116–118/0.16 | 63 |
| *(114c)* | H | $CH_2C_6H_5$ | 155–157/0.12 [a] | 23 |
| *(114d)* | $CH_3$ | $CH_3$ | 93/11 | 48 |
| *(114e)* | $CH_3$ | $C(CH_3)_3$ | [b] | 62 |
| *(114f)* | $CH_3$ | $C_6H_5$ | 78/0.09 | 66 |
| *(114g)* | $CH_3$ | $CH_2C_6H_5$ | 177–179/12 [c] | 69 |
| *(114h)* | $C_2H_5$ | $C_2H_5$ | 107/11 | 77 |
| *(114i)* | $n\text{-}C_3H_7$ | $n\text{-}C_3H_7$ | 129–130/12 | 77 |
| *(114j)* | $i\text{-}C_3H_7$ | $i\text{-}C_3H_7$ | 115–117/12 [d] | 69 |
| *(114k)* | $i\text{-}C_3H_7$ | $CH_2C_6H_5$ | 128–131/0.06 | 73 |
| *(114l)* | $n\text{-}C_4H_9$ | $n\text{-}C_4H_9$ | 153/12 | 80 |
| *(114m)* | $-(CH_2)_5-$ | | 143–145/11 | 76 |
| *(114n)* | $-(CH_2)_2-O-(CH_2)_2-$ | | 173/11 [e] | 45 |

[a] m.p. 63–64 °C; [b] m.p. 50–50.5 °C; [c] two isomers with m.p. ≈ 7 and 67.5–68 °C; [d] two isomers with m.p. 59.5–60.5 and 67.5 to 68 °C; [e] m.p. 67–68 °C.

The carboxymethyl dithiocarboxylates *(115)*[148,159,160] have gained considerable importance for preparative work; they react not only with amines but also with amino acids.

$$R{-}CS{-}SCH_2COOH + H_2NR' \rightarrow R{-}CS{-}NHR' + HSCH_2COOH$$

*(115)*

A good survey of this method, with many examples of its application, has been published by *Kurzer*[161]. *Walter* and *Curts*[162] obtained alkylenebisthiobenzamides *(116)* in good yields by thiobenzoylation of diamines.

$$C_6H_5{-}CS{-}NH{-}(CH_2)_x{-}NH{-}CS{-}C_6H_5 \quad (116)$$

$x = 1-6$

The method fails with sterically hindered amines, and is unsuitable for the preparation of thioformamides.

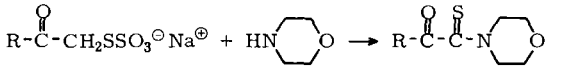
A variant of this method is the acylation of amines with ethyl dithiocarboxylates in accordance with Equation (h).

$$R{-}CH_2{-}NH_2 + R'{-}CS{-}SC_2H_5 \rightarrow R{-}CH_2{-}NH{-}CS{-}R' + C_2H_5SH \quad (h)$$

*(117)*

In this way, *N*-(2-arylethyl)thiocarboxamides [*(117)*, $R = ArCH_2$] have been obtained in yields of 86 to 99%[163].

The reaction of *S*-acylmethylthiosulfates (acyl Bunte salts) *(118)* with amines, which was discovered by *Milligan* and *Swan*[164,165], can also be regarded as thioacylation.



*(118)* R = $C_6H_5$, $CH_3$ *(119)*

This procedure, which leads to good yields of *N,N*-disubstituted α-oxothiocarboxamides, is regarded by the authors as a variant of the Willgerodt-Kindler reaction. However, there is some doubt about the mechanism proposed by *Milligan* and *Swan*[144], so that, despite the similarity of the reaction conditions to those of the Willgerodt-Kindler reaction, this method is dealt with in the present Section.

Finally, the unsubstituted thiocarboxamides are also stable thioacylating agents, since they react with primary aliphatic amines under mild conditions to give *N*-alkyl thiocarboxamides. This reaction is referred to in the literature[166] as the Wallach reaction. (However, it should not be confused with the reaction of the same name in which amines are alkylated with aldehydes or ketones and formic acid[167]). A detailed description of the reaction is given by *Hurd*[166], who used it to prepare a number of previously unknown dithiooxamide derivatives. An interesting reaction is that of monothiooxamide with aliphatic amines, since only the thioamide group reacts[81,168]. Two unsubstituted thioamide groups in the same molecule react one after the other. In the reaction of morpholine with dithiooxamide, for example, it was possible to obtain the previously unknown *N*-morpholinodithiooxamide[40]. *Persson* and *Sandström* recently used this method for the preparation of a number of thiooxamides[169]. Amino acids can also be acylated with dithiooxamide[170].

$$2\,R{-}CH_2{-}NH_2 + H_2N{-}CS{-}CS{-}NH_2 \rightarrow R{-}CH_2NH{-}CS{-}CS{-}NH{-}CH_2{-}R + 2\,NH_3$$

*(120)* R = COOH, $SO_3H$

The reaction of *N,N*-dimethylthioformamide with amines, on the other hand, leads to amidines[170a].

[158] *W. Walter* and *G. Maerten*, Liebigs Ann. Chem. *669*, 66 (1963).

[159] *B. Holmberg*, Ark. Kem., Mineralog. Geol. Ser. *A17*, 23 (1944), Chem. Abstr. *39*, 4065 (1945).

[160] *K. A. Jensen* and *C. Pedersen*, Acta chem. scand. *15*, 1087 (1961).

[161] *F. Kurzer*, Chem. and Ind. *1961*, 1333.

[162] *W. Walter* and *J. Curts*, Liebigs Ann. Chem. *649*, 88 (1961).

[163] *S. Yamada*, *A. M. M. E. Omar*, and *T. Hino*, Chem. pharmac. Bull. (Japan) *12*, 244 (1964), Chem. Abstr. *60*, 14426 (1964).

[164] *B. Milligan* and *J. M. Swan*, J. chem. Soc. (London) *1959*, 2969.

[165] *B. Milligan* and *J. M. Swan*, J. chem. Soc. (London) *1961*, 1194.

[166] *R. N. Hurd*, *G. De La Mater*, *G. C. McElheny*, *R. J. Turner*, and *V. H. Wallingford*, J. org. Chemistry *26*, 3980 (1961), and references cited there.

[167] *H. Krauch* and *W. Kunz*: Namenreaktionen der organischen Chemie. Hüthig, Heidelberg 1961, p. 488.

[168] *R. P. Welcher*, *M. E. Castellion*, and *V. P. Wystrach*, J. Amer. chem. Soc. *81*, 2541 (1959).

[169] *B. Persson* and *J. Sandström*, Acta chem. scand. *18*, 1059 (1964).

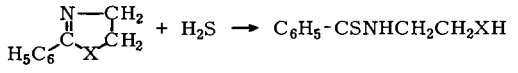
[170] US-Pat. 3023232 (Feb. 27th, 1962), Mallinckrodt, inventor: *V. H. Wallingford*, Chem. Abstr. *57*, 2082 (1962).

[170a] *G. R. Pettit* and *L. R. Garson*, Canad. J. Chem. *43*, 2640 (1965)

## 7. Cleavage of Heterocycles

Thiocarboxamides are often used as starting materials for the synthesis of sulfur heterocycles [171]. The reverse of this process, leading back to the thiocarboxamides, is therefore of no interest in this connection. However, some heterocyclic systems, obtained by another route, also give thiocarboxamides on cleavage.

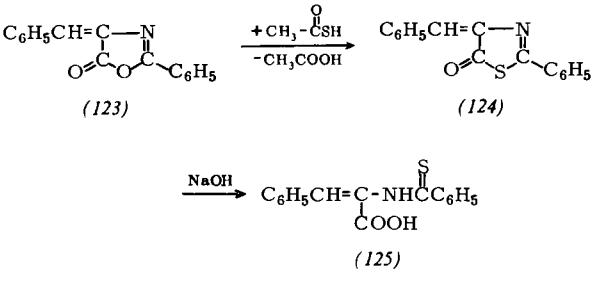
Thioamides are obtained when $\Delta^2$-oxazolines *(121a)* react with hydrogen sulfide in basic solutions [152].



*(121)* *(122)*

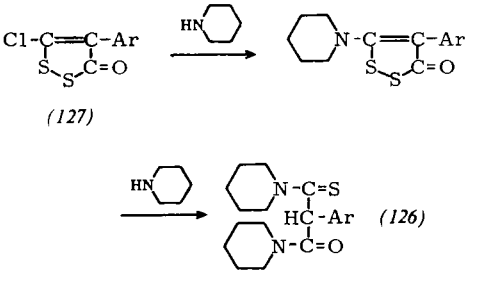
*a*: X = O, *b*: X = S

The corresponding reaction with 2-phenyl-$\Delta^2$-1,3-thiazoline *(121b)*, which could lead to *N*-(β-mercaptoethyl)-thiobenzamide *(122b)*, does not appear to have been studied as yet. The reaction of 4-benzylidene-2-phenyl-(4*H*)-oxazol-5-one *(123)* with thioacetic acid leads to a thiazolone *(124)*, which is cleaved by dilute sodium hydroxide to form the thioamide *(125)* [172].



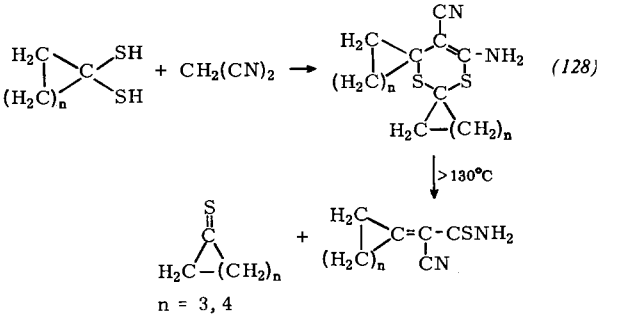
*(123)* *(124)* *(125)*

This reaction is reversed when *(125)* is heated in acetic anhydride. *Boberg* and *Marei* [173] recently observed the formation of arylmonothiomalonodiamides *(126)* in the reaction of 3-chloro-4-aryl-1,2-dithiolones *(127)* with amines.



*(127)* *(126)*

Geminal dithiols react almost quantitatively with malonodinitrile to form 1,3-dithiins *(128)*, which decompose into the thioketone and the thioamide when heated above their melting points [173a].

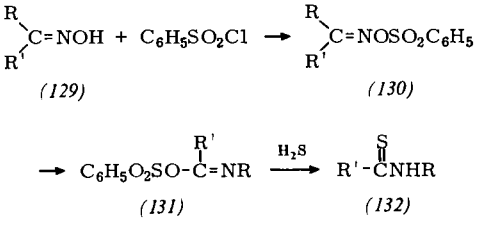


*(128)*

n = 3, 4

## 8. Rearrangement of the Benzenesulfonates of Ketoximes

An interesting preparation of *N*-substituted thiocarboxamides was discovered by *Huisgen* and *Witte* [174] and by *Kopecky* [175]. Ketoximes *(129)* are benzenesulfonated in pyridine, and the products are left to undergo spontaneous Beckmann rearrangement in the presence of hydrogen sulfide. The resulting imidosulfonates *(131)* react with the hydrogen sulfide to give thioamides *(132)* in yields of 50 to 90%.



*(129)* *(130)* *(131)* *(132)*

This method failed in only two of 21 open-chain, cyclic, aliphatic, aromatic, and mixed ketoximes (cf. Table 13). The process is similar to the synthesis of alkyl thioimidates by the reaction of imidosulfonates with alkylthiols [176].

Table 13. Thiocarboxamides *(132)* from ketoximes.

| Compd. | R | R' | M.p. [°C] | Yield [%] |
|---|---|---|---|---|
| *(61)* | $CH_3$ | $C_6H_5$ | 75.5–76 | 77 |
| *(132a)* | $CH_3$ | *p*-Cl–$C_6H_4$ | 139–140 | 46 |
| *(132b)* | $CH_3$ | 2,4-$(OCH_3)_2C_6H_3$ | 91–92 | 73 |
| *(132c)* | $C_2H_5$ | $C_2H_5$ | oil | 64 |
| *(132d)* | n-$C_5H_{11}$ | $C_6H_5$ | 43–45 | 71 |
| *(132e)* | *p*-$CH_3$–$C_6H_4$ | *p*-$CH_3$–$C_6H_4$ | 166–167 | 57 |
| *(132f)* | $-(CH_2)_4-$ | | 105.5–106.5 | 90 |
| *(132g)* | $-(CH_2)_5-$ | | 82–83 | 74 |

## 9. Procedures

a) *Cyanothioacetamide (3)* [27] (reaction type 1)

66 g of malonodinitrile is dissolved in 200 ml of ethanol, and 6 to 8 drops of triethylamine are added. Hydrogen sulfide is introduced into this solution with stirring. The cyanothio-

[171] *A. Albert*: Chemie der Heterocyclen. Verlag Chemie, Weinheim/Bergstr. 1962.

[172] *S. T. Lur'e* and *L. G. Gatsenko*, Zh. obshch. Khim. *22*, 262 (1952), Chem. Abstr. *47*, 2168 (1953).

[173] *F. Boberg* and *A. Marei*, Liebigs Ann. Chem. *666*, 88 (1963).

[173a] *R. Mayer* and *J. Jentzsch*, Angew. Chem. *74*, 292 (1962); Angew. Chem. internat. Edit. *1*, 217 (1962).

[174] *R. Huisgen* and *J. Witte*, Chem. Ber. *91*, 972 (1958); *J. Witte* and *R. Huisgen*, *ibid. 91*, 1129 (1958).

[175] *J. Kopecky*, Chemie (Prague) *10*, 901 (1958), Chem. Zbl. *1964*, 4-0791.

[176] Hungarian Pat. 135418 (April 25th, 1949), Chinoin Gyógyszer, inventors: *Kereszty*, *Wolf*, and *Z. Foldi*, Chem. Abstr. *48*, 10060 (1954).

acetamide that precipitates is filtered off from time to time. Recrystallization gives 90 g (90% yield) of cyanothioacetamide of m.p. 116–117 °C.

b) *Chlorothioacetamide (24)* [38] (reaction type 1)

30 g of chloroacetonitrile is cooled to −15 °C, and 74 g of *O,O'*-diethyl dithiophosphate is added slowly with stirring, the temperature never rising above −10 °C. The mixture is stirred for 30 min at this temperature, and is then treated with HCl gas; this is accompanied by a temperature rise. When the evolution of heat has stopped, the mixture is stirred with 200 ml of petroleum ether. The yellow product is filtered off and extracted with petroleum ether. Chlorothioacetamide [yield 35 g (80%), m.p. 78–79 °C] is obtained as colorless needles.

c) *N-Isopropyl-C-(p-nitrobenzoyl)thioformamide (45a)* [53] (reaction type 2)

10 g of *N*-isopropyl-*p*-nitrobenzoylformimidoyl chloride is dissolved in 50 ml of dry benzene and 50 ml of dry chloroform. The solution is saturated with hydrogen sulfide, poured into water, and the organic phase is washed with $NaHCO_3$ solution and water and dried with sodium sulfate. When the solvent is evaporated, a red oil is left, which crystallizes on cooling. Compound *(45a)* forms orange-red crystals on recrystallization from petroleum ether [yield 8.7 g (87%), m.p. 76–78 °C].

d) *N,N-Dimethyl-C-ethoxycarbonylthioformamide (62)* [81] (reaction type 3)

72.5 g of *N,N*-dimethyl-*C*-ethoxycarbonylformamide is dissolved in 500 ml of dry pyridine and refluxed for 1 hour with 42 g of phosphorus pentasulfide. The mixture is concentrated to 1/3 of its original volume and poured into 1 l of water with vigorous stirring. The product that separates is filtered off, and the filtrate is extracted repeatedly with chloroform. The brown residue obtained when the chloroform is evaporated is combined with the main fraction and dissolved in ethanol, and the solution is boiled with activated charcoal. When the filtrate is concentrated, pale yellow crystals of *(62)* separate [yield 34 g (42%); m.p. 46–47 °C].

e) *2-Amido-2-cyanothioacetanilide (87a)* [115] (reaction type 4b)

1.95 g of potassium is dissolved in a mixture of 20 ml of anhydrous t-butyl alcohol and 10 ml of anhydrous tetrahydrofuran. 4.2 g of malonodinitrile is added to the suspension, and a solution of 6.75 g of phenyl isothiocyanate in 10 ml of anhydrous tetrahydrofuran is added dropwise over 30 min at 10 °C, with stirring. After 15 min, the clear yellow solution is concentrated *in vacuo* at 30 °C, and the residual syrup is dissolved in 300 ml of water and filtered. The yellowish filtrate is washed with water to remove residual isothiocyanate, and acidified to pH 3 with 2N HCl. 7.0 g (64%, based on $C_6H_5$–NCS) of almost colorless crystals of *(84a)* precipitate; these are recrystallized from ethanol with activated charcoal (m.p. 186–187 °C).

Many examples of reaction type 5 are given in [130].

f) *N-(p-Cyanobenzyl)thiobenzamide* [177] (reaction type 6)

19 g of *p*-cyanobenzylamine is dissolved in 90 ml of methanol and poured into a solution of 31 g of *S*-thiobenzoyl-2-thioglycolic acid *(115)* and 6 g of NaOH in 90 ml of water. The thiocarboxamide separates immediately with slight evolution of heat. After the solution is cooled, the product is filtered off, washed with 50% methanol, and dried. The crude product is recrystallized from ligroin (120–125 °C) [yield 29.5 g (81%), m.p. 143 °C].

g) *N,N-Di-n-propylthioformamide (114i)* [158] (reaction type 6)

23 g of sodium is dissolved in 350 ml of anhydrous ethanol. The resulting sodium ethoxide solution is cooled with ice water, and 34 g of hydrogen sulfide is introduced; some sodium hydrogen sulfide is precipitated. 25 g of di-n-propylamine and 59.5 g of chloroform are added to this suspension. The mixture is refluxed for about 25 hours, while a slow stream of nitrogen is continuously passed through the apparatus. When the reaction is complete, the NaCl that has precipitated is filtered off, and the filtrate is concentrated *in vacuo*. The residue is triturated with chloroform and filtered, and the filtrate is diluted with water and carefully acidified with concentrated HCl. The organic phase is washed three times with water and dried over calcium chloride. When the solvent is evaporated, it leaves behind a yellow oil, which is vacuum distilled [yield 28 g (77%), b.p. 129–130 °C/12 mm Hg].

h) *Thioacetanilide (61)* [174] (reaction type 8)

A solution of 13.5 g of acetophenone oxime in 50 ml of pyridine is treated with 19.5 g of benzenesulfonyl chloride at 0 °C, and the mixture is allowed to stand for 1 hour at room temperature. The introduction of hydrogen sulfide leads to an exothermic reaction; the temperature should not be allowed to rise above 50 °C. After being allowed to stand for 5 hours under $H_2S$ pressure, the solution is heated for 1 hour at 60 °C. The pyridine is evaporated off *in vacuo*, the residue is dissolved in dichloromethane, and the solution is extracted with 2N HCl and water. The organic layer is then shaken with 2N NaOH, and carbon dioxide is passed through to precipitate the thioacetanilide. After filtration, washing with water, and drying, 11.7 g of a bright yellow, crystalline crude product melting at 68–73 °C is obtained (77%). Recrystallization from petroleum ether/benzene yields 10.9 g (72%) of long, pale yellow needles (m.p. 75–76 °C).

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# Reactions of Elementary Silicon

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*Dedicated to Professor Hans Kautsky on the occasion of his 75th birthday*

*Elementary silicon is normally treated "dry" with gaseous reactants in a fluidized bed. The apparent inertness of ordinary silicon is due to surface passivation. Non-passivated silicon reacts as a strongly electropositive element. Finely divided silicon is pyrophoric and forms surface compounds with many substances (e.g. alcohol, water, and metal or organic halides) even at room temperature. An alternative to the "dry" process is a new suspension process, in which finely divided activated silicon, preferably suspended in its liquid reaction products (possibly in the presence of soluble catalysts) reacts at elevated pressures, generally with liquids. The reactions in suspension can be easily controlled, and all the silicon is consumed. Polysilanes often are the only initial products, and these react further in the homogeneous liquid phase to give monosilanes. For example, dissolution of ordinary silicon in methanol leads smoothly to methoxysilanes, which can add to unsaturated hydrocarbons.*

## I. Reactions of Elementary Silicon with Gases

A silicon crystal formally is a giant polysilane molecule. Substitutive cleavage of Si–Si bonds thus is formally equivalent to the breaking of polysilane bonds. Two particularly important reactions of elementary silicon are the reaction (a) with methyl chloride and the reaction (b) with chlorobenzene.

$$Si + CH_3Cl \xrightarrow{290\,^\circ C} (CH_3)_2SiCl_2 + CH_3SiCl_3 + (CH_3)_3SiCl \quad (a)$$

(by-products: $CH_3SiHCl_2$, $(CH_3)_4Si$, $HSiCl_3$, $SiCl_4$, HCl, $H_2$, lower hydrocarbons, soot)

$$Si + C_6H_5Cl \xrightarrow{350\,^\circ C} C_6H_5SiCl_3 + (C_6H_5)_2SiCl_2 \quad (b)$$

(by-products: biphenyl, benzene, HCl, $SiCl_4$, $HSiCl_3$, chlorinated biphenyls).

These reactions (Rochow reactions [1]) are used in industry for the preparation of methyl- and phenylchlorosilanes. These react with water to form organosilanols, which are polycondensed to organosiloxanes and silicones. This subject is discussed in a number of reviews [2–5].

### 1. Passivation Phenomena

The reaction of "dry" silicon with gases requires temperatures above 250 °C, with the result that many of the primary products undergo disproportionation, rearrangement, or decomposition; reactions (a) and (b) cannot be formulated as equilibrium reactions.

Reactions of silicon in the heterogeneous system solid/gas are relatively sluggish owing to inhibition. The following types of inhibition can be distinguished:

a) passivation by oxide formation

b) passivation by formation of other surface compounds

c) passivation by decomposition products.

Passivation by oxide formation occurs already when dry silicon is ground (particle size 0.1 to 100 μ) in air. However, passivation of this type can also be caused by moisture and by oxygen-containing impurities in the gaseous reactants, particularly at high temperatures. To break open such passive oxide layers, reaction (a) generally is carried out at an initial temperature of about 340 °C, this being reduced to about 290 °C after the reaction has started. The lower the reaction temperature in the heterogeneous solid/gas system, the smaller is the number of Si–Cl bonds in the products; thus the highest yield of Si–C bonds is obtained at the lowest temperature at which the reaction still proceeds sufficiently fast.

If the reactants are not completely free from oxygen and its compounds, the passive oxide layer is continuously reformed. Particles of the silicon-copper alloy, particularly those in which the surface is already "swollen" by the reaction, act as gas purifiers. The gaseous reactant is highly purified and parts of the Si surface become passive. Experience has shown that very pure substances react only slowly with one another.

Further, as the reaction proceeds, the surface is passivated by surface compounds, which are precursors of the silanes that subsequently escape as gases. This passivation is characteristic of the gaseous reactant, and is particularly pronounced in reactions with aryl halides (large organic radical).

Passivation by decomposition products such as soot and silicon carbide is typical of "dry" reactions of Si

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[1] US.-Pat. 2380995 (1945), General Electric, inventor: *E. G. Rochow*.

[2] *E. G. Rochow*: Einführung in die Chemie der Silikone. Verlag Chemie, Weinheim/Bergstr. 1952.

[3] *A. Hunyar*: Chemie der Silikone. VEB Verlag Technik, Berlin 1959, 2nd ed.

[4] *W. Noll*: Chemie und Technologie der Silicone. Verlag Chemie, Weinheim/Bergstr. 1960.

[5] *J. J. Zuckerman*, Advances inorg. Chem., Vol. 6, p. 383–432 (1964).

with organic halides, and increases with increasing consumption of silicon [27]. The formation of solid decomposition products is due to local overheating (low specific heat of gases). Soot is formed from methyl chloride above about 400 °C. In addition to this effect, the silicon content of the surface of copper-alloyed silicon particles decreases steadily as the reaction proceeds.

All these phenomena are opposed by mechanical abrasion of the surfaces, *e.g.* by friction between the particles; this explains why better results are obtained in large-scale production.

## 2. Examples of "Dry" Reactions

### a) Methylchlorosilanes

Methylchlorosilanes are prepared in a "Rochow furnace", which is operated at from 1 to 6 atm (types: flying dust [79], stirrer [80], vibration [81], or fluidized-bed reactors [9]). The silicon-copper alloy may also contain Zn, Ag, and other metals [6–27,49–57] (see Tables 1 and 2).

*Table 1. Methylchlorosilanes from elementary silicon and methyl chloride.*

| Notes | Si-alloy with | T [°C] | Ref. |
|---|---|---|---|
| $CH_4$, $CH_2{=}CH_2$, $H_2$ also formed | Cu | 260–400 | [6] |
| Fixed-bed reaction at 1 atm or 4–5 atm; addition of $CH_3SiCl_3$ does not increase the yield of $(CH_3)_2SiCl_2$ | Cu | 260–400 | [7] |
| Reactivity difference between various reaction mixtures of Si powder + $CuCl_2$ | Cu (up to 20 %) | 260–400 | [8] |
| Fluidized-bed process at 4–5 atm | Cu | 350–370 | [9] |
| Until 45 % of the Si used has been consumed; optimum yield at 300 to 350 °C | Cu | 300–470 | [10] |
| Almost 90 % $(CH_3)_2SiCl_2$ when chemically pure Si is used | Cu | 300 | [11] |
| $CH_3Cl/HCl$ gives up to 17.7 % of $CH_3SiHCl_2$ | Cu | 200–300 | [12] |
| Without copper, with addition of HCl | Fe | 200–400 | [13] |
| Reaction mixture of Si and copper hydroxide by reduction in a current of $H_2$ at 400 °C; yield: $(CH_3)_2SiCl_2$ 30 %; $CH_3SiCl_3$ 31 %; $CH_3SiHCl_2$ 32 % | Cu | 400 | [14] |
| Fluidized-bed reactor; yield: $(CH_3)_2SiCl_2$ 43 % | Cu (11 %)<br>Sb(0.004 %) | 340–390 | [15] |
| Fluidized-bed reaction at 4 atm with added $CH_3SiCl_3$; yield: $(CH_3)_2SiCl_2$ 47 %; $CH_3SiCl_3$ 32 % | Cu (18 %) | 350–370 | [16] |
| Increased $(CH_3)_3SiCl$ and $(CH_3)_4Si$ contents on addition of Ca metal | Cu | 350–375 | [17] |
| Increased $CH_3SiHCl_2$ content (up to 24 %) on addition of tertiary alkyl chlorides | Cu, Zn | 300–375 | [18] |
| $CH_3Cl/HCl$ mixtures give increased yields of $CH_3SiHCl_2$ | Cu, Ag | 250–350 | [19] |
| Increased yields of $CH_3SiHCl_2$ or $C_2H_5SiHCl_2$ with $CH_3Cl$ or $C_2H_5Cl$ | Cu, Al, Zr | 250–350 | [20] |
| Fluidized-bed process at 3 atm; yield: 66 % $(CH_3)_2SiCl_2$ | Cu | 320 | [21] |
| Increased $CH_3SiHCl_2$ content (up to 30 %) | Cu, $BCl_3$ | 290 | |
| | $AlCl_3$ [*] | 350 | [22] |
| Methylchlorosilane synthesis; industrial procedure (review) | | | [23] |
| Methylchlorosilane synthesis with methane/chlorine mixtures instead of $CH_3Cl$ | Cu | 400–850 | [24] |
| Fluidized-bed process (1 to 7.6 atm), continuous grinding of the solid | Cu | 300–340 | [25] |
| After-treatment of pyrophoric Si residues with chlorobenzene | Cu | 300–600 | [26] |
| Utilization of Si residues with addition of $AlCl_3$ | Cu<br>$AlCl_3$ [*] | 250–350 | [27] |

[*] The chlorides are added as follows: Porous, sintered Si-metal mixtures are soaked with solutions of the chlorides; volatile chlorides are mixed with the gas phase.

Table 2. Conditions of preparation and use of the silicon reaction mixtures.

| Notes | Si-alloy with | T [°C] | Ref. |
|---|---|---|---|
| Reaction mixture is treated with $CH_3Cl$, with addition of diethyl ether | Cu, Zn | 250–350 | [49] |
| Sintered contact mass prepared in a current of $H_2$ at 600 to 1200 °C; up to 75 % yield of $(CH_3)_3SiCl_2$ | Cu, Zn | 250–350 | [50] |
| Reaction material with 5–7 % Fe, 0.2–0.02 % Al, <0.08 % Ca | Cu, CuCl | 300–350 | [51] |
| Preparation of the reaction mixture from Si powder and copper chloride; reduced in a current of $H_2$ at 360 °C; addition of $ZnCl_2$ and sodium silicate | Cu, Zn<br>Cu, Zn | 350<br>350 | [52]<br>[52] |
| Sb (0.002–0.005 %) as promoter; traces of Ti, Al, Bi favor the formation of $CH_3SiHCl_2$ | Cu, Sb | 350–370 | [53] |
| Pb favors the formation of $CH_3SiHCl_2$ | Cu–Pb | 400 | [54] |
| $H_2S$ as promoter favors the formation of $(CH_3)_2SiCl_2$ (80–85 % yield) | Cu | 400 | [55] |
| Doped Si: 0.005–1 % P, As, Sb, Bi, In, Tl | Cu | 250–350 | [56] |
| Contact mass of Si/Cu powder and kieselguhr with water-glass solution; dried at 100–140 °C | Cu | 300 | [57] |


[6] *W. S. Fichtenholz* and *A. L. Klebanski*, Zh. obshch. Khim. *26*, 2502 (1956).

[7] *A. L. Klebanski* and *W. S. Fichtenholz*, Zh. obshch. Khim. *27*, 2648 (1957).

[8] *W. S. Fichtenholz* and *A. L. Klebanski*, Zh. obshch. Khim. *27*, 2475 (1957).

[9] *K. A. Andrianow et al.*, J. appl. Chem. USSR (Engl. transl.) *32*, 2385 (1959).

[10] *K. Setinek*, *V. Bažant*, and *F. Šorm*, Collect. czechoslov. chem. Commun. *22*, 1192 (1957).

[11] *J. Joklik* and *V. Bažant*, Collect. czechoslov. chem. Commun. *26*, 417 (1961).

[12] *J. Joklik* and *V. Bažant*, Collect. czechoslov. chem. Commun. *29*, 834 (1964).

[13] *B. Lengyel* and *B. Csakvan*, Acta chim. Acad. Sci. hung. *39*, 27 (1963).

[14] USSR.-Pat. 130882 (1959), inventors: *S. L. Leltchuk*, *J. I. Wabel*, and *A. M. Klenia*.

[15] USSR.-Pat. 154542 (1962), inventors: *M. A. Ezerts et al.*

[16] USSR.-Pat. 154859 (1962), inventors: *S. A. Golubtsov et al.*

The reaction is carried out with methyl chloride or methyl chloride/hydrogen chloride mixtures, often with added hydrogen or nitrogen (for the technical scheme see [23]). The methylchlorosilane mixture, which is condensed by cooling when prepared at atmospheric pressure, is characterized by the ratio methyltrichlorosilane/dimethyldichlorosilane [25]. Since the subsequent preparation of polymethylsiloxanes requires more dimethyldichlorosilane than methyltrichlorosilane, the aim should be to obtain a $CH_3SiCl_3/(CH_3)_2SiCl_2$ ratio of about 0.25, and to stop the reaction when the ratio rises to about 0.4. In many cases only 40 to 50 % of the silicon has reacted when this stage is reached.

An important problem is to minimize or to find a use for the residues, which generally are pyrophoric. The relatively high cost of methylchlorosilanes is due partly to the fact that the silicon is not efficiently utilized. Thus a considerable part of the silicon simply serves to bind "excess" of halogen from organic halides whose organic groups have been lost by decomposition.

In order to increase the utilization of silicon to about 80 % at a $CH_3SiCl_3/(CH_3)_2SiCi_2$ ratio $\leq$ 0.4, it has been suggested that the silicon grains [which paradoxically become larger instead of smaller during the reaction in the fluidized bed, while the concentration of copper in the surface increases (> 10 %)] should be continuously removed, reground in a jet mill operated with liquid methyl chloride at the speed of sound, and then returned to the fluidized bed [25, 27]. The pyrophoric residues from the methyl chloride reaction can be made to react with chlorobenzene at 400 to 500 °C to form phenyltrichlorosilane [26]. A number of publications deal with methods of increasing the proportion of $CH_3SiHCl_2$ [12, 18–20, 22], which is a valuable intermediate in the production of organofunctional silanes and siloxanes, and which can at present be obtained only as a by-product in the Rochow synthesis.

### b) Ethylchlorosilanes

The "dry" reaction of silicon with ethyl chloride or ethyl chloride/hydrogen chloride mixtures [28–32] (see Table 3) is of little industrial importance. The reaction involves residence times of from 10 to 20 sec at temperatures between 320 and 380 °C. The silicon balance is even less favorable than in the reaction with methyl chloride. At a silicon consumption (Cu-content up to 20 wt-%) of 10 to 20 %, the $(C_2H_5)SiCl_3/(C_2H_5)_2SiCl_2$ ratio is found to be from 0.4 to 0.5. At higher silicon conversions, the amounts of $SiCl_4$ and $HSiCl_3$ in the product increase rapidly, and the yield of ethylchlorosilanes decreases. The only industrial product marketed is ethyltrichlorosilane; however, this is not produced directly, but *via* trichlorosilane by Pt-catalysed addition of ethylene.

Table 3. Ethylchlorosilanes from elementary silicon (alloyed with Cu) and ethyl chloride

| Notes | T [°C] | Ref. |
|---|---|---|
| Metal composition: 70.2 % Si, 21.2 % Cu, 1.8 % Fe; yield: 200–300 g of ethylchlorosilane mixture [$C_2H_5SiHCl_2$ 14 %, $C_2H_5SiCl_3$ 25 %, $(C_2H_5)_2SiCl_2$ 43 %] per kg of charge per hour in the fluidized-bed process | 270–300 | [28] |
| | 270–300 | [28] |
| Ethylchlorosilane synthesis in the flow reactor | 200–320 | [29] |
| Fluidized-bed reactor; Cu 17 wt-%; yield: $C_2H_5SiHCl_2$ 50–60 %; $C_2H_5SiCl_3$ 22–28 % | 370 | [30] |
| Reactions in the fixed bed with $C_2H_5Cl/CH_2{=}CH_2/HCl$ mixtures; yield: up to 50 % $C_2H_5SiHCl_2$, 30 % $C_2H_5SiCl_3$, 20 % $(C_2H_5)_2SiCl_2$ | 320 | [31] |
| Fluidized-bed reactor, $N_2$ as protective gas | 360–370 | [32] |

A process which, in view of the high reaction temperature used, should be regarded as a "dry" rather than as a suspension process (cf. Section II. 3a) has received little attention. This process permits the use of ethylene/HCl mixtures instead of ethyl chloride; when all the silicon has been consumed, the product consists of approximately equal quantities of diethyldichlorosilane and ethyltrichlorosilane, together with up to 20 % of ethyldichlorosilane ($C_2H_5SiHCl_2$). In this process, a slurry of silicon and copper powder in liquid paraffin is treated with ethyl chloride or ethylene/HCl at 270 to 320 °C [33]. Unfortunately, at temperatures above 300 °C, liquid paraffin generally is not inert in the presence of small quantities of $AlCl_3$, and the cleavage products interfere with the separation of the ethylchlorosilanes in the mixture. It has therefore been proposed that the reaction should be carried out in $ZnCl_2/KCl/NaCl$ melts [34].

### c) Phenylchlorosilanes

The production of phenylchlorosilanes from silicon and chlorobenzene by the Rochow process requires the use

[17] US.-Pat. 2887501 (1956), General Electric, inventor: *B. A. Bluestein.*

[18] US.-Pat. 2887502 (1959), General Electric, inventor: *B. A. Bluestein.*

[19] French Pat. 1278517 (1961), Shinetsu Kagaku.

[20] German Published Pat. Appl. 1134671 (1961), Wacker-Chemie, inventors: *S. Nitzsche* and *P. Buchheit.*

[21] *E. F. Boon*, Ingenieur ('s-Gravenhage) *70*, Ch. 89, Ch. 95 (1958).

[22] *B. Csakavari, G. Garzo*, and *S. Jenei*, Acta chim. Acad. Sci. hung. *39*, 33 (1963).

[23] *D. G. Weaver* and *R. J. O'Connors*, Ind. Engng. chem. *50*, 132 (1958).

[24] USSR.-Pat. 117200 (1958), inventors: *O. M. Fedorow* and *S. M. Schtschelokow.*

[25] German Published Pat. Appl. 1155128 (1963), General Electric, inventor: *J. M. Dotson.*

[26] East German Pat. 20721/120 (1961), inventor: *G. Seitz.*

[27] German Published Pat. Appl. 1171429 (1964), General Electric, inventor: *J. Mackinnon.*

[28] *K. A. Andrianow et al.*, Zh. obshch. Khim. *30*, 1277 (1957).

[29] *V. Bažant* and *M. Kraus*, Collect. czechoslov. chem. Commun. *26*, 2028 (1961).

[30] *K. A. Andrianow et al.*, Izvest. Akad. Nauk SSSR, Ser. khim. *1963*, 87.

[31] *K. A. Andrianow et al., ibid. 1962*, 1788.

[32] USSR.-Pat. 157348 (1963), inventor: *R. A. Turetskaja.*

[33] German Pat. 887343 (1951), BASF, inventors: *Wo. Schmidt* and *K. Jost.*

[34] German Pat. 920187 (1952), BASF, inventors: *Wo. Schmidt* and *K. Jost.*

of specially active silicon containing copper (up to 20 wt-%) together with silver, zinc, and aluminum (only low Al contents are permissible, since the aluminum trichloride formed cleaves Si–C bonds). However, if mixtures of chlorobenzene with hydrogen chloride are used, aluminum trichloride catalyses the reaction of Si–H compounds with chlorobenzene, *e.g.*:

$$Cl_3SiH + C_6H_5Cl \xrightarrow[-HCl]{} Cl_3Si{-}C_6H_5$$

From the point of view of silicon consumption, phenylchlorosilanes are more economically synthesized *via* mono-, di-, and trichlorosilane [35–40]. The majority of the processes operate (see Table 4) above the critical range (critical data for chlorobenzene: 359 °C, 44.6 atm).

The principal product at temperatures between 200 and about 350 °C is trichlorosilane, formed in accordance with the overall Equation (c). By-products include $SiCl_4$

$$Si + 3\ HCl \rightarrow HSiCl_3 + H_2\ (\Delta H = -40\ kcal/mole) \qquad (c)$$

and small quantities of dichlorosilane, together with polysilicon chlorides $Si_nCl_{2+n2}$ (mainly $Si_2Cl_6$). Reaction (d) cannot become the principal reaction under the conditions of the "dry" process, since dichlorosilane

$$Si + 2\ HCl \rightarrow H_2SiCl_2 \qquad (d)$$

undergoes a further relatively fast reaction with excess of hydrogen chloride in accordance with Eq. (e), which is catalysed by Friedel-Crafts catalysts, particularly aluminum trichloride.

$$H_2SiCl_2 + HCl \rightarrow HSiCl_3 + H_2 \qquad (e)$$

Table 4. Phenylchlorosilanes from elementary silicon and chlorobenzene.

| Notes | Si-alloy with | T [°C] | Ref. |
|---|---|---|---|
| At pressures up to 39 atm; reaction mixture of Si powder, Al nitrate, and Cu nitrate solution, reduced in a current of $H_2$ after drying | Cu, Al | 300–340 | [35] |
| Phenylchlorosilane synthesis from chlorobenzene and SiH-chlorosilanes (possibly in the presence of Si) | Cu | 400–600 | [36] |
| Si/Cu alloy in the form of dust; reaction with chlorobenzene in a current of HCl; yield: 17 % $C_6H_5SiCl_3$ | Cu | 600–630 | [37] |
| Fixed-bed reaction in the presence of $H_2$ | Cu | 430–445 | [38] |
| With addition of NaCl | Ag | 300–400 | [39] |
| Zn as promoter | Cu, Ag, Zn | 400–480 | [40] |

## d) Chlorosilanes

Chlorosilanes $H_nSiCl_{4-n}$ (n = 1,2,3) are important intermediates for the synthesis of organosilicon compounds. Si–H compounds can be added catalytically or thermally to alkenes and alkynes [82]. Chlorosilanes are produced by the reaction of elementary silicon with hydrogen chloride in the presence of copper [42–47] (see Table 5) in a fluidized-bed process, laboratory preparations generally being carried out in silica fluidized-bed furnaces.

## e) Alkoxysilanes

Dimethoxy- and trimethoxysilanes are reported to be formed when a mixture of Si, CuCl, and $ZnCl_2$ reacts with methanol at about 300 °C in the presence of hydrogen as a fluidizing gas [48]. According to our

Table 5. Chlorosilanes from elementary silicon and HCl (or $Cl_2$).

| Notes | Si-alloy with | T [°C] | Ref. |
|---|---|---|---|
| $SiCl_4$ as "fluidizing gas", reaction with $Cl_2$; preparation of $Si_2Cl_6$, $Si_3Cl_8$, $Si_4Cl_{10}$; up to 21 % polysilicon chlorides | Fe, Mn, Cr, Ni, Ca | 175–300 | [41] |
| Continuous-process fluidized-bed reactor; preparation of $SiCl_4$ and $HSiCl_3$ | | 260–1200 | [42] |
| Fluidized-bed reactor; $HSiCl_3$ yield up to 90 % | Cu | 170–350 | [43] |
| Formation of $HSiCl_3$ from Si and HCl; kinetic studies | | | [44] |
| Si + HCl in the fluidized-bed process; production of $HSiCl_3$, $H_2SiCl_2$ | | 275–300 | [45] |
| Without Cu 300 °C, with Cu 215 °C; $HSiCl_3$ + $SiCl_4$ approx. 80 % yield, 20 % polysilicon chloride, 5.8 % $H_2SiCl_2$ | Cu | 150–300 | [46] |
| In $NaAlCl_4$ melts for the production of $HSiCl_3$ from Si and HCl | $AlCl_3$ [*] | 180–220 | [47] |

[*] See footnote to Table 1.


[35] French Pat. 1046295 (1951), French Addition Pat. 70976 (1957), Office National d'Etudes et de Recherches Aeronautiques, inventors: *Ch. Horny* and *M. G. Guinet.*

[36] German Published Pat. Appl. 1046619 (1958), 1130807 (1959), Wacker-Chemie, inventors: *S. Nitzsche* and *R. Riedle.*

[37] USSR.-Pat. 130514 (1960), inventors: *A. S. Golubtsow, N. N. Tischina,* and *A. P. Sjabkin.*

[38] Jap. Pat. 1112 (1957), Bureau of Industrial Technics, inventor: *Yasuo Takaaji.*

[39] US.-Pat. 2579341 (1951), General Electric, inventor: *W. A. Schwenker.*

[40] German Pat. 1019306 (1957), Tsunao Araki, inventor: *Yasuo Takami.*

[41] US.-Pat. 2602728 (1952), General Electric, inventor: *W. L. Walton.*

[42] German Published Pat. Appl. 1105398 (1960), Wacker-Chemie, inventors: *E. Enk, J. Nickl,* and *R. Teich.*

[43] German Published Pat. Appl. 1143797 (1960), Pechiney Comp. Paris, inventors: *P. Chassaing* and *F. Collomb.*

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[47] USSR.-Pat. 155154 (1963), inventors: *G. L. Groshev et al.*

[48] German Published Pat. Appl. 1127338 (1960), Union Carbide, inventor: *N. P. M. Dewit.*

[49] German Published Pat. Appl. 1062700 (1959), Th. Goldschmidt A.-G., inventor: *G. Rossmy.*

[50] German Published Pat. Appl. 1088051 (1960), Th. Goldschmidt A.-G. inventor: *G. Rossmy.*

[51] German Published Pat. Appl. 1076131 (1960), Wacker-Chemie, inventors: *E. Enk* and *S. Nitzsche.*

results, the reaction leads to about 2 % of trimethoxysilane [see Eq. (f)] together with 98 % of tetramethoxysilane (based on silicon used).

$$Si + 3\ CH_3OH \xrightarrow{300\,^\circ C/H_2} (CH_3O)_3SiH + H_2 \qquad (f)$$

No reaction occurs below 290 °C. The difficulties mentioned in connection with the control of the Rochow reaction are even greater here, since the heat of reaction is greater.

### 3. Mechanism of the Reaction between Silicon and Methyl Chloride

*Hurd* and *Rochow*[58] studied the mechanism of the reaction of gaseous methyl chloride with solid silicon and the catalytic action of copper, and the subject has been re-examined by *Müller* and *Gümbel*[59–61]. Methyl radicals probably are formed by the action of copper on methyl chloride [Eq. (g)]. Copper(I) chloride reacts with

$$Cu + CH_3Cl \xrightarrow{> 250\,^\circ C} CuCl + \cdot CH_3 \qquad (g)$$

silicon above 250 °C in accordance with Equation (h). Both reactions are catalysed by aluminum trichloride[59,60]. Unfortunately, however, aluminum

$$CuCl + -\overset{|}{\underset{|}{Si}}- \longrightarrow [SiCl] + Cu \qquad (h)$$

chloride also catalyses the decomposition of methyl radicals into methane, carbon, hydrogen, *etc.* Free methyl radicals presumably attack polysilane bonds in the surface of silicon crystals at the points where chlorine atoms are already attached.

$$-\overset{Cl}{\overset{|}{Si}}-\overset{Cl}{\overset{|}{Si}}- + \cdot CH_3 + CuCl \longrightarrow -\overset{CH_3}{\overset{|}{Si}}- + Cl\overset{|}{Si}- + Cu \qquad (i)$$

A surface reaction of the type (i) appears even more likely in that it has been shown that such "polysilane bonds" can react directly with olefins to give Si–(C–C)–Si linkages[62]. On the other hand, attempts to make elementary silicon react directly with methyl radicals produced by the action of heat on tetramethyl-lead were unsuccessful[58].


[52] *K. A. Andrianov et al.*, Izvest. Akad. Nauk SSSR *1962*, 1005.

[53] *K. A. Andrianov et al.*, Zh. obshch. Khim. *32*, 841 (1962).

[54] *R. I. H. Voorhoeve* and *I. Vlugter*, Recueil Trav. chim. Pays-Bas *82*, 605 (1963).

[55] *R. I. H. Voorhoeve* and *I. C. Vlugter*, Chem. Weekbl. *59*, 617 (1963).

[56] German Published Pat. Appl. 1165026 (1959), Th. Goldschmidt A.-G., inventor: *G. Rossmy*.

[57] ČSR-Pat. 97529, inventors: *O. Czerný*, *I. Cermák*, and *V. Bažant*.

[58] *D. T. Hurd* and *E. G. Rochow*, J. Amer. chem. Soc. *67*, 1057 (1945).

[59] *R. Müller* and *H. Gümbel*, Z. anorg. allg. Chem. *327*, 286 (1964).

[60] *R. Müller* and *H. Gümbel*, Z. anorg. allg. Chem. *327*, 293 (1964).

[61] *R. Müller* and *H. Gümbel*, Z. anorg. allg. Chem. *327*, 302 (1964).

[62] German Pat. 1173255 (1960), BASF, inventor: *E. Bonitz*.


## II. Reactions of Elementary Silicon in Suspensions

The work described in Section I suggests that silicon is a relatively unreactive element. However, *Kautsky*[63–65] has described a particularly reactive form of elementary silicon, which is obtained in accordance with Equation (k).

$$3\ CaSi_2 + 2\ SbCl_3 \xrightarrow[\text{in } o\text{-}Cl_2C_6H_4]{140-180\,^\circ C} 6\ [Si] + 2\ Sb + 3\ CaCl_2 \qquad (k)$$

It seemed likely that ordinary silicon could be made reactive if the surface passivation, which appears to be caused mainly by atmospheric oxygen, were eliminated or prevented. This possibility was first suggested by *Kautsky*: "The fresh cleavage surface of a silicon crystal strives to saturate the free valences produced, and surface compounds may therefore be formed"[63].

### 1. A New Route to Active Silicon

In 1955, with *Kautsky*'s experience as a basis, the author began a search for a simpler method for the production of active silicon. It was found that a chlorine carrier such as antimony trichloride [see Equation (k)] is not required, and that it actually interferes with the separation of the reaction products. Chlorine gas reacts directly and quantitatively with calcium disilicide at room temperature to form active silicon[66], which is thus readily obtainable [Eq. (l)]. $CaSi_2$ is ground in

$$CaSi_2 + Cl_2 \xrightarrow{20-40\,^\circ C} 2\ [Si] + CaCl_2 \qquad (l)$$

$CCl_4$ or $SiCl_4$ under conditions such that the fresh fracture surfaces cannot be passivated by atmospheric oxygen. Calcium disilicide that has been ground in the presence of air does not undergo this smooth and stoichiometric reaction.

Reaction (l), *i.e.* the reaction of a completely insoluble solid with a gas at atmospheric pressure to form a second solid, is unusual in silicon chemistry.

### 2. Reactivity of Active Silicon

The silicon obtained by the action of chlorine on $CaSi_2$ is even more reactive than that produced with antimony trichloride. It is pyrophoric, and ignites in methanol or water, where it "burns" to give mainly $SiO_2$; the reaction is accompanied by vigorous evolution of hydrogen. If the reaction with methanol is carried out in a diluent such as tetraethoxysilane, a quantitative yield of tetramethoxysilane is obtained; the reaction (m) can be catalysed with sodium methoxide.

$$[Si] + 4\ CH_3OH \xrightarrow{20-60\,^\circ C} Si(OCH_3)_4 + 2\ H_2 \qquad (m)$$

Active silicon reacts quantitatively with a further mole of chlorine to give silicon monochloride [Eq. (n)]. This compound is a yellow-red to orange solid which, like active silicon, is insoluble in all solvents.

$$2\ [Si] + Cl_2 \xrightarrow{20-40\,^\circ C} 2\ [SiCl] \qquad (n)$$


[63] *H. Kautsky*, Z. Naturforsch. *7b*, 174 (1952).

[64] *H. Kautsky* and *L. Haase*, Z. Naturforsch. *8b*, 45 (1953).

[65] *H. Kautsky* and *L. Haase*, Chem. Ber. *86*, 1226 (1953).

[66] *E. Bonitz*, Chem. Ber. *94*, 220 (1961).

Silicon monochloride reacts with further chlorine to give the following succession of products[67]:

$$n\,[SiCl] + (n-4)/2\,Cl_2 \rightarrow Si_nCl_{2n-4}\ (M \approx 1000)\ [*] \quad (o)$$

$$n\,[SiCl] + (n-2)/2\,Cl_2 \rightarrow Si_nCl_{2n-2}\ (M = 850\text{–}950)\ [*] \quad (p)$$

$$n\,[SiCl] + n/2\,Cl_2 \rightarrow Si_nCl_{2n}\ (M = 670\text{–}690)\ [*] \quad (q)$$

$$n\,[SiCl] + (n+2)/2\,Cl_2 \rightarrow Si_nCl_{2n+2}\ (M = 170\text{–}700)\ [**] \quad (r)$$

Mixed halides can be obtained by reactions similar to (n) to (r) if mixtures of halogens are used, or if different halogens are used in succession (reaction conditions: atmospheric pressure; maximum temperature 60 °C; copper and iron halides have a catalytic effect).

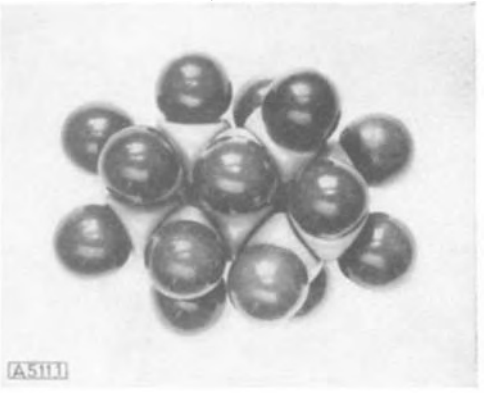
$$n\,[SiCl] + (n-2)/2\,Br_2 \rightarrow Si_nCl_nBr_{n-2} \quad (s)$$

Reaction (r) yields linear, colorless polysilicon chlorides, most of which can be distilled. The polysilicon chlorides obtained by reactions (o) to (q) become more intensely colored with increasing molecular weight, and fluoresce in ultraviolet light. Both properties had previously been observed only in cyclic silicon compounds. The cryoscopic molecular weights of compounds prepared by reactions (o) to (q) would also agree with cyclic structures. For example, $Si_{10}Cl_{18}$, a halide having the general formula $Si_nCl_{2n-2}$, is obtained in almost quantitative yield. It is a dark brown to yellow-red viscous liquid, which fluoresces yellow to orange-yellow in ultraviolet light, and crystallizes on prolonged standing under nitrogen.

Figs. 1 and 2 show Stuart-Briegleb molecular models of cyclic polysilicon chlorides. It is clear from these models that a silicon layer is enveloped by chlorine atoms, and they also show why the progressive chlorination of silicon crystals can stop with the formation of such polysilicon chlorides.

$Si_{10}Cl_{18}$ was discovered by *Schwarz* and *Köster*[68]. They obtained it by heating $Si_{10}Cl_{20}H_2$, prepared from $SiCl_4$ and silicon carbide in a current of $H_2$ in a quenching tube at 1000 °C[69]. Owing to the poor reproducibility of the experiments, the data published by these authors have repeatedly been questioned. However, we are able to confirm the properties described, particularly the solubility in benzene, the color, and the molecular weight.

In the active silicon obtained from the two-dimensional lattice of $CaSi_2$, practically all the polysilane bonds are accessible from the surface, owing to the lepidoidal structure[*]. On the other hand a compact silicon crystal can at first react only at its surface, and the reaction penetrates to deeper layers only when the products have been removed from the surface, either by mechanical means[70,71] or by a liquid reaction



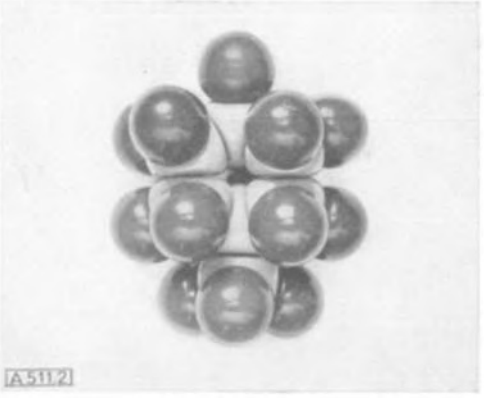


Fig. 2. $Si_7Cl_{14}$ ($M = 694$).

medium in which they are soluble[72]. There is no reason to believe that the active silicon obtained by the action of chlorine on $CaSi_2$ is fundamentally different from ordinary silicon[**] once the passive layer has been removed from the latter.

In any case, identical silicon compounds have been obtained from the two types under identical reaction conditions, and particularly at the same temperature[***]. This is also true in the case of ferrosilicon grades containing from 15 to 98 % of silicon. In continuous processes, the small quantity of impurities present in ordinary silicon makes it superior to active silicon, which contains about 66.5 wt-% of $CaCl_2$.

Active silicon produced from $CaSi_2$, as well as solid [SiCl], [SiBr] and [$SiOCH_3$], are excellently suited to the study of heterogeneous reactions of polysilane bonds. $Si_{10}Cl_{18}$ is very useful for the study of homogeneous reactions, owing to its ready solubility in hydrocarbons; it reacts in the same way as silicon dichloride (it formally contains 80 % of $SiCl_2$ groups).

Investigations on these test substances have led to the discovery of new reactions of the Si-Si bond. Thus ethylene reacts with polysilanes to form Si–(C–C)–Si linkages[62]; this reaction was first observed with [SiCl]. Polymerization of olefins in the presence of polysilanes, which may contain halogen or organic substituents, leads to polyolefins with silicon atoms in the polymer chains[73,74].

[67] German Pat. 1132901 (1960), BASF, inventor: *E. Bonitz*.

[*] M denotes the average molecular weight of all the reaction products, as found cryoscopically in cyclohexane.

[**] M denotes the average molecular weight, averaged over all fractions and the residue, as found cryoscopically in cyclohexane.

[68] *R. Schwarz* and *A. Köster*, Z. Naturforsch. *7b*, 57 (1952).

[69] *G. Brauer*: Handbuch der präparativen anorganischen Chemie. 2nd ed. F. Enke, Stuttgart 1960, pp. 606–619.

[*] Lepidoids are scale-like crystals with a two-dimensional macroscopic structure.

[70] German Published Pat. Appl. 1100006 (1958), BASF, inventor: *E. Bonitz*.

[71] German Pat. Appl. B 42296 IVb 120 (Oct. 17th, 1956), inventor: *E. Bonitz*

[72] German Pat. 1079607 (1958), BASF, inventor: *E. Bonitz*.

[**] Debye-Scherrer diagrams have also failed to provide evidence of the existence of another modification of silicon (*E. Hengge*, personal communication).

[***] The only difference is in the rates of the reactions. For example, the rate of reaction of a 98 % technical silicon with $Cl_2$ in tetrachloroethane suspension is generally from one fifth to one tenth of the rate for an active silicon obtained from $CaSi_2$.

### 3. Activation of Ordinary Silicon

#### a) Action of Ethyl Chloride on Silicon Suspended in Ethylchlorosilanes

Ethyl chloride is much less suitable for reaction with silicon than the thermally more stable methyl chloride. Ethyl chloride decomposes relatively quickly above 250 °C, giving ethylene and hydrogen chloride; consequently, satisfactory yields of ethylchlorosilanes cannot be obtained above this temperature. Thus the problem is to activate technical silicon to such an extent that the reaction can be carried out below 300 °C, and to maintain the activity throughout the reaction.

The best method is to produce fresh fracture surfaces by grinding the silicon in liquid alkylchlorosilanes, for example. Elementary silicon then becomes extremely reactive. Thus *Köster* [75] writes:

> If, after the pulverization of silicon in extremely pure argon, the vibratory mill is stopped and chlorine introduced, no reaction occurs. When the mill is switched on again, however, the reaction proceeds with explosive violence....

We offer the following explanation: The dry grinding of the silicon produces only a few active sites, on which silicon monochloride is formed instantaneously, so protecting underlying layers from further attack by chlorine at normal temperatures. However, if the surface chloride is rubbed off by further grinding, it reacts vigorously. Since the heat of reaction cannot be led away rapidly enough, the reaction leads mainly to silicon tetrachloride. If, on the other hand, activation by grinding is carried out in a liquid diluent (generally the products of an earlier reaction), the activity of the silicon in suspension is retained indefinitely.

An active silicon suspension is dark brown to brick and greasy, whereas an inactive suspension is graphite grey and hardly greasy. An active suspension of this type reacts with ethyl chloride at 90 °C in accordance with Equation (t) [76], with consumption of the silicon crystals and formation of polyethylchlorosilane as almost

$$n\,Si + n\,C_2H_5Cl \xrightarrow{90\text{-}150^\circ C} -\left[\begin{array}{c} C_2H_5 \\ | \\ -Si- \\ | \\ Cl \end{array}\right]_n- \qquad (t)$$

the only product. Reaction of the same starting materials at 180 to 220 °C leads quantitatively to ethylchloromonosilanes, possibly in accordance with Scheme (u).

$$-\left[\begin{array}{c} C_2H_5 \\ | \\ -Si- \\ | \\ Cl \end{array}\right]_n- + n\,C_2H_5Cl \xrightarrow{>150^\circ C}$$

$$\frac{n}{a}(C_2H_5)_2SiCl_2 + \frac{n}{b}C_2H_5SiCl_3 + \frac{n}{b}(C_2H_5)_3SiCl \qquad (u)$$

$(n/a + 2n/b = 1)$

No difficulties arise in connection with heat exchange, since the liquid and subsequently vaporizing alkyl halide can remove almost any amounts of heat produced in the reaction. It is preferable to use elevated pressures.

The smoothness of reactions (t) and (u) is reminiscent of the analogous reaction (v) of aluminum with ethyl chloride, which leads to the formation of "ethylaluminum sesquichloride" [77, 78].

$$2\,Al + 3\,C_2H_5Cl \xrightarrow{40\text{–}180\,^\circ C} Cl_3Al_2(C_2H_5)_3 \qquad (v)$$

#### b) Reaction of Silicon with Methyl and Ethyl Chlorides in Liquid Paraffin

In attempts to carry out the Rochow reaction "dry" in a tube with active silicon produced from calcium silicide, the silicon reacted spontaneously in the methyl chloride stream at about 200 °C. To avoid this spontaneous reaction, active silicon was slurried in liquid paraffin (b.p. 340–380 °C). If methyl chloride is introduced at 180 to 200 °C and normal pressure, methylchlorosilanes distil off after a time. The reaction does not require additional catalysts, but it is facilitated particularly by paraffin-soluble copper compounds, such as copper(II) acetylacetonate.

Though the technical calcium silicide [*] used contained about 10 % by weight of ordinary silicon, the solid reaction residue consisted entirely of calcium chloride. The ordinary silicon had evidently been activated in a mixture with "active" silicon and consumed. The silicon component of ferrosilicon (25 wt-% Si) suspended in liquid paraffin also reacted quantitatively with methyl chloride. The residue consisted of silicon-free, pyrophoric iron (a sort of "Raney iron") [70, 71] [**].

### 4. New "Halogen-Free" Syntheses

Organosilanols cannot generally be isolated as the primary products of the hydrolysis of organochlorosilanes, but immediately condense under the influence of the hydrochloric acid formed to give organic polysiloxanes.

There had previously been no industrially useful syntheses of silanes not involving halogen compounds. It was therefore desirable to seek for a "halogen-free" silane synthesis, and for a method for the synthesis of organosilanes, organosilanols, or organosiloxanes from

[73] *M. Schmeisser* and *M. Schwarzmann*, Z. Naturforsch. *11b*, 278 (1956).

[74] *H. Seibt*, Diploma Thesis, Universität München, 1956.

[75] *A. Köster*, Angew. Chem. *69*, 563 (1957).

[76] German Pat. 1161430 (1961), BASF, inventor: *E. Bonitz*.

[77] *A. V. Grosse* and *J. M. Mavity*, J. org. Chemistry *5*, 106 (1940).

[78] *K. Ziegler* and *H. Martin*, Makromolekulare Chem. *18/19*, 186 (1956).

[79] US.-Pat. 2389931 (1945), General Electric, inventors: *J. E. Sellers* and *J. L. Davis*.

[80] US.-Pat. 2449821 (1943). General Electric, inventors: *C. E. Reed* and *J. T. Coe*.

[81] German Published Pat. Appl. 1102119 (1959), Wacker-Chemie, inventors: *E. Euk*, *J. Nickl*, *O. Harbich*, and *W. Schindelin*.

[82] See [4], pp. 39–43.

[*] Süddeutsche Kalkstickstoff-Werke AG., Trostberg/Oberbayern (Germany).

[**] These studies were carried out in 1956-1958 with a stainless steel agitator having a ball mill in the hemispherical bottom.

elementary silicon, unsaturated hydrocarbons (or their derivatives) and water [83,84].

Elementary silicon dissolves readily in lower alcohols, particularly methanol, to form alkoxysilanes. (The reaction conditions and methods are identical with those described earlier.)

Reactions (w) and (x) take place between 20 and about 220 °C (preferably between 150 and 200 °C) and at 1 atm or slightly higher pressures. The yields per unit volume and per unit time are higher than in any other reaction of elementary silicon, and no metal catalysts are required.

$$Si + 3\,CH_3OH \rightarrow (CH_3O)_3SiH + H_2 \quad (w)$$

$$Si + 2\,CH_3OH \rightarrow (CH_3O)_2SiH_2 \quad (x)$$

Compounds containing more than two Si–H bonds may be obtained by disproportionation, *e.g.* in accordance with Equation (y).

$$2\,(C_3H_7O)_2SiH_2 \rightarrow (C_3H_7O)_4Si + SiH_4 \quad (y)$$

An example is the production of propylsilanetriol from silicon (98 % Si, 1.8 % Fe, 0.1 % Al, 0.1 % Ca), propene, and water. The methanol required to dissolve the silicon is regenerated on hydrolysis of the propyltrimethoxysilane, and can be recycled to reaction (z) if desired.

$$Si + 3\,CH_3OH \xrightarrow[5-7\ atm]{180-190\,^\circ C} HSi(OCH_3)_3 + H_2 \quad (z)$$

$$HSi(OCH_3)_3 \xrightarrow[40-50\ atm]{150\,^\circ C,\ +\,CH_3-CH=CH_2,\ Fe(CO_5)\ [85]} C_3H_7Si(OCH_3)_3$$

$$C_3H_7Si(OCH_3)_3 \xrightarrow{+3H_2O} C_3H_7Si(OH)_3 + 3\,CH_3OH$$

If the temperature rises above 250 °C during the reaction of silicon with lower alcohols, the reaction may become explosive, with intense evolution of heat and formation of $SiO_2$, SiC, soot, $H_2$, and hydrocarbons as the only products.

## III. Comparison of the Two Processes

In the "dry" process, the gaseous reactant is always present in excess relative to the amount of silicon in the active part of the surface of the solid. The reaction products are therefore monosilanes. In the suspension process, the active silicon phase is present in excess, the other reactant being added as it is consumed. Consequently, the primary products are polysilanes, which are initially solid, and subsequently become liquid. Liquid polysilanes are autoxidizable, and so protect the active silicon phase against oxide passivation. Polysilanes formed have an autocatalytic effect. Liquid polysilanes react in solution with compounds that cleave Si–Si bonds (*e.g.* halogen compounds, metal alkyls, alkali metals, or bases), to give monosilanes.

The "dry" process never even approaches chemical equilibrium. The losses due to thermal decomposition are too great to allow recycling of unwanted reaction products. In the suspension process, on the other hand, equilibria can be established, and unwanted reaction products can be recycled.

The "dry" process requires temperatures of about 300 °C or higher, whereas a maximum temperature of 200 °C generally suffices in the suspension process. Heat exchange is difficult to control in the "dry" process. In the suspension process, on the other hand, the heat of reaction can be compensated by the heat of vaporization of liquid components (solvent, reactant).

Processes in which the grinding and the reaction are carried out in separate vessels are preferred. To avoid spontaneous reactions, it is recommended that the mill should be cooled. Dry silicon powdered in the presence of air and slurried in liquids may react suddenly when an attempt is made to start the reaction. Grinding and reaction in alcohols, ethers, esters, and ketones is particularly dangerous.

It appears that any substance that reacts with silicon can also form passive layers. Even pure halogens can passivate the surface of the silicon crystals against further attack by halogen. These thin passive layers can apparently be broken open when the temperature is raised, with the result that a spontaneous reaction takes place.

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[83] Belg. Pat. 661697 (1965), BASF, inventor: *E. Bonitz.*

[84] Belg. Pat. 668907 (1966), BASF, inventor: *E. Bonitz.*

[85] *R. Ch. Freidlina, Ye. Z. Chukowskaja,* and *I. Zao,* Dokl. Akad. Nauk SSSR *127*, 352 (1959).

# Syntheses and Reactions of O,N,N′-Trisubstituted Isoureas

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*The $CuCl_2$-catalysed addition of alcohols to aliphatic carbodiimides (particularly diisopropylcarbodiimide) to form O,N,N′-trialkylisoureas may, in the case of bifunctional hydroxy compounds (esters of α-hydroxycarboxylic acids, diols, halogeno alcohols, amino alcohols, and cyclic hydroxy ethers), continue to give 5-, 6-, and 7-membered 1,3-O,N or 1,3-N,N heterocycles. O,N,N′-Trialkylisoureas are selective alkylating agents. Thus alcohols with allyl structures can be etherified with diisopropylcarbodiimide; a new method of esterification via O,N,N′-trialkylisoureas has been applied to mesitylenecarboxylic acid.*

## Introduction

The addition of alcohols to carbodiimides has been known since the end of the last century [1]. The isourea ethers *(1)* were prepared from "carbodiphenylimide", di-(*o*-tolyl)-, or di-(*p*-tolyl)-carbodiimide under pressure and at elevated temperatures [2] or with the aid of sodium alkoxides [3,4], and until about 10 years ago these were the only known compounds of this class [5].

$$ROH + R'N{=}C{=}NR'' \longrightarrow R'N{=}\underset{\displaystyle OR}{\overset{\displaystyle |}{C}}{-}NHR'' \quad (1)$$

The lack of interest in this reaction probably was due to the fact that the carbodiimides available at that time were troublesome to prepare [1,6] and had a marked tendency to polymerize [1,7]. This is particularly true of the only aliphatic carbodiimides known in 1938 [8], *viz.* diethyl- [9] and di-(n-propyl)carbodiimides [10,11]. The first indication that dicyclohexylcarbodiimide is not attacked by alcohols came in 1939 [12]. During the preparation of a number of new *N,N′*-diarylisoureas by the alkoxide method, *Khorana* [13] found that dicyclohexylcarbodiimide does not react with alcohols (*e.g.* n-butanol) under these conditions. *Erich Schmidt*'s work on the stabilities [14,15] of aliphatic carbodiimides and economical methods for their preparation [16] laid the foundations for an investigation of the addition of alcohols to aliphatic carbodiimides. It is now possible to obtain most *O,N,N′*-trialkylisoureas by addition of alcohols to aliphatic carbodiimides.

### 1. O,N,N′-Trialkylisoureas from Monofunctional Alcohols

The only cases of spontaneous addition of hydroxy groups are found in the cyclization of *N*-(β-hydroxyethyl)-*N′*-alkylcarbodiimides *(2)* formed *in situ* from thioureas and mercuric oxide. The products are 2-iminooxazolidines *(3)*, which may be regarded as cyclic isourea ethers. Similarly, the product obtained from 3-(hydroxypropyl)allylcarbodiimide has been assumed to have the structure of a 2-allyliminotetrahydro-1,3-oxazine [14].

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[1] *H. G. Khorana*, Chem. Reviews *53*, 145 (1953).

[2] *F. Lengfeld* and *J. Stieglitz*, Ber. dtsch. chem. Ges. *27*, 926 (1894).

[3] *J. Stieglitz*, Ber. dtsch. chem. Ges. *28*, 573 (1895).

[4] *F. B. Dains*, J. Amer. chem. Soc. *21*, 136 (1899).

[5] The first known compound with the isourea ether structure was the "ethoxymethylenedianthranilic acid" [*O*-ethyl-*N,N′*-bis-(*o*-carboxyphenyl)isourea] prepared by *T. Sandmeyer* from anthranilic acid and ethyl iminocarbonate; cf. Ber. dtsch. chem. Ges. *19*, 2650 (1886).

[6] *W. Weith*, Ber. dtsch. chem. Ges. *7*, 10 (1874).

[7] *F. Zetzsche*, *H. E. Meyer*, *H. Overbeck*, and *W. Nerger*, Ber. dtsch. chem. Ges. *71*, 1512 (1938).

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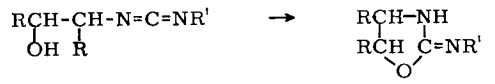
[14] *E. Schmidt* and *W. Striewsky*, Ber. dtsch. chem. Ges. *74*, 1285 (1941).

[15] *E. Schmidt*, *W. Striewsky*, and *F. Hitzler*, Liebigs Ann. Chem. *560*, 222 (1948).

[16] a) *E. Schmidt* and *M. Seefelder*, Liebigs Ann. Chem. *571*, 83 (1951); cf. Houben-Weyl: Methoden der organischen Chemie, 4th ed., Thieme, Stuttgart 1952, vol. 8, p. 178. Since then, other methods have been developed for the preparation of carbodiimides: b) Organic Syntheses *43*, 31 (1963); c) *B. V. Bocharov*, Usp. Khim. *34*, 212 (1965); d) *E. Schmidt*, *D. Ross*, *J. Kittl*, and *H. H. von Düsel*, Liebigs Ann. Chem. *612*, 11 (1958); e) *H. Walther*, East German-Pat. 22437 (1959), Chem. Abstr. *58*, 2382f (1963); f) *E. Dyer* and *R. E. Read*, J. org. Chemistry *26*, 4388 (1961); g) *W. Neumann* and *P. Fischer*, Angew. Chem. *74*, 801 (1962), Angew. Chem. internat. Edit. *1*, 621 (1962); h) *T. W. Campbell*, Österr. Chemiker-Ztg. *63*, 209 (1962); i) *W. S. Wadsworth* and *W. D. Emmons*, J. Amer. chem. Soc. *84*, 1316 (1962); k) *H. H. Ulrich* and *A. A. R. Sayigh*, Angew. Chem. *74*, 900 (1962); Angew. Chem. internat. Edit. *1*, 595 (1962); J. chem. Soc. (London) *1963*, 5558; Angew. Chem. *76*, 781 (1964), Angew. Chem. internat. Edit. *3*, 639 (1964); l) *P. Schlack* and *G. Keil*, Liebigs Ann. Chem. *661*, 164 (1963); m) *A. Messmer*, *I. Pintér*, and *F. Szegö*, Angew. Chem. *76*, 227 (1964), Angew. Chem. internat. Edit. *3*, 228 (1964); n) *H. Eilingsfeld*, *G. Neubauer*, *M. Seefelder*, and *H. Weidinger*, Chem. Ber. *97*, 1232 (1964); o) *B. Anders* and *E. Kühle*, Angew. Chem. *77*, 430 (1965), Angew. Chem. internat. Edit. *4*, 430 (1965); p) *R. Neidlein* and *E. Heukelbach*, Tetrahedron Letters *1965*, 149; q) *P. Schnegg*, Dissertation, Universität München, 1965.



*(2a)*, R = $C_6H_5$; R' = Alkyl, Aryl [17] *(3)*
*(2b)*, R = H; R' = Allyl [8]

The addition of alcohols to aliphatic carbodiimides became possible with the discovery by *Schmidt* and *Moosmüller*[18] that the reaction is catalysed by copper salts. In the presence of copper(I) or copper(II) chloride (*e.g.* 0.075 mmole of $CuCl_2$ per 100 mmole of diisopropylcarbodiimide[19]), equimolar amounts of primary, secondary, or tertiary alcohols without solvents react at room temperature in a slightly exothermic reaction. The *O,N,N'*-trialkylisoureas *(1)* that have so far been prepared by this method are shown in Table 1.

Carbodiimides are weakly electrophilic. As shown by the reactivities of differently substituted carbodiimides in the addition of water[23], the electrophilic strength of the central carbodiimide carbon atom increases as the basicity of the adjacent N atoms decreases. This is taken into account in the use of diarylcarbodiimides, though the effect achieved with phenyl and tolyl groups is very small: high temperatures and pressures are required for the addition of alcohols[2].

Although the presence of alkoxide[3,4] increases the chance of nucleophilic attack by the alcohol, the tendency of the carbodiimide to undergo addition remains weak, so that aliphatic carbodiimides such as dicyclohexylcarbodiimide cannot react under these conditions.

Acid catalysis increases the electrophilic strength of the carbodiimide to such an extent that vigorous addition of water takes place; similarly, the many known additions of H-acids[1] are initiated by a proton addition[24]. The possibility of acid-catalysed addition of alcohol was noted by *Stieglitz*[2] in his first preparations of "isourea ethers".

Table 1. *O,N,N'*-Trialkylisoureas *(1)* from monohydric alcohols and dialkylcarbodiimides.

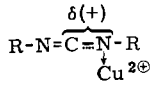
| ROH | R' [a] | R'' | Yield [%] | B.p. [°C/mm Hg] (M.p. [°C]) | $n_D^{20}$ | $c_4^{20}$ | Ref. |
|---|---|---|---|---|---|---|---|
| Methanol | i-Pr | i-Pr | 98 | 54/10 | 1.4379 | 0.88045 | [18] |
| Methanol | n-Bu | c-Hex | 93 | 132–134/11 | 1.4772 | 0.9446 | [18] |
| Methanol | c-Hex | c-Hex | 94 | 162–163/11 (32–33) | 1.4945 [b] | — | [18,20] |
| Methanol | Me | t-Bu | 90 | 51–53.5/11 | 1.4460 | 0.9053 | [18] |
| Ethanol | Me | t-Bu | 85 | 58–60/10 | 1.4438 | 0.8894 | [21] |
| Ethanol | i-Pr | i-Pr | 94 | 64–65/10 | 1.4340 | 0.8649 | [18] |
| 2-Ethoxyethanol | i-Pr | i-Pr | 88 | 103–105/10 | 1.4414 | 0.9071 | [18] |
| 2-Diethylaminoethanol | i-Pr | i-Pr | 92 | 123/11 | 1.4509 | 0.8833 | [18] |
| n-Butanol | i-Pr | i-Pr | 81 | 87–89/10 | 1.4397 | 0.8582 | [21] |
| n-Butanol | n-Bu | n-Bu | 65 | 58/0.001 | 1.4478 [b] | — | [20] |
| 1,2-*O*-Isopropylideneglycerol | i-Pr | i-Pr | 99 | 86–88/0.006 | 1.4516 | 0.9745 | [22] |
| 2-Nitro-2-methylpropan-1-ol | i-Pr | i-Pr | 73 | (53) | — | — | [22] |
| n-Octanol | i-Pr | i-Pr | 93 | 140–141/10 | 1.4458 | 0.8569 | [18] |
| Furfuryl alcohol | i-Pr | i-Pr | 88 | 65–67/0.002 | 1.4764 | 0.9887 | [22] |
| Tetrahydrofurfuryl alcohol | i-Pr | i-Pr | 97 | 72–74/0.003 | 1.4649 | 0.9674 | [22] |
| Isopropyl alcohol | i-Pr | i-Pr | 93 | 66–67/10 | 1.4298 | 0.8508 | [18] |
| Cyclohexanol | i-Pr | i-Pr | 92 | 115–117/10 | 1.4632 | 0.9144 | [18] |
| Cyclohexanol | n-Bu | n-Bu | 65 | 58/0.001 | 1.4478 [b] | — | [20] |
| Menthol | i-Pr | i-Pr | 88 | 75–77/0.002 | 1.4584 | 0.8395 | [22] |
| Borneol | i-Pr | i-Pr | 82 | 84–86/0.002 | 1.4726 | 0.9343 | [22] |
| t-Butanol | i-Pr | i-Pr | 64 | 67–68/9 | 1.4264 | 0.8377 | [18] |
| t-Amyl alcohol | i-Pr | i-Pr | 51 | 81.5–82.5/10 | 1.4331 | 0.8491 | [18] |
| t-Amyl alcohol | Me | t-Bu | 68 | 80–82/10 | 1.4431 | 0.8750 | [18] |
| *N*-Methyl-*N*-(2-hydroxyethyl)-aniline | i-Pr | i-Pr | 97 | 123/0.01 | 1.5213 | 0.9830 | [19,19a] |
| *N*-Methyldiethanolamine | i-Pr | i-Pr | 86 | 128.5–130/0.001 | 1.4663 | 0.9337 | [19] |
| *N*-(2-Hydroxyethyl)aniline | i-Pr | i-Pr | 99 | 122.5/0.001 | 1.5248 | 0.9948 | [19,19a] |
| 2-Phenoxyethanol | i-Pr | i-Pr | 97 | 97–98/0.005 | 1.5010 | 0.9960 | [19,19a] |
| Citronellol | i-Pr | i-Pr | 97 | 102–103/0.01 | 1.4597 | 0.8703 | [19,19a] |
| Cholesterol | i-Pr | i-Pr | 94 | (83.5–84) | — | — | [19,19a] |
| Allyl alcohol | i-Pr | i-Pr | 98 | 75–76/10 | 1.4503 | 0.8829 | [19,19a] |
| Benzyl alcohol | i-Pr | i-Pr | 98 | 92–93/0.01 | 1.5001 | 0.9620 | [19,19a] |
| *p*-Nitrobenzyl alcohol | i-Pr | i-Pr | 71 | (42) | — | — | [19a] |
| Quinine | i-Pr | i-Pr | 72 | (110–111) | — | — | [19a] |

[a] The following abbreviations are used in this and the following tables: i-Pr = isopropyl; c-Hex = cyclohexyl; n-Bu = n-butyl; Me = methyl.
[b] $n_D^{25}$.

*Khorana* has also prepared an *O*-methylisourea from dicyclohexylcarbodiimide and methanol in the presence of di-(*p*-nitrophenyl) hydrogen phosphate[25].


[17] *H. G. Söderbaum*, Ber. dtsch. chem. Ges. *28*, 1897 (1895).
[18] *E. Schmidt* and *F. Moosmüller*, Liebigs Ann. Chem. *597*, 235 (1955).
[19] *E. Däbritz*, Dissertation, Universität München, 1963.
[19a] *E. Schmidt, E. Däbritz*, and *K. Thulke*. Liebigs Ann. Chem. *685*, 161 (1965).
[20] *S. E. Forman, C. A. Erickson*, and *H. Adelman*, J. org. Chemistry *28*, 2653 (1963).
[21] *W. Carl*, Dissertation, Universität München, 1960.
[22] *E. Schmidt* and *W. Carl*, Liebigs Ann. Chem. *639*, 24 (1961).
[23] *S, Hünig, H. Lehmann*, and *G. Grimmer*, Liebigs Ann. Chem. *579*, 87 (1953).
[24] *E. Vowinkel*, Chem. Ber. *96*, 1702 (1963), has studied the solvent-dependence of the addition of phenols to carbodiimides, and concluded that the reaction proceeds by simultaneous addition of the proton and the phenoxide ion.
[25] *H. G. Khorana*, Canad. J. Chem. *32*, 261 (1954).

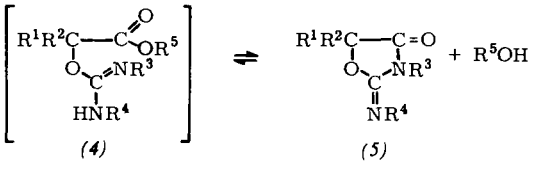
The catalytic action of metal halides such as copper(II) chloride and zinc chloride [26] presumably is due to coordination by nitrogen, with a consequent marked increase in the reactivity of the carbodiimide carbon towards nucleophiles.



## 2. O,N,N′-Trialkylisoureas Containing Another Functional Group

### 2.1. Esters of α-Hydroxycarboxylic Acids and Dialkylcarbodiimides

The first example of a secondary reaction following the $CuCl_2$-catalysed addition of alcohols was observed in the reaction of esters of α-hydroxycarboxylic acids with dialkylcarbodiimides to give 2-imino-4-oxazolidones *(5)* [22] (cf. Table 2); this reaction presumably proceeds *via* the initial product *(4)*, which cannot be isolated. The alcohol $R^5OH$ that is formed must be removed from the equilibrium by a second mole of carbodiimide.



*(4)* *(5)*

This cyclization was the first indication that the dominant chemical characteristic of *O,N,N′*-trisubstituted isoureas is the nucleophilic activity of the imino nitrogen. This nucleophilic activity is the basis of nearly all the reactions described in the present paper.

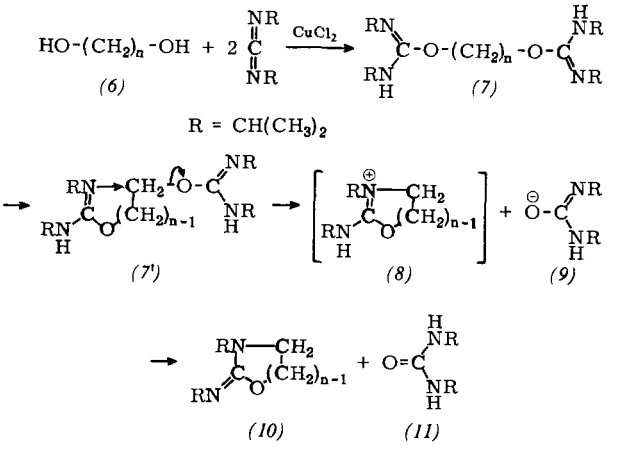
Table 2. 2-Imino-4-oxazolidones *(5)* prepared from methyl or ethyl α-hydroxycarboxylates and aliphatic carbodiimides [21,22].

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield [%] | B.p. [°C/mm Hg] | $n_D^{20}$ | $d_4^{20}$ |
|---|---|---|---|---|---|---|---|
| H | H | i-Pr | i-Pr | 91 | 96–98/10 | 1.4662 | 1.0161 |
| H | H | Me | t-Bu | 96 | 101–103/13 | 1.4755 | 1.0510 |
| $CH_3$ | H | i-Pr | i-Pr | 92 | 92–94/11 | 1.4569 | 0.9798 |
| $CH_3$ | H | Me | t-Bu | 90 | 89–91/10 | 1.4638 | 1.0061 |
| $CH_3$ | $CH_3$ | Me | t-Bu | 72 | 85–87/10 | 1.4560 | 0.9783 |

### 2.2. Bifunctional Alcohols and Dialkylcarbodiimides

The reactions of diols *(6)* with diisopropylcarbodiimide can be represented by the following sequence, which leads either to *O,O′*-alkylenebisisoureas *(7)* or 1,3-oxaza compounds *(10)* and *N,N′*-diisopropylurea *(11)*.

[26] *E. Schmidt, A. Reichle, M. Wandel*, and *W.-R. Carl*, German Published Pat. Appl. 1181202 (1962).



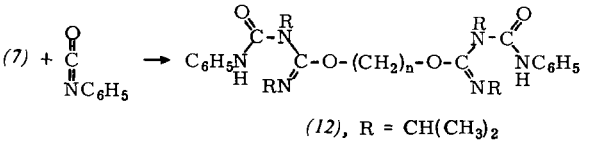
*(6)* *(7)*

R = $CH(CH_3)_2$

*(7′)* *(8)* *(9)*

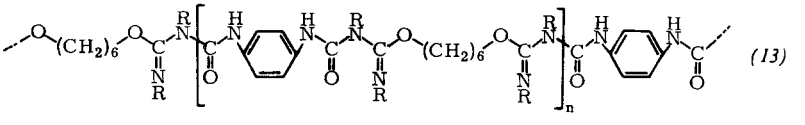
*(10)* *(11)*

The addition of the diol to two moles of carbodiimide leads to the acyclic product if the alcohol contains more than three methylene groups (n > 3). The *O,O′*-alkylenebis-(*N,N′*-diisopropylureas) *(7)* (n = 4,6) [19,19a], which are obtained in almost quantitative yields, react with phenyl isocyanate to form biuret-like adducts *(12)*, which may be regarded as derivatives of *N,N′*-diisopropyl-*N*-(*N*-phenylcarbamoyl)isourea.



*(12)*, R = $CH(CH_3)_2$

Diisocyanates such as n-hexylene diisocyanate or *p*-phenylene diisocyanate react with *O,O′*-alkylenebis-isoureas such as *(7)* (n = 6) to form linear macromolecules *(13)*.



*(13)*

The primary adducts of ethylene glycol and 1,3-propanediol with diisopropylcarbodiimide undergo spontaneous cyclization, initiated by an intramolecular $S_N2$ attack by the imino nitrogen. This step of the reaction can be followed by the color changes [19], which are probably due to the coordinated copper(II) ion in the activated carbodiimide.

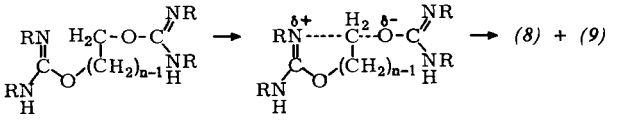
Proton transfer from the resonance-stabilized cyclic isouronium ion *(8)* to the strongly basic isourea anion *(9)* [27] leads to 3-isopropyl-2-(isopropylimino)oxazolidine *(10)* (n = 2) [28] or 3-isopropyl-2-(isopropylimino)tetrahydro-1,3-oxazine *(10)* (n = 3), together with *(11)* [19a].

[27] *D. V. Kashelikar* and *C. Ressler*, J. Amer. chem. Soc. *86*, 2467 (1964), have also proposed an intramolecular substitution with displacement of the isourea anion for the dehydration of carbobenzoxy-L-asparagine and carbobenzoxy-L-glutamine with dicyclohexylcarbodiimide to the nitriles of the corresponding ω-amino acids.

[28] 2-Arylimino-3-methyloxazolidines can be prepared from isocyanide dichlorides and *N*-methylethanolamine: *E. Kühle*, Angew. Chem. *74*, 861 (1962), Table 2; Angew. Chem. internat. Edit. *1*, 647 (1962).

The reaction with ethylene cglyol is so vigorous that cooling is necessary in order to avoid a reduction in yield. The formation of the sterically less favored tetrahydrooxazine ring requires longer reaction times and slight heating if good yields are to be obtained. *O,O'*-Butylenebisisourea *(7)* (n = 4) can be isolated, and must be heated for 15 hours at 120 °C to obtain *(11)* and the strained 7-membered ring system of 3-isopropyl-2-(isopropylimino)hexahydro-1,3-oxazepine *(10)* (n = 4)[19].

These reactions, like all the other $S_N2$ reactions described below, which are characterized by charge separation in the transition state *(8a)*, should be favored by polar solvents,

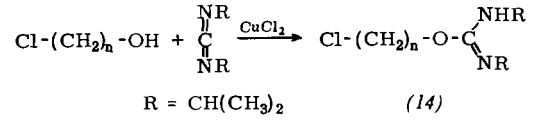


*(7)* *(8a)*

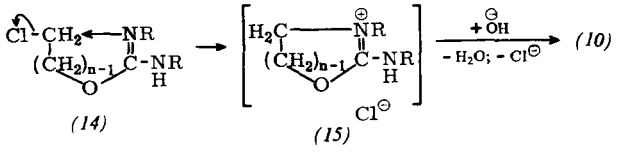
as has been found experimentally. The usual solvent is dimethylformamide, which also facilitates the removal of the *N,N'*-diisopropylurea, since this is only sparingly soluble in cold dimethylformamide. It has also been found advantageous to add dimethylformamide in some additions that proceed without secondary reactions.

### 2.3. Dialkylcarbodiimides and Halogeno Alcohols Containing Primary Hydroxy Groups

α,ω-Halogeno alcohols undergo ring closure, *e.g.* to form iminium chlorides *(15)*, from which the 2-imino 1,3-oxaza compound *(10)* is liberated by aqueous $K_2CO_3$, NaOH, or KOH.



R = $CH(CH_3)_2$ *(14)*



*(14)* *(15)*

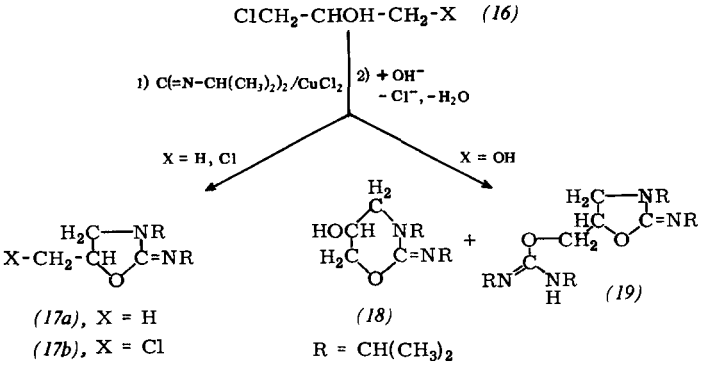
An exception is 4-chlorobutan-1-ol, from which the open-chain isourea *(14)* (n = 4) can be obtained; the 1,3-oxazepine *(10)*, n = 4, is formed only after prolonged heating.

Table 3. 2-Imino-1,3-oxaza compounds *(10)* synthesized from diisopropylcarbodiimide and diols (method I) or halogeno alcohols (method II).

| n | B.p. [°C/mm Hg] | $n_D^{20}$ | $d_4^{20}$ | Infrared C=N band [cm⁻¹] | Yield [%] method I | Yield [%] method II | Ref. |
|---|---|---|---|---|---|---|---|
| 2 | 86–87/9 | 1.4603 | 0.9398 | 1682 | 91 | 78 | [19, 19a] |
| 3 | 95/9 | 1.4709 | 0.9448 | 1642 | 91 | 74 | [19, 19a] |
| 4 | 96–97/10 | 1.4659 | 0.9247 | 1684 | 83 | 34 | [19] |

### 2.4. Dialkylcarbodiimides and Halogeno Alcohols Containing Secondary Hydroxy Groups

Alcohols of the type *(16)* react in accordance with the following scheme:



*(17a)*, X = H
*(17b)*, X = Cl

*(18)*
R = $CH(CH_3)_2$

*(19)*

1-Chloropropan-2-ol [*(16)*, X = H] and 1,3-dichloropropan-2-ol [*(16)*, X = Cl] give 5-methyl- and 5-chloromethyl-2-iminooxazolidines *(17a)* and *(17b)*; the yields of these products are lower than those obtained from primary halogeno alcohols.

Treatment of 1-chloropropane-2,3-diol [*(16)*, X = OH] with two moles of diisopropylcarbodiimide in dimethylformamide does not lead to the expected halogenated 5-membered cyclic bases and diisopropylurea. Instead, the product is a mixture of two compounds, to which the structures *(18)* and *(19)* have been assigned on the basis of their infrared spectra and elementary analyses.

Table 4. Products obtained by the reaction of halogeno alcohols Cl–$CH_2$–CH(OH)–$CH_2$X with diisopropylcarbodiimide.

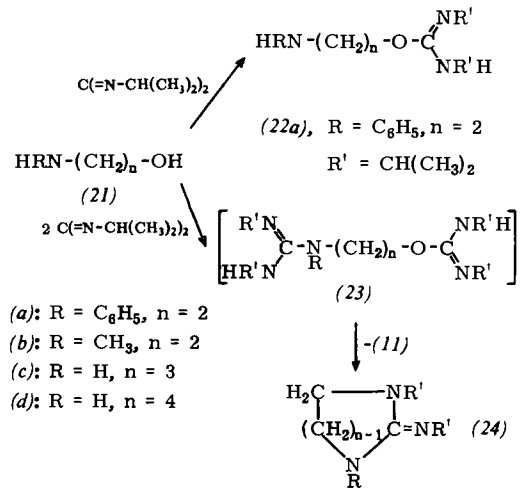
| X | End product | Yield [%] | B.p. [°C/mm Hg] | $n_D^{20}$ | $d_4^{20}$ | Infrared C=N band [cm⁻¹] |
|---|---|---|---|---|---|---|
| Cl | *(17b)* | 62 | 113–114/9 | 1.4791 | 1.0448 | 1682 |
| H | *(17a)* | 33 | 92–93/10 | 1.4597 | 0.9170 | 1685 |
| OH | *(18)* | (81) | 105–106/0.02 | 1.4788 | – | 1665 |
| | *(19)* | 74 (19) | 124–125/0.02 | 1.4755 | – | 1682 |

### 2.5. Dialkylcarbodiimides and Amino Alcohols Containing Primary or Secondary Amino Groups

Alcohols such as *(20)* containing tertiary amino groups react with diisopropylcarbodiimide almost quantitatively to give *O,N,N'*-trialkylisoureas or *O,O'*-al-

$R^1R^2N$–$CH_2$–$CH_2OH$ *(20a)* $R^1$, $R^2$=$C_2H_5$
*(20b)* $R^1$=$CH_3$, $R^2$=$C_6H_5$
*(20c)* $R^1$=$HOCH_2$–$CH_2$, $R_2$=$CH_3$

kylidenebis-*N,N'*-dialkylisoureas (cf. Table 1) without secondary reactions. On the other hand, primary or secondary amino groups in the β, γ, or δ positions with respect to the hydroxy group [as in the amino alcohols *(21)*] cause intramolecular substitutions in the diisopropylcarbodiimide adduct:



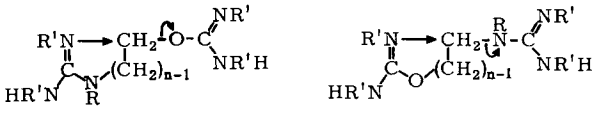
Whereas the amino alcohol *(21a)* reacts with diisopropylcarbodiimide (molar ratio 1:1) to give the *O,N,N'*-substituted isourea *(22a)* (yield 99%) [19,19a], the corresponding compound *(21b)* with aliphatic instead of aromatic substituents gives a number of products. For a stoichiometric reaction it is necessary to use two moles of carbodiimide per mole of *N*-methylethanolamine *(21b)*; cyclization to 2-isopropylimino-1-methylimidazolidine *(24a)* then occurs. Similarly, *(21c)* and *(21d)* react to form 3-isopropyl-2-(isopropylimino)hexahydropyrimidine *(24c)* and 3-isopropyl-2-(isopropylimino)heptahydro-1,3-diazepine *(24d)*, respectively.

Table 5. Cyclic guanidines *(24)* obtained from amino alcohols and diisopropylcarbodiimide.

| End product | Yield [%] | B.p. [°C/mm Hg] | $n_D^{20}$ | $d_4^{20}$ | Infrared C=N band [$cm^{-1}$] |
|---|---|---|---|---|---|
| *(24b)* | 84 | 93–94/9 | 1.4766 | 0.9133 | 1662 |
| *(24c)* | 82 | (m.p. 71 °C) | — | — | 1599 [*] |
| *(24d)* | 77 | 107–109/13 | 1.4741 | — | 1620 |

[*] In KBr.

The first step in the reaction of carbodiimides with the amino alcohols *(21b)* to *(21d)* probably is similar to the first step in the formation of bisisoureas *(7)* from diols. In the former case, however, instead of two hydroxy groups, one hydroxy group and an amino group add to two molecules of the carbodiimide to form the hypothetical adduct *(23)* in the primary step[29]. The subsequent ring closure is again induced by the influence of a neighboring group. In the diol cyclization, the imino nitrogen displaces an isourea group [see formula *(7')*]; in the asymmetric adduct *(23)*, on the other hand, the substitution can follow one of two courses, giving either cyclic guanidines [*via (25)*] or oxaza compounds [*via (26)*].



*(25)* *(26)*

R = $CH_3$, H; R' = $CH(CH_3)_2$; n = 2, 3, 4

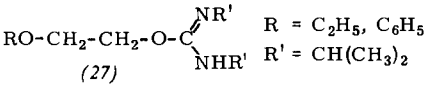
[29] The amino group is added more readily than the alcohol group; the preparation of substituted guanidines from carbodiimides has been known for a very long time, cf. *W. Weith*, Ber. dtsch. chem. Ges. *8*, 1530 (1875); Houben-Weyl: Methoden der organischen Chemie, 4th ed., Thieme, Stuttgart 1952, vol. 8, p. 182.

The products obtained [evidently *via* the complex *(25)*] are the 1,3-diaza compounds *(24b)* to *(24d)*, in agreement with theoretical expectations. The urea anion can leave the complex more easily than the guanidine anion. *Hammett* and *Pfluger*[30] showed, from the rates of displacement of other substituents by the trimethylamino group, that substituents that would react readily as entering groups are slow to leave the molecule. Thus the high nucleophilic activity of the guanidine group is in agreement with its reluctance to leave the molecule as a guanidyl anion in accordance with the model *(26)*.

Ring closures with acylated carbodiimides[31] probably are also based on intramolecular substitutions involving the guanidine group.

### 2.6. Hydroxy Ethers and Dialkylcarbodiimides

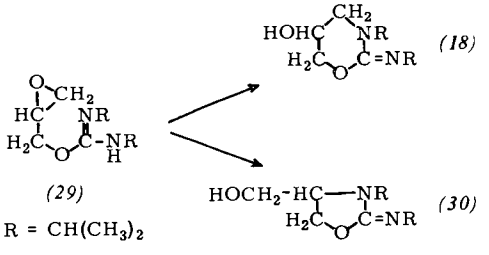
The carbodiimide adducts *(27)* of β-alkoxy alcohols do not enter into secondary reactions as shown by the



*(27)*

cases of the monoethyl[18] and monophenyl[19,19a] ethers of ethylene glycol (cf. also Table 1).

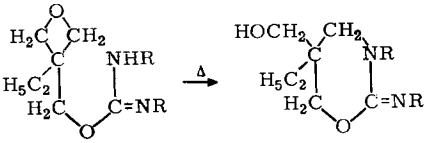
Strained cyclic ethers with β- or γ-hydroxy groups (cf. Table 6) can undergo ring cleavage following the addition step. 2,3-Epoxy-1-propanol *(28)* reacts first to form *(29)*, which then suffers spontaneous cleavage of the strained 3-membered ring. The strongly exothermic reaction leads to a mixture of two products, for which the structures *(18)* and *(19)* have been proposed[19].



*(29)* *(18)* *(30)*

R = $CH(CH_3)_2$

The oxetane *(31)* is less strained, so that the adduct *(32)* of 3-ethyl-3-hydroxymethyloxetane and diisopropylcarbodiimide is partially converted into the tetrahydro-1,3-oxazine *(33)* only on distillation; prolonged boiling in petroleum ether leads to *(33)* as the sole product. The ring cleavage can be followed by the disappearance of the characteristic oxetane band at 978 $cm^{-1}$ in the infrared spectrum[32].



*(32)* R = $CH(CH_3)_2$ *(33)*

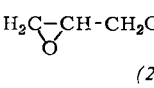
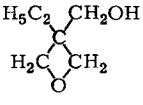
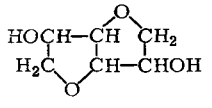
[30] *L. P. Hammett* and *H. L. Pfluger*, J. Amer. chem. Soc. *55*, 4079 (1953).

[31] *K. Hartke* and *J. Bartulin*, Angew. Chem. *74*, 214 (1962), Angew. Chem. internat. Edit. *1*, 211 (1962).

[32] *L. J. Bellamy*: The Infrared Spectra of Complex Molecules. Methuen, London, 1958, p. 119.

As was shown for the adducts of carbodiimides with furfuryl and tetrahydrofurfuryl alcohols (see Table 1), the strainless 5-membered ring containing ether oxygen is stable towards the –N=C(OR)–NH grouping. Thus 1,4;3,6-dianhydro-D-sorbital *(34)* reacts with diisopropylcarbodiimide to form a crystalline monoadduct or a liquid diadduct, depending on the conditions [19].

Table 6. Products obtained by the reaction of cyclic hydroxy ethers with diisopropylcarbodiimide [19].

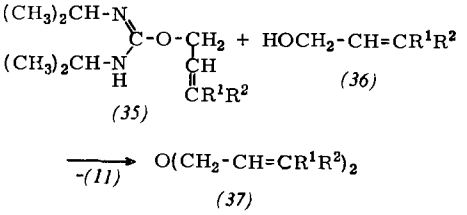
| Starting material | End products | Fraction of total [%] | Yield [%] | B.p. [°C/mm Hg] (m.p. [°C]) | $n_D^{20}$ | $d_4^{20}$ | Infrared C–N band [cm$^{-1}$] |
|---|---|---|---|---|---|---|---|
|  *(28)* | *(30)* | 65 | 72 | (69–69.5) | – | – | 1660 |
| | *(18)* | 35 | | (cf. Table 4) | | | 1665 |
|  *(31)* | *(32)* | | 82–89 [*] | 93/0.01 | 1.4662 | 0.9604 | 1662 |
| | *(33)* | | | (71.5) | – | – | 1601 [**] |
|  *(34)* | *O,N,N'*-trisubst. Isourea *O,O'*-linked bis-(*N,N'*-diisopropylisourea) | 44–53 [*] 47–56 [*] | 94–96 [*] | (91.5) 164–166/0.001 | – 1.4800 | – 1.0394 | 1642 1662 |

[*] Depending on reaction conditions [19].
[**] In KBr.

## 3. Alkylations and Condensations with O,N,N'-Trialkylisoureas

### 3.1. Etherification of Allyl Alcohols

The $CuCl_2$-catalysed reaction of equimolar amounts of diisopropylcarbodiimide with allyl alcohol leads to the isourea *(35a)*. Cinnamyl alcohol *(36b)*, and geraniol *(36c)* give mixtures of the ethers *(37b)* or *(37c)*, respectively, with diisopropylurea *(11)*. It appears that the carbodiimide adduct *(35b)* or *(35c)* initially formed alkylates unchanged alcohol *(36)*.



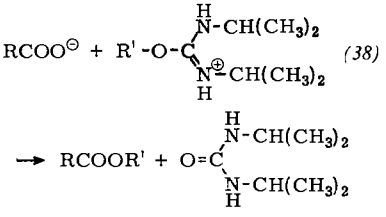
*(a)*: $R^1$, $R^2$ = H
*(b)*: $R^1$ = $C_6H_5$; $R^2$ = H
*(c)*: $R^1$ = $(CH_3)_2C{=}CH{-}CH_2{-}CH_2$; $R^2$ = $CH_3$

Allyl alcohol also can be etherified if the alcohol and the carbodiimide are used in a molar ratio of 2:1. The ethers *(37a)* to *(37c)* (yields 16, 37, and 60 %, respectively [19]) obtained when the alcohol is heated for 130 hours at 80 to 120 °C with diisopropylcarbodiimide are contaminated with allyl rearrangement products and resins.

[33] *M. S. Newman*, J. Amer. chem. Soc. *63*, 2431 (1941).

### 3.2. Esterifications

*O,N,N'*-Trialkylisoureas thus can act as alkylating agents. Carboxylic acids should be much more readily "alkylated" with these agents than are the allyl alcohols. The 1:1 combination of a monobasic carboxylic acid with the monoacid isourea ether should provide the carboxylate anion formed immediately with an electrophilic partner *(38)*, from which the preformed urea molecule can be easily displaced.



*(38)*

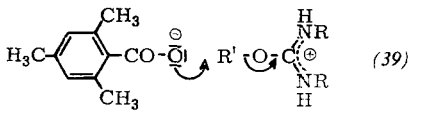
It was in fact found that ethyl acetate can be prepared in this way from *O*-ethyl-*N,N'*-diisopropylisourea and glacial acetic acid. The purified reactants were left to stand for 96 hours at room temperature, and the ethyl acetate was then separated from the diisopropylurea by distillation (yield 78 %) [19]. Probably the strongest evidence for reaction *via (38)* is the formation of esters of mesitylenecarboxylic acid (cf. Table 7). In this case the carboxylate anion makes a nucleophilic attack, as indicated in *(39)*, on the alkylating agent, *i.e.* the protonated isourea ether *(38)*. Since there is no transition state involving a tetrahedral carbonyl carbon,

Table 7. Esters of mesitylenecarboxylic acid obtained from *O*-alkyl-*N,N'*-diisopropylisourea (25 mmole in 10–20 ml of DMF).

| R | Conditions [hr/°C] | Yield [%] | B.p. [°C/mm] | $n_D^{20}$ | IR C=O band [cm$^{-1}$] |
|---|---|---|---|---|---|
| Ethyl | 140/75 | 80 | 120–121/10 | 1.5007 [*] | 1732 |
| *n*-Butyl | 50/50 | 94 | 144.5–145/10 | 1.4963 | 1728 |
| Benzyl | 15/50 | 89 | 127–128/0.01 | 1.5528 | 1725 |

[*] $n_D^{20}$ = 1.5008 [33].

this provides a new and simple method for the esterification of sterically hindered carboxylic acids.

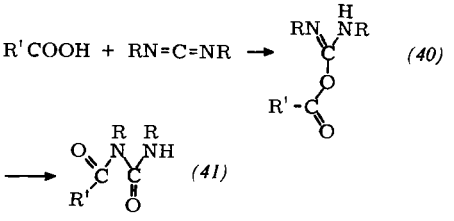


*(39)*

Phenol is alkylated similarly. As with carboxylic acids, a proton is first transferred to the isourea ether, which then alkylates the resulting phenoxide anion. n-Butyl phenyl ether was obtained in 91 % yield when phenol and *O*-n-butyl-*N,N'*-diisopropylisourea were heated at 120 °C for 15 hours [19]. *Vowinkel* [34] converted alcohols, phenols, and dicyclohexylcarbodiimide into aryl alkyl ethers by a similar method. The use of phenol labeled with $^{18}O$ recently showed that this "direct reaction" also involves the *O*-alkyl-*N,N'*-dicyclohexylisourea as an intermediate [35].

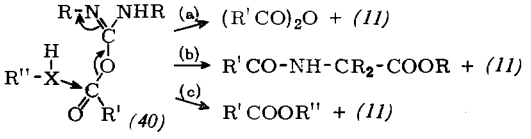
### 3.3. Dialkylcarbodiimides as Condensing Agents

A feature common to all known condensations involving carboxylic acids and carbodiimides is that these compounds first react to form the *O*-acylisourea *(40)*, which can either rearrange to give the *N*-acylurea *(41)* or react with a nucleophile R''XH [36–39].



*(40)* *(41)*

The nucleophile may be the carboxylic acid itself, which is acylated to give the anhydride by path (a). When aromatic carbodiimides are used, the reaction generally leads to *N*-acylureas *(41)* [37–41], whereas with aliphatic carbodiimides, the acid anhydride [39,41,42] or a mixture of the anhydride and *(41)* [41,42] generally are obtained.



*(40)* *(11)*

*(a)*: X = O; R'' = R'CO
*(b)*: X = NH; R'' = $CR_2COOR$
*(c)*: X = O; R'' = Alkyl

The *N*-acylureas *(41)* correspond to the trisubstituted ureas obtained by the reaction of phenols with diphenylcarbodiimide [43] or with dicyclohexylcarbodiimide [44]. Thus phenols, and particularly nitrophenols, also behave in the same way as carboxylic acids in the reaction with carbodiimides. However, no diaryl ethers were ever obtained in this reaction. The rearrangement of the initially formed *O*-phenylisourea to *N*-phenylisourea [43,44], which is analogous to the reaction *(40)* → *(41)*, may be classed as a Chapman rearrangement [45,46].

The formation of anhydrides with the aid of carbodiimides is of considerable importance in the preparation of esters of pyrophosphoric acid and of nucleotides [42,47,48]. Peptides can be obtained by route (b) if esters of amino acids are present to act as coupling components for *(40)* [16c,49].

For route (c), *i.e.* the alcoholysis of *(40)*, the results of previous esterification experiments with carbodiimide are summarized in Table 8.

Table 8. Reaction of carboxylic acids and hydroxy compounds in the presence of carbodiimides to form esters.

| Acid | Hydroxy compound | Yield of Ester [%] | Ref. | Remarks |
|---|---|---|---|---|
| $C_6H_5$—COOH | $CH_3OH$ | 60 | [12] | [c] |
| Salicylic | $CH_3OH$ | 72 | [50] | [b] |
| $C_6H_5$—O—$CH_2$—COOH | $CH_3OH$ | 94 | [50] | [b] |
| $ClCH_2$—COOH | $ClCH_2$—$CH_2OH$ | 83 | [50] | [d, f] |
| $ClCH_2$—COOH | $ClCH_2$—$CH_2OH$ | 99 | [50] | [a, f] |
| Mixture of fatty acids | $CH_3OH$ | 94 | [50] | [b] |
| $ClCH_2$—COOH | Acetylcellulose[e] | 11 | [50] | [a, f] |
| 3,5-Dinitrobenzoic | prim., sec., and tert. alcohols | — | [51] | [a] |
| $ClCH_2$—COOH | n-$C_4H_9OH$ | 74 | [52] | [a] |
| $C_6H_5$—$CH_2$—COOH | n-$C_4H_9OH$ | 76 | [52] | [a] |
| $Cl_3C$—COOH | n-$C_4H_9OH$ | 70 | [52] | [a] |
| $Cl_3C$—COOH | $C_6H_5$—$CH_2OH$ | 70 | [52] | [a] |
| n-$C_3H_7$—COOH | $C_6H_5$—$CH_2OH$ | 40 | [52] | [a] |
| $C_6H_5$—COOH | $C_6H_5$—$CH_2OH$ | 17 | [52] | [a] |
| 3,5-Dinitrobenzoic | $C_6H_5$—$CH_2OH$ | 76 | [52] | [a] |
| $ClCH_2$—COOH | sec-$C_4H_9OH$ | 41 | [52] | [a] |
| $C_6H_5$—$CH_2$—COOH | sec-$C_4H_9OH$ | 53 | [52] | [a] |
| $Cl_3C$—COOH | sec-$C_4H_9OH$ | 51 | [52] | [a] |
| $Cl_3C$—COOH | $C_6H_{11}$—OH | 58 | [52] | [a] |
| $ClCH_2$—COOH | tert-$C_4H_9OH$ | 10 | [52] | [a] |
| $ClCH_2$—COOH | $(CH_3)_2C(OH)$-$CH_2$—CO—$CH_3$ | 35 | [52] | [a, f] |
| $C_6H_5$—$CH_2$—COOH | $(CH_3)_2C(OH)$-$CH_2$—CO—$CH_3$ | 0 | [52] | [a] |
| *N*-Carbobenzoxyaniline | D-Glucose | 60 | [53] | [a, f] |
| *N*-Formylalanine | Methyl α-D-glucoside | 14 | [53] | [a, f] |
| *N*-Acyl amino acids | *p*-Nitrophenol | — | [54] | [a] |
| Carbobenzoxy amino acids | *p*-Nitrophenol | 43–90 | [54] | [a] |
| HOOC—$CH(CH_2OH)$—HN—$C(C_6H_5)_3$ | | 15 | [55] | [d, g] |

[a] With *N,N'*-dicyclohexylcarbodiimide.
[b] With *N*-methyl-*N'*-t-butylcarbodiimide.
[c] With *N,N'*-diphenylcarbodiimide.
[d] With *N,N'*-diisopropylcarbodiimide.
[e] With 2.24 acetyl groups and 0.76 free OH groups per glucose unit.
[f] With addition of pyridine.
[g] Formation of β-lactone.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[46] *K. B. Wiberg* and *B. I. Rowland*, J. Amer. chem. Soc. *77*, 2205 (1955).

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The suggested alcoholysis mechanism explains the large difference in the esterification yields or the complete failure of the reaction[56]: The competing reactions *(40)* → *(41)* and (a) are much more important in the esterification than in the peptide synthesis, since the alcoholic hydroxy group is much less nucleophilic than the amino group[57].

As an alternative to the aminolysis of *(40)*, another acylation mechanism has been suggested for the peptide synthesis[57a,58]. This mechanism is based on experiments in which, in the absence of the coupling component $H_2N-CR_2-COOR$, the symmetrical anhydrides of *N*-benzyloxycarbonyl and *N*-phthalylamino acids[59] and formic acid[60] were isolated with dicyclohexylcarbodiimide, and treated with esters $H_2N-CR_2-COOR$ of amino acids to form peptides. This acylation with anhydrides instead of *via* the intermediate *(40)* is possible not only for these peptide syntheses, but also for the esterifications described above.

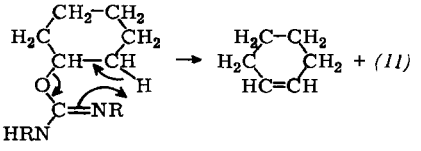
It is likely that both mechanisms are involved, depending on the reaction conditions and on the constitutions of the reactants.

The only experimental difference between the esterification *via* the *O,N,N'*-trisubstituted isoureas as intermediates with "activated alcohol", and the previous esterifications with carbodiimide is that in the method described here the carboxylic acid is added later. The new method[61] has two important advantages: The formation of *N*-acylthiourea and anhydride as by-products is avoided, and any steric hindrance of the carboxyl group is no longer troublesome, owing to the alkylation mechanism.

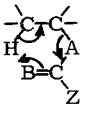
## 4. Thermal Cleavage of Isourea Ethers

The first indication of a new synthesis of olefins was obtained in the pyrolysis of isourea ethers. For example, if the *O*-cyclohexyl-*N,N'*-diisopropylisourea prepared from cyclohexanol and diisopropylcarbodiimide is heated for several hours at 204 to 213 °C, cyclohexene is formed in 35 % yield.

Formation of cyclohexene by 1,2-elimination would be comparable to the *Tschugaeff* dehydration [model




*(42a)*][62,63], the pyrolysis of esters [model *(42b)*][63–65], and the Cope-Mamlock-Wolffenstein reaction [model *(43)*][63,66,67], and like these syntheses, it should proceed as a *cis*-elimination[63].

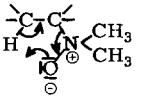



*(42)*

*(42a)*: A = O, B = S, Z = S-$CH_3$

*(42b)*: A, B = O, Z = Alkyl, Aryl

*(42c)*: A = O, B = N-Alkyl, Z = NH-Alkyl




*(43)*

Further experiments are in progress with the object of developing a stereospecific olefin synthesis *via* *O,N,N'*-trialkylisoureas *(42c)*.

*All the work described in this paper, except that based on the publications cited, was carried out under the guidance of Prof. Dr. Erich Schmidt, to whom I am indebted for his interest and for his generous support of this work.*

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[57] *N*-Acylureas *(41)* and anhydrides are sometimes also obtained as by-products in peptide syntheses, *e.g.*: a) *H. G. Khorana*, Chem. and Ind. 1087 (1955); b) *D. T. Gish*, *P. G. Katsoyannis*, *G. P. Hess*, and *R. J. Stedman*, J. Amer. chem. Soc. *78*, 5954 (1956); c) *H. Zahn* and *J. F. Diehl*, Z. Naturforsch. *12b*, 85 (1957); d) *A. Buzas*, *C. Egnell*, and *P. Fréon*, C. R. hebd. Séances Acad. Sci. *252*, 896 (1961); e) *T. L. Goodfriend*, *L. Levine*, and *G. D. Fasman*, Science (Washington) *144*, 1344 (1964).

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[60] *I. Muramatsu*, *M. Itoi*, *M. Tsuji*, and *A. Hagitani*, Bull. chem. Soc. Japan *37*, 756 (1964).

[61] So far, the only esterifications with isourea ethers have been attempted by *Khorana* [13,25]; tertiary phosphates were obtained in good yields from mono- and dihydrogen phosphates.

[62] *L. Tschugaeff*, Ber. dtsch. chem. Ges. *32*, 3332 (1899).

[63] *D. J. Cram* in *M. S. Newman*: Steric Effects in Organic Chemistry. Wiley, New York 1956, p. 305.

[64] *W. Hückel*, *O. Neunhoeffer*, *A. Gercke*, and *E. Frank*, Liebigs Ann. Chem. *477*, 99 (1930).

[65] *D. H. R. Barton*, J. chem. Soc. (London) *1949*, 2174.

[66] *L. Mamlock* and *R. Wolffenstein*, Ber. dtsch. chem. Ges. *33*, 159 (1900).

[67] *A. C. Cope et al.*, J. Amer. chem. Soc. *71*, 3929 (1949); *75*, 3212 (1953).

# Spectroscopy with Polarized Light

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*Polarized light is used in electronic spectroscopy not only to obtain information about the positions, intensities, and fine structures of absorption and luminescence bands, which can be obtained by normal electronic spectroscopy of solutions, but also to determine the orientation of the transition moments in relation to the molecular framework. The theoretical and experimental principles of molecular optical anisotropy are briefly described, and the three most successful methods (spectroscopy after mechanical alignment of the molecules on films and in crystals, or after electrical alignment in solution, and luminescence polarization of solid solutions) are discussed in detail and illustrated by typical examples. In connection with luminescence polarization, special emphasis is placed on triplet-singlet phosphorescence. Reference is made to the importance of polarization measurements on liquid solutions in biochemistry (study of intermolecular interactions of macromolecules by measurement of the rotational relaxation times).*

## A. Introduction

Methods for the determination of the orientation of optical transition moments in complex molecules with the aid of polarized light have been known for some time (for a review, see [1]). In molecules with some symmetry, the classification of excited electronic states is facilitated greatly by a knowledge of the transition directions. These methods of polarization spectroscopy have recently found increasingly wide application, mainly for the following reasons:

(a) The development of theoretical chemistry and the study of reaction mechanisms has led to increased interest in the electronic structures of excited molecules in general.

(b) The electronic states, energies, and density distributions of many molecules have recently been calculated by approximation methods. Polarization spectra can provide criteria for testing the theoretical conclusions, and hence also indications of how the calculation can be improved.

(c) The improvement of amplifier technology has led to an appreciable increase in the sensitivity of optical measurements, particularly those involving electrical orientation of the molecules.

(d) As a result of the development of efficient light sources and photoelectric detectors, high resolution can be obtained over a wide range of wavelengths in the study of luminescence polarization.

In the following survey of methods for the determination of the orientation of the transition moments, we place special emphasis on the method of luminescence polarization, which can be easily adapted for routine work. This method has recently been extended to the study of the mechanism of triplet-singlet phosphorescence.

[1] *F. Dörr* and *M. Held*, Angew. Chem. *72*, 287 (1960).

## B. Molecular States and Energy Levels

The various stationary states of a molecule are described by functions $\Phi_i$ of the coordinates and spins of all electrons and nuclei. The energies $E_i$ corresponding to the various states are represented in an energy-level diagram (Fig. 1). To a close approximation [*], the energy can be expressed as the sum of the electronic energy and the vibrational energy of the nuclei, $E_i = E^i_{el} + E^i_v$, and the state functions $\Phi_i$ as the product of an electronic eigenfunction $\Theta_i$ and a vibrational eigenfunction $\chi_{iv}$ for a vibrational quantum number v:

$$\Phi_i = \Theta_i \cdot \chi_{iv} \qquad (1a$$

Molecular rotation is restricted in solution and will therefore not be taken into account. In organic molecules with even numbers of electrons, singlet states $^1\Theta$ in which the electron spins are paired to give a total spin $S = 0$ and triplet states $^3\Theta$ with two parallel electron spins giving a total spin $S = 1$ are known. Free radicals containing an unpaired electron exist in doublet states; higher multiplicities occur, for example, in complexes with transition elements.

Also to a good approximation, the electronic function $\Theta$ can be expressed as the product of a "space function" $\psi$, which depends only on the positions of the electrons, and a spin function $\Omega$. For two electrons, there are one singlet and three triplet spin functions. The spin-independent space component of the state function (1a) is then:

$$\Phi'_i = \psi_i \cdot \chi_{iv} \qquad (1b)$$

Fig. 1 is an energy-level diagram with singlet and triplet levels $S_i$ and $T_i$ and a number of superimposed vibrational levels. The absorption $T_1 \leftarrow S_0$ [**] is extremely weak, since the transition is forbidden by multiplicity. After an excitation to higher levels, the $S_1$ and $T_1$ levels

[*] Born-Oppenheimer approximation.

[**] According to *Herzberg*, the higher state is written first, and the direction of the transition is indicated by an arrow.

are reached by radiationless transitions; these are indicated by wavy arrows.

The arrows $A_S$ and $A_T$ denote allowed absorption transitions in the singlet and triplet systems, F denotes the fluorescence transitions, which generally take place from only one electronic level (usually $S_1$), and Ph denotes the slowly decaying triplet-singlet phosphorescence observed at low temperatures.

The various spectra of molecules having an energy-level diagram as shown in Fig. 1 are given schematically in Fig. 2. The absorptions $A_T$ can be observed only when excited molecules "accumulate" in the high energy state $T_1$ as a result of intense irradiation (see Section C). Below 300 °K, practically all molecules are in the ground state.

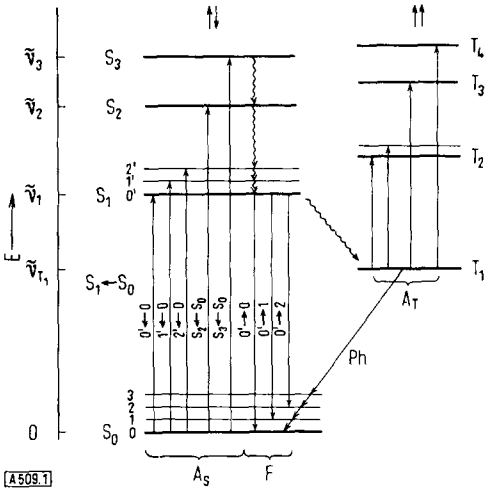



Fig. 1. Energy-level diagram of a molecule.
→ optical, ⇝ radiationless transitions.

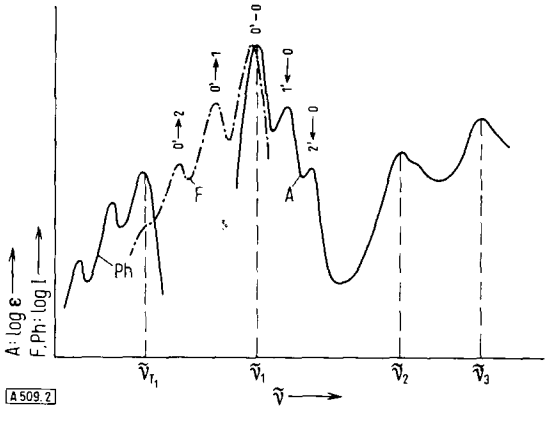



Fig. 2. Schematic representation of spectra corresponding to the energy-level diagram in Fig. 1.

A absorption, F fluorescence, Ph phosphorescence.
Ordinate: Logarithm of the extinction coefficient ε (for A) or logarithm of the intensity (for F and Ph, in arbitrary units).

## C. Transition Moments and Selection Rules

### 1. Electric Dipole Transitions

All intense electronic transitions are electric dipole transitions. A molecule in the state $\Phi_a$ (*e.g.* $S_0$), having an energy $E_a$, can be excited to a state of energy $E_e$ by absorption of a quantum of wave number

$$\tilde{\nu}_{ae} = \frac{E_e - E_a}{hc} \text{ [cm}^{-1}\text{]} \quad (2)$$

The intensity (probability) of the transition is proportional to the square of the transition dipole moment $\mathbf{M}_{ae}$ [Equation (3)]

$$\mathbf{M}_{ae} = e\int \Phi_a^* \mathfrak{P}_M \Phi_e \cdot d\tau \quad (3)$$

where

$$\mathfrak{P}_M = \Sigma Z_i \mathbf{r}_i. \quad (3a)$$

$\mathfrak{P}_M$ is the dipole moment operator and $\Phi_a^*$ is the complex conjugate of $\Phi_a$; the functions are usually real in the case of molecules. $Z_i$ and $r_i$ are the charge number and position vector, respectively, of the i-th particle (electron or nucleus); the integration extends over the space and spin coordinates of all particles.

The vector $\mathbf{M}_{ae}$ has a definite orientation in relation to the molecular skeleton. The probability of absorption is highest for light quanta whose electric vectors vibrate parallel to $\mathbf{M}_{ae}$. The intensity of the light emission $\Phi_e \rightarrow \Phi_a$ (*e.g.* $S_1 \rightarrow S_0$) is proportional to $\tilde{\nu}_{ae}^3 |\mathbf{M}_{ae}|^2$.

If $\mathbf{M}_{ae}$ is zero, the dipole transition is forbidden. This is always the case when $\Phi_a$ and $\Phi_e$ have different total electron spins. If we assume that the initial and final states $\Phi_a$ and $\Phi_e$ have the same multiplicity, we can also operate with the pure space functions $\Phi_e'$ and $\Phi_a'$. It can now be decided, without knowing the exact eigenfunctions, whether $\mathbf{M}_{ae} = 0$. It is only necessary to know how the functions contributing to $\mathbf{M}_{ae}$ behave towards symmetry operations (rotations and reflections) that bring the molecule into coincidence with itself. In order that the component $M_x$ is not zero, the integrand in Equation (3) with $r_i = x_i$ must remain unchanged in relation to all possible coincidence operations of the molecule, *i.e.* it must be totally symmetric, or in other words, must belong to the totally symmetric representation of the symmetry group of the molecule. This is the case when the product of the irreducible representations $\Gamma_i$ of $\Phi_a'$, x, and $\Phi_e'$ is or contains the totally symmetric representation $A_1$.

$$\Gamma(\Phi_a') \times \Gamma(x) \times \Gamma(\Phi_e') = A_1 \quad (4)$$

The allowed transition is then polarized along the x-direction.

Similar rules apply to interactions of different molecular states, which are discussed in Section C.2; in this case, however, the dipole moment operator is replaced by the corresponding interaction operator. For this reason, it is very useful to classify the molecular states according to symmetry characteristics. If $\Phi_a'$ and $\Phi_e'$ are known, the fulfilment of condition (4) can easily be checked with the aid of a character table for the symmetry group of the molecule in question. If the functions $\Phi'$ are real, the so-called characters of the three irreducible representations $\Gamma_i$ in Equation (4) are simply multiplied with one another for every possible symmetry operation and to see whether the result obtained is +1. (Somewhat more effort is required for degenerate states[2,3].)

[2] *C. Sandorfy*: Die Elektronenspektren in der theoretischen Chemie. Verlag Chemie, Weinheim/Bergstr. 1961.

[3] *F. A. Cotton*: Chemical Applications of Group Theory. Interscience Publishers, New York 1964.

## 2. Weakening of Selection Rules for Dipole Transitions

### a) Vibronic Interactions

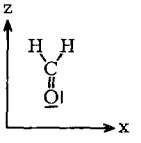
In the approximation (1b), the state function $\Phi_i'$ of a vibration-electronic ("vibronic") state belong to the representation

$$\Gamma(\Phi_i') = \Gamma(\psi_i) \times \Gamma(\chi_i) \tag{5}$$

The satisfaction of condition (4) therefore depends on the symmetry of the vibrational functions $\chi_a$ and $\chi_b$. It follows that a nuclear vibration that is not totally symmetric can make a forbidden electron transition allowed, or can even change the polarization direction of an allowed transition (see below). A simplification exists when one of the states involved is the vibrationless ground state $S_0$, which is always totally symmetric. To satisfy Equation (4) the other (higher) state need only belong to the same representation as the coordinate x.

For example, formaldehyde belongs to the symmetry group $C_{2v}$, which has the irreducible representations $A_1(z)$, $A_2$, $B_1(x)$, and $B_2(y)$; the direct products of these representations are shown in the following multiplication table.

| $C_{2v}$ | $A_1$ | $A_2$ | $B_1$ | $B_2$ |
|---|---|---|---|---|
| $A_1$ | $A_1$ | $A_2$ | $B_1$ | $B_2$ |
| $A_2$ | $A_2$ | $A_1$ | $B_2$ | $B_1$ |
| $B_1$ | $B_1$ | $B_2$ | $A_1$ | $A_2$ |
| $B_2$ | $B_2$ | $B_1$ | $A_2$ | $A_1$ |




A transition moment in the z direction leads from the vibrationless ground state $S_0(A_1)$ to another state of the same symmetry $A_1$ (*e.g.* the $\pi^* \leftarrow \pi$ transition to $S_2$). On the other hand the vibrationless excited state $S(n\pi^*) = S_1$, which is reached by excitation of a non-bonding (n)-electron on oxygen into an empty $\pi$-orbital ($\pi^*$), belongs to the representation $A_2$, which does not represent any coordinate of the molecule. If, however, a vibration of symmetry $b_2$ [*] (rocking vibration of the O atom out of the $CH_2$ plane) is superimposed on the $S_1$ electronic state, the transition $S_{1,1} \leftarrow S_0$ is polarized along x and is allowed, since $A_2 \times B_2 = B_1$ and x belongs to $B_1$.

Thus, owing to the coupling of an electronic state with a vibration that is not totally symmetric, a symmetry-forbidden electron transition becomes allowed. In other cases, a low-intensity transition that is allowed in accordance with Equation (4) is intensified by vibronic mixing. The validity of Equation (4) gives no information about the intensity of an allowed transition; this information is obtained by insertion of the explicit functions $\Phi_a$ and $\Phi_e$ in Equation (3).

The theoretical treatment of intensification by vibronic mixing is due to *Herzberg* and *Teller* [4], and was refined and applied to larger molecules (particularly benzene) whose state functions are approximately known by *Liehr* [5], *Murrell* and *Pople* [6], and *Kalantar* and *Albrecht* [7,8]. A displacement Q of the nuclei from the equilibrium position (Q = 0) also leads to a change in the electronic component $\psi$ of the state function (1b), since the electrons are light enough to immediately adjust themselves to the potential due to the nuclei. For a given electron function $\psi_K(Q)$ at a displacement Q of the nuclei from the equilibrium position corresponding to $\psi_K$, the deviation from the equilibrium function $\psi_K(0)$ is described by a series expansion in the other unperturbed electron eigenfunctions $\psi_S(0')$ of the molecule, which form a complete orthogonal set (S = 1, 2, ..., but S ≠ K). The equilibrium position corresponding to $\psi_S$ is generally different from that corresponding to $\psi_K$; this is expressed by the symbol 0′ in the case of $\psi_S$. Thus

$$\psi_K(Q) = \psi_K(0) + \sum_{S \neq K} c_{KS}(Q)\psi_S(0'). \tag{6}$$

The change in the Hamiltonian operator of the electrons for a displacement Q of the nuclei from the equilibrium position is described by the perturbation operator $\mathfrak{H}_e'$. Then [4–8]

$$c_{KS}(Q) = \frac{1}{E_S - E_K} \int \psi_K^*(0)\mathfrak{H}_e'(Q)\psi_S(0')d\tau \tag{7}$$

where $E_S$, $E_K$ are the energies of the corresponding molecular states.

The value of $c_{KS}$ is a measure of the extent of mixing of $\psi_S$ with $\psi_K$ as a function of the vibrational amplitude Q. Mixing of the ground state with higher states $\psi_S$ generally can be neglected, mainly because the denominator $(E_S - E_0)$ in Equation (7) is large, so that $c_{0S}$ becomes small, and because at normal temperatures vibrations in the ground state generally are not appreciably excited ($Q \approx 0$).

For a non-zero $c_{KS}$, a symmetry condition similar to (4) must be satisfied:

$$\Gamma(\psi_S(0')) \times \Gamma(\mathfrak{H}_e'(Q)) \times \Gamma(\psi_K(0)) = A_1 \tag{8}$$

in the simple non-degenerate case:

$$\Gamma(\psi_S(0')) \times \Gamma(\mathfrak{H}_e'(Q)) = \Gamma(\psi_K(0)) \tag{9}$$

$\mathfrak{H}_e'$ is approximated by the linear term in the expansion of the Hamiltonian operator for displacement Q (normal coordinates) [4]. For illustration, Fig. 3 shows an electronic state $\psi_K(0)$ to which a higher state $\psi_S(0')$ is added at time t by a vibration of suitable symmetry $Q = Q(t)$; the transition B to $\psi_S(0')$ is allowed. The transition A then "steals" intensity from the allowed transition B.

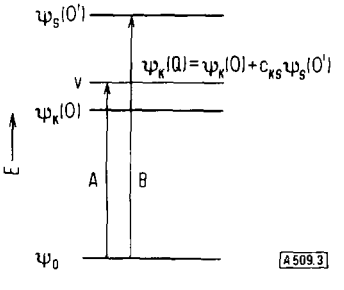



Fig. 3. Energy-level diagram for vibronic coupling.

Since several states $\psi_S$ of different symmetries can be mixed simultaneously with $\psi_K$ by means of vibrations of different types (*i.e.* with different symmetry behavior of

[*] Vibrations are denoted by lower-case letters to distinguish them from electronic states.


[4] *G. Herzberg* and *E. Teller*, Z. physik. Chem. B *21*, 410 (1933).

[5] *A. D. Liehr*, Z. Naturforsch. *13a*, 596 (1958).

[6] *J. N. Murrell* and *J. A. Pople*, Proc. physic. Soc. A *69*, 245 (1956).

[7] *A. H. Kalantar* and *A. C. Albrecht*, Ber. Bunsenges. physik. Chem. *68*, 377 (1964).

[8] *A. C. Albrecht*, J. molecular Spectroscopy *6*, 84 (1961).

the corresponding vibrational eigenfunctions $\chi_i$), the resulting transition may consist of several superimposed components with different polarization directions. In Fig. 3, for example, the transition A is intensified by a component with the polarization direction of the transition B. It is therefore desirable in polarization spectra to obtain such a high spectral resolution that vibrations of different types are separated as far as possible, thus enabling the polarization of the 0,0 transitions to be measured separately (cf. Section G).

Insertion of Eq. (7) into Eq. (6) gives the following equation for the transition (dipole) moment of the absorption $\psi_K(Q) \leftarrow \psi_0$ [Eq. (3)]:

$$\mathbf{M}_{0K}(Q) = \mathbf{M}_{0K}(0) + \int \sum_{S \neq K} \frac{\int \psi_K^*(0)\mathfrak{H}_e'(Q)\psi_S(0')d\tau_e \int \psi_S^* \mathfrak{H}_M \psi_0 d\tau}{E_S - E_K} \quad (10)$$

Thus the selection rules for mixing [(Eq. (8)] and for the optical transitions [(Eq. (4)] must both be satisfied before any enhancement is possible. (This can lead to an appreciable change in the intensity distribution of an electron-vibration band in relation to that given by the Franck-Condon principle alone.)

### b) Triplet-Singlet Transitions and Spin-Orbit Coupling

The long-lived phosphorescence of many compounds in vitreous solvents was interpreted by *Lewis* and *Kasha* [9] as a $T_1 \rightarrow S_0$ spin-forbidden transition. This interpretation has been confirmed by electron-spin resonance spectra of molecules in the metastable excited state [10, 11].

Intensification of spin-forbidden transitions can be explained in molecules, as in heavy atoms, by spin-orbit interaction. Owing to its orbital motion in the electric field of the molecular skeleton, an electron "sees" a magnetic field, which acts on its magnetic moment. The result is that it is no longer possible to rigorously distinguish between singlet and triplet states. To describe this case, we say that a small component of triplet states of suitable symmetry is "mixed" with a singlet state by spin-orbit coupling; similarly, singlet states can also be mixed with triplet states.

The theory and the selection rules for this mixing and for the resulting optical transitions have been formulated by various authors in terms of the usual approximation methods for unsaturated molecules [12–18]. Since the magnetic interaction energy is small in comparison with the electrostatic energy, a perturbation method can be used.

By analogy with Equation (6), the triplet state ${}^3\Theta_{Kj}$ perturbed by mixing with singlet states ${}^1\Theta_S$ is described by the expansion (11):

$${}^3\Theta'_{Kj} = {}^3\Theta_{Kj} + \sum_S c_{KjS}{}^1\Theta_S \quad (11)$$

($\Theta$ electron eigenfunctions including spin, cf. Eq. (1a); j = 1, 2, 3 denotes the three components of the triplet spin function).

The coefficients $c_{KjS}$ of the expansion are found by an equation similar to (7), *i.e.*

$$c_{KjS} = \frac{1}{E({}^1\Theta_S) - E({}^3\Theta_{Kj})} \cdot \int {}^3\Theta_{Kj}^* \mathfrak{H}'_{ls} {}^1\Theta_S d\tau \quad (12)$$

The spin-orbit operator $\mathfrak{H}'_{ls}$ causing the mixing consists of several (relativistic) components, but usually only one of these is retained in approximate calculations. For a system of n electrons and m nuclei with Cartesian coordinates:

$$\mathfrak{H}'_{ls} \approx \frac{e^2}{2m^2c^2} \sum^{n} \left[ \sum_{k=1}^{m} \frac{Z_k}{r_k^3} (l_{xk} \cdot s_x + l_{yk} \cdot s_y + l_{zk} \cdot s_z) \right] \quad (13)$$

$Z_k$: effective charge on the nucleus k;

$r_k$: distance from the electron in question to the nucleus k;

$l_{xk}$: x-component of the orbital angular momentum operator of an electron in relation to the nucleus k;

$s_x$: x-component of the spin operator of an electron; *etc.*

The summation in brackets extends over the nuclei, and that outside the brackets over the electrons.

The factor $Z/r^3$ is particularly large near heavy nuclei. Thus the intensification of singlet-triplet transitions by substituted heavy atoms (or by adjacent heavy atoms in the solvent) is explained as a result of the more pronounced mixing of S and T states in accordance with Equation (12) ("heavy-atom effect") [19]. The components of $\mathfrak{H}_{ls}$ have the same symmetry properties as the rotations $R_x$, $R_y$, and $R_z$ about the x, y, or z axes. If, as an approximation, the electron eigenfunctions $\Theta$ are written in the form (1a) as the product of a space function $\psi$ and a spin function $\Omega$, the integration in Equation (12) can be carried out separately over the space coordinates and the spin coordinates. The spin-dependent part gives one or two finite contributions for each component of s when ${}^3\Omega_{Kj}$ and ${}^1\Omega_S$ differ only in the spin of a single electron. Thus the selection rules for mixing depend only on the integral (14) over the space functions $\psi$.

$$\int {}^3\psi_K^* \mathfrak{H}'_{ls} {}^1\psi_S d\tau \quad (14)$$

${}^3\psi_K$: orbital function for the triplet state ${}^3\Theta_K$

${}^1\psi_S$: orbital function for the singlet state ${}^1\Theta_S$.

If the integral (14), and hence $c_{KjS}$ in Equation (11) are to be non-zero, a condition similar to Equation (8) must again be satisfied, except that in this case $\Gamma(\mathfrak{H}'_{ls})$ must be replaced by the irreducible representations of the rotations $R_x$, $R_y$, and $R_z$, which are obtained from character tables. Similarly, the singlet ground state

[9] *G. N. Lewis* and *M. Kasha*, J. Amer. chem. Soc. *66*, 2100 (1944).

[10] *C. A. Hutchinson* and *B. W. Mangum*, J. chem. Physics *29*, 952 (1958).

[11] *J. H. van der Waals* and *M. S. DeGroot*, Molecular Physics *2*, 233 (1959); *3*, 190 (1960).

[12] *D. S. McClure*, J. chem. Physics *17*, 665 (1949); *20*, 682 (1952).

[13] *S. J. Weissman*, J. chem. Physics *18*, 232 (1950).

[14] *M. Mizushima* and *S. Koide*, J. chem. Physics *20*, 765 (1952).

[15] *H. F. Hameka* and *L. J. Oosterhoff*, Molecular Physics *1*, 358 (1958).

[16] *E. Clementi* and *M. Kasha*, J. molecular Spectroscopy *2*, 297 (1958).

[17] *J. W. Sidman*, J. molecular Spectroscopy *2*, 333 (1958).

[18] *V. G. Krishna* and *L. Goodman*, J. chem. Physics *36*, 2217 (1962).

[19] *D. S. McClure*, *N. W. Blake*, and *P. L. Hanst*, J. chem. Physics *22*, 255 (1954).

generally mixes with higher triplet states of suitable symmetry; the selection rules for mixing (15) are the same:

$$\Gamma(^3\psi_K) \times \Gamma(R_i) \times \Gamma(^1\psi_S) = A_1; \quad i = x, y, z \tag{15}$$

Thus the intensity of the dipole transition between the states $^1\Theta_0 \equiv S_0$ and $^3\Theta_1 = T_1$ ($T_1 \leftarrow S_0$ absorption, or $T_1 \rightarrow S_0$ phosphorescence), which are perturbed by spin-orbital interaction, contains contributions from several components, each generally differently polarized, with transition moments (16a) and (16b).

$$\mathbf{M}' = \underbrace{\int \frac{^3\Theta^*_{1j}\mathfrak{H}'_{ls}{}^1\Theta_S}{E(^1\Theta_S)-E(^3\Theta_{1j})}\,d\tau}_{c_{1js}} \cdot \int {}^1\Theta^*_0 \mathfrak{H}_M {}^1\Theta_S d\tau \tag{16a}$$

$$\mathbf{M}'' = \int \frac{^1\Theta^*_0\mathfrak{H}'_{ls}{}^3\Theta_{Kj}}{E(^3\Theta_{Kj})-E(^1\Theta_0)}\,d\tau \cdot \int {}^3\Theta^*_{1j}\mathfrak{H}_M {}^3\Theta_{Kj} d\tau \tag{16b}$$

The other terms vanish because the functions involved have different multiplicities. (The asterisks again denote complex conjugate functions.) Thus the transition $T_1 - S_0$ gains intensity from the allowed transitions between the singlet states $^1\Theta_S$ mixed with the $^3\Theta_{1j}$ states [see Eq. (16a)] and between the triplet states $^3\Theta_{Kj}$ mixed with the $^1\Theta_0$ state [see Eq. (16b)]. It is found in practice that, for organic molecules, a T–S transition is $10^6$ times weaker than a fully allowed S–S transition.

The above relationships are illustrated in Fig. 4 for the simple case in which only the singlet state $S_n$ mixes appreciably with $T_1$, only the triplet state $T_m$ mixes appreciably with the ground state $S_0$, and none of the states involved is degenerate. For simplicity, the symbols $S_0$, $S_m$, $T_1$, and $T_m$ represent the spin-independent space functions $\Phi'$ of Equation (1b), *i.e.* they are approximate functions which would be improved if interactions were taken into account. The irreducible representations are: $\Gamma(S_0) = A_1$ (totally symmetric); $\Gamma(\mathfrak{H}'_{ls}) = \Gamma(R_i)$, i = x, y, or z (the components of the spin-orbital operator have the symmetry of rotations about the coordinate axes [12]).

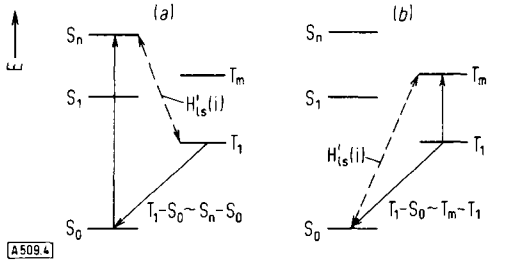



Fig. 4. Energy-level diagram for spin-orbit coupling.
(a) $T_1$ mixes with $S_n$; (b) $S_0$ mixes with $T_m$.

*Selection rules for the polarization of the $T_1 \rightarrow S_0$ phosphorescence*

I. State mixture, Eq. (15)

Fig. 4a:

a) $\Gamma(T_1) \times \Gamma(R_i) \times \Gamma(S_n) = A_1$
hence
b) $\Gamma(T_1) = \Gamma(R_i) \times \Gamma(S_n)$

Fig. 4b:

α) $\Gamma(S_0) \times \Gamma(R_i) \times \Gamma(T_m) = A_1$
hence, since $\Gamma(S_0) = A_1$
β) $\Gamma(T_m) = \Gamma(R_i)$

II. Optical transition, Eq. (4)

c) $\Gamma(S_n) \times \Gamma(x_j) \times \Gamma(S_0) = A_1$
hence since $\Gamma(S_0) = A_1$
d) $\Gamma(S_n) = \Gamma(x_j)$
inserted in b)

γ) $\Gamma(T_m) \times \Gamma(x_j) \times \Gamma(T_1) = A_1$
from β)
δ) $\Gamma(R_i) \times \Gamma(y_j) \times \Gamma(T_1) = A_1$
hence

$$\Gamma(R_i) \times \Gamma(x_j) = \Gamma(T_1); \; R_i = R_x, R_y, R_z; \; x_j = x, y, z \tag{17}$$

The transition $T_1 - S_0$ is then polarized along $x_j$.

*Example:* In formaldehyde (cf. Section C.2a) the triplet state $T_1 = T(n\pi^*)$ (a non-bonding electron raised to an empty π-orbital) belongs to the irreducible representation $A_2$. It can mix with an $A_1$ state, most probably with $S_2 = S(\pi\pi^*)$ (a π-electron raised from the double bond into an empty π-orbital) by means of the z-component of the spin-orbit operator [$\Gamma(R_z) = \Gamma(x) \times \Gamma(y) = B_1 \times B_2 = A_2$]. The $T_1 - S_0$ transition is then allowed with low intensity and with polarization direction $z(A_1)$, in accordance with Equation (17). This transition is in fact observed; the same mechanism is probably also responsible for the $T(n\pi^*)$–$S_0$ transitions of ketones having lower symmetries [20].

Spin-orbit coupling is influenced in a number of ways by vibration of the nuclei. For example, a singlet state $S_n$, which, according to condition (a) under Fig. 4, does not mix directly with the triplet state $T_1$, can be mixed by vibration coupling, in accordance with Equation (7), with a little of another singlet state $S_K$ with which $T_1$ has spin-orbital interaction. The spin-orbit operator [cf. Eq. (14)] itself can also be changed by vibration. The theory of triplet-singlet transitions was developed by *Albrecht* [21] with this effect in mind, and was applied by *El-Sayed* [22] to the symmetrical dihalogenonaphthalenes.

For extremely weak spin-orbit coupling, *Hameka* [23] has also discussed the direct interaction of the spin with the magnetic field of the light wave; this can cause a magnetic quadrupole transition between triplet and singlet states. The intensity of this transition was estimated to be $10^{-11}$ times the intensity of a fully allowed transition. In the case of benzene, which has a triplet lifetime $\tau > 10$ sec, this mechanism could be appreciable in addition to spin-orbit coupling. Finally, an S–T transition may be facilitated by external perturbation due to paramagnetic molecules, particularly oxygen, by two different mechanisms [24–26].

### 3. Magnetic Dipole Transitions

If the magnetic moment (which is related to the orbital angular momentum of the electrons) changes during the transition between the states $\Phi_a$ and $\Phi_e$, magnetic dipole radiation may be absorbed and emitted. The probability of this effect is about $10^6$ times smaller than for a normal electric dipole transition [27, 28]. However,

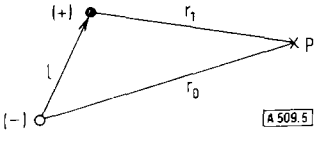

[20] *V. E. DiGiorgio* and *G. Wilse Robinson*, J. chem. Physics *31*, 1678 (1959).
[21] *A. Albrecht*, J. chem. Physics *38*, 354 (1963).
[22] *M. A. El-Sayed*, J. chem. Physics *43*, 2864 (1965).
[23] *H. F. Hameka*, J. chem. Physics *37*, 328 (1962).
[24] *D. F. Evans*, J. chem. Soc. (London) *1957*, 1351, 3885.
[25] *G. J. Hoijtink*, Molecular Physics *3*, 67 (1960).
[26] *J. N. Murrell*, Molecular Physics *3*, 319 (1960).
[27] *S. F. Mason*, Molecular Physics *5*, 343 (1962).
[28] *R. E. Ballard* and *S. F. Mason*, J. chem. Soc. (London) *1963*, 1624.

if the latter is forbidden, a magnetic dipole transition may be observed under certain circumstances.

It is very probable, for example, that in the spectrum of formaldehyde vapor a number of lines in the region of the forbidden $S_1(n\pi^*) \leftarrow S_0$ transition (see Section C.2a) are due to magnetic dipole transition [29]. In the plane of observation perpendicular to the orbital momentum vector **L**, the magnetic vector of this radiation is parallel to **L**. Relatively intense magnetic dipole radiation was found [30] in the spectral lines of rare earths, together with another type of radiation, which is produced by rotating electric and magnetic dipoles. Magnetic dipole transitions have not yet been definitely detected in the spectra of solutions of aromatic molecules.

### 4. Electric Quadrupole Transitions

In classical physics, a radiating quadrupole consists of two equal parallel dipoles vibrating with opposed phase, the distance between them being much smaller than the wavelength corresponding to their frequency. The intensity of optical quadrupole transitions is several orders of magnitude smaller, and the polarization relationships of the radiation are more complex than in electric dipole transitions. "Multipole transitions" are generally expected when the approximation $r_1 \approx r_2 = \text{const.}$ is replaced by the more accurate expression for $r_1$ in the calculation of the field of an oscillating dipole at a point P (cf. Fig. 5)




Several experimental methods distinguishing the various types of transitions are known. Typical distinguishing features are: (a) the intensity of the transition, (b) the distribution of the intensity in space, (c) the polarization of the radiation, (d) level splitting in the Zeeman effect (observed only in line spectra), and (e) circular dichroism.

### 5. Nature of the Oscillators in Organic Molecules

The spatial intensity distribution of the interference field of two wave trains emitted from an atomic system with a large angle between them is characteristically dependent on the multipole character of the emitting oscillator [31] ("wide angle interference"). It is not so easy to measure the intensity distribution as to measure the polarization of the luminescence radiation at various emission angles, on excitation with polarized light. According to *Feofilow* [30], the various multipole transitions also give characteristic "polarization diagrams", from which it is possible to establish the nature of both the absorbing and the emitting oscillators.

On the basis of wide-angle interference and polarization diagrams, it has been shown for a large number of organic compounds that all absorption transitions, as well as the $S_1 \rightarrow S_0$ fluorescence [32] and the $T_1 \rightarrow S_0$ phosphorescence [33, 34], are electric dipole transitions. It therefore seems reasonable to assume that this is true for all organic molecules, except certain complexes of transition metals and rare earths, in which magnetic dipole radiation is observed. Experimental methods for determining the orientation of the electric dipole transition moments in a molecule are discussed below.

## D. Mechanical Orientation of Molecules

### 1. Adsorption on Oriented Films

Natural fibers such as cotton, that have been dyed with substantive dyes, show distinct dichroism under the polarization microscope [35]. Quantitative studies can be carried out with clear films of cellulose hydrate, polyvinyl alcohol, polyethylene, *etc.*, which are dyed and then stretched to several times their original length [36]. In some cases it is better to stretch the film before it is dyed. Depending on the substrate and on the solvent, sufficiently strong adsorption is also observed with compounds that are not dyes in the technical sense. "Dyeing" may be assisted by gradual reduction of the solubility of the dye in the liquid phase (*e.g.* by addition of water). In favorable cases, orientation of the adsorbed dye molecules may be as high as 90 %. If the extinction of such a film is measured as a function of the wavelength of light polarized parallel ($E_p$) to and perpendicular ($E_s$) to the stretching direction, the spectra obtained are of the type shown in Fig. 6 (methylene blue [37]), which also shows the dichroic ratio DV defined as

$$DV \equiv \frac{E_p - E_s}{E_p + E_s} \qquad (18)$$

Maxima of the dichroic ratio correspond to oscillators with preferential orientation parallel to the stretching directions, and minima to those with transverse orientation. This method is confined to elongated molecules, and does not give very clear results, particularly in shorter-wavelength transitions. It is assumed that the molecules always orient themselves with their longitudinal axis parallel to the direction of stretching. The orientation of the long-wavelength oscillator of dyes is often known from quite reliable theoretical considerations, and the other bands can then be referred to this. It is more difficult to distinguish between the short axis in the molecular plane and in the direction perpendicular to the molecular plane. In a few cases the orienta-

[29] *J. H. Callomon* and *K. K. Innes*, J. molecular Spectroscopy *10*, 166 (1963).

[30] *P. P. Feofilow*: The Physical Basis of Polarized Emission. Consultants Bureau, New York 1961.

[31] *O. Halpern* and *F. Doermann*, Physic. Rev. *52*, 937 (1937); *53*, 420 (1938); *55*, 486 (1939).

[32] *A. N. Sevchenko*, Dokl. Akad. Nauk SSSR *42*, 349 (1944).

[33] *S. Freed* and *S. J. Weissman*, Physic. Rev. *60*, 440 (1941).

[34] *S. J. Weissman* and *D. Lipkin*, J. Amer. chem. Soc. *64*, 1916 (1942).

[35] *H. Ambronn*, Ber. dtsch. bot. Ges. *6*, 85, 226 (1888).

[36] *A. Jablonsky*, Acta physica polon. *3*, 421 (1934).

[37] *J. Kern* and *F. Dörr*, Z. Naturforsch. *16a*, 363 (1961).

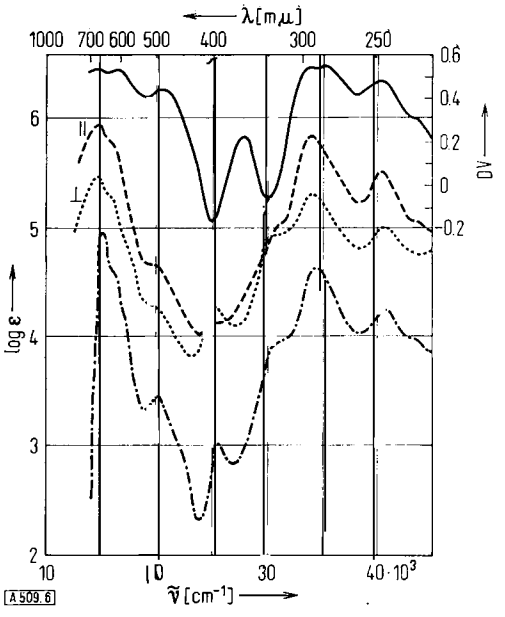



Fig. 6. Dichroisn of methylene blue on stretched polyvinyl alcohol [37]. Absorption spect a (at 20 °C) in ethanol (—·—·—) and on film with light polarized p rallel (— — — —) to and perpendicular (·····) to the direction of s etching.

tion on the film could be determined directly from the anisotropy of infrared bands of characteristic stretching vibrations of substituents (*e.g.* $-C\equiv N$) [38]. As expected, the longitudinal axis of the molecule was found to lie parallel to the stretching direction. By way of example, Fig. 7 shows the anisotropy of the ultraviolet absorption bands and of the $C\equiv N$ stretching band of *p*-dimethylaminobenzonitrile [38].

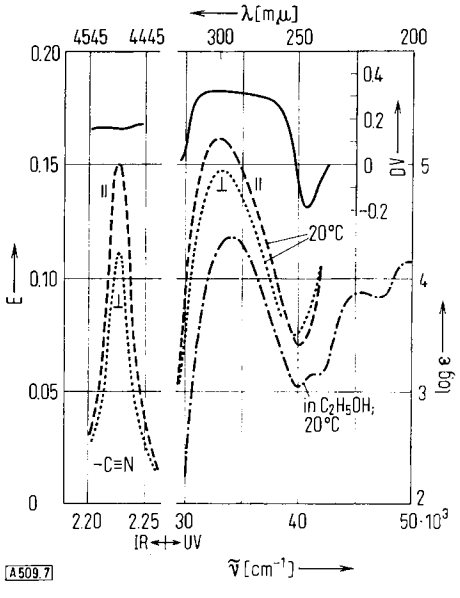



Fig. 7. Dichroism of the $C\equiv N$ stretching vibration and of the long-wavelength electronic band for *p*-dimethylaminobenzonitrile on stretched polyamide film (at 20 °C) [38].

A substantial refinement of the film method was recently introduced by *Eggers* and *Thulstrup* [39]. These authors studied large aromatic molecules and a number of aromatic hetero compounds embedded in stretched polyethylene.

[38] *J. Kern*, Z. Naturforsch. *17a*, 271 (1962).

[39] *J. H. Eggers* and *E. W. Thulstrup*, Lecture at the 8th European Congress on Molecular Spectroscopy, in Copenhagen (Denmark) on August 17th, 1965.

The luminescence of such films is also, of course, polarized to some extent. From their degree of polarization on excitation with natural light or with polarized light, information can be obtained about the orientation of the oscillators [40]. Other applications of the film technique are described by *Hanle* [41] and by *Eckert* and *Kuhn* [42]. When used in combination with a method developed by *Lewis* [43] and refined by *Zanker* and *Miethke* [44] for the measurement of triplet-triplet absorption transitions ($A_T$ in Fig. 1), dichroically dyed films permit determination of the polarization of these transitions [45, 46].

For this purpose, the films are placed in a Dewar cell (see Section G.2) cooled to the temperature of liquid air, and exposed to intense ultraviolet radiation (*e.g.* high pressure mercury lamp HBO 200 with filter UG 2 + $CuSO_4$ solution). This leads to a steady state in which up to 70 % of the adsorbed molecules are excited into the long-lived ($\tau \approx 1$ sec) triplet state $T_1$. These then give rise to the allowed, and therefore intense, absorption transitions $T_2 \leftarrow T_1$, $T_3 \rightarrow T_1$, *etc.*, which are situated in the red and near infrared regions of the spectrum. The dichroic ratio of these transitions can be determined from Eq. (18).

*Example* [46]: *The 3,6-diaminoacridinium cation on polyvinyl alcohol at 100 °K.* The $S_1 \leftarrow S_0$ transition occurs at 468 mμ; its polarization is parallel to the longitudinal axis of the molecule. The $T_2 \leftarrow T_1$ transition polarisation at 1100 mμ is oriented at 90° to the $S_1 \leftarrow S_0$ transition. However, this method does not show whether the $T_2 \leftarrow T_1$ transition is polarized in or perpendicular to the molecular plane; the former is expected on theoretical grounds.

## 2. Single Crystals and Mixed Crystals

At 4 °K, molecular single crystals often give very complex, sharp absorption and luminescence spectra with pronounced dichroism of the individual bands. However, these spectra are usually difficult to analyse, since interactions between the molecules in one unit cell lead to splitting of the electronic and vibrational levels, and so give numerous adjacent bands having different polarizations (crystal-field splitting, Davydow splitting).

Complete interpretation of the polarization measurements also requires knowledge of the crystal structure and of the interaction energies [47]. New eigenfunctions are formed for the unit cell as a whole by linear combination of the molecular states, and the selection rules for transitions between these eigenfunctions are determined. This is again best done on the basis of group theory, taking into account the symmetry of the individual molecule and that of the unit cell [47, 48].

[40] *P. Pringsheim*, Acta physica polon. *4*, 381 (1935).

[41] *W. Hanle, A. Kleinpoppen*, and *A. Scharmann*, Z. Naturforsch. *13a*, 64 (1958).

[42] *R. Eckert* and *H. Kuhn*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 356 (1960).

[43] *G. N. Lewis, D. Lipkin*, and *T. T. Magel*, J. Amer. chem. Soc. *63*, 3005 (1941).

[44] *V. Zanker* and *E. Miethke*, Z. physik. Chem. N.F. *12*, 13 (1957); Z. Naturforsch. *12a*, 385 (1957).

[45] *F. Dörr, J. Kern, J. Thies*, and *V. Zanker*, Z. Naturforsch. *17a*, 93 (1962).

[46] *V. Zanker* and *J. Thies*, Z. physik. Chem. N.F. *33*, 46 (1962).

[47] *A. S. Davydov*: Theory of Molecular Excitons. McGraw-Hill, New York 1962.

[48] *H. C. Wolf* in: Advances in Solid State Physics. Academic Press, New York 1959, Vol. 9.

Further complications are nearly always encountered in the luminescence spectra of single crystals. The absorbed energy migrates to a defect in the crystal, either a foreign molecule or an incorrectly situated or oriented molecule, where it is emitted. The polarization of the luminescence is then characteristic, not of the normally arranged molecules, but of the disturbed molecule. These difficulties are avoided if the molecules in question can be embedded in a host crystal at a high dilution and with defined orientation. The built-in molecules can, to a good approximation, be treated as an "oriented gas".

*Examples*: Naphthalene (1:$10^3$) is built into monoclinic 1,2,4,5-tetramethylbenzene with its long molecular axis parallel to the b-axis of the crystal. It was found that the longest-wavelength transition $S_1 \leftarrow S_0$ ($^1B_{3u} \leftarrow {}^1A_{1g}$) in naphthalene is polarized parallel to the long axis[49], whereas the triplet-triplet transition $T_2 \leftarrow T_1$ is polarized parallel to the short axis ($^3B_{3g} \leftarrow {}^3B_{1u}$)[50]. The long-wavelength $\pi^* \leftarrow n$ band of azobenzene built into stilbene has a transition moment that is rotated through approximately 36° from the N–C direction; the "forbidden" transition gains intensity by vibronic coupling (Section C.2a) with a $\pi^* \leftarrow \pi$ transition[51]. Mixed crystals with benzophenone[52] as the host crystal have not yet led to any definite conclusions since the crystal structure is not accurately known.

Mention should be made of some recent studies on pure single crystals (cf. also[48]). The polarization of the anthracene bands, which are split in the crystal field, indicates that in the free molecule the longest-wavelength transition is polarized parallel to the short axis ($^1B_{2u} \leftarrow {}^1A_{1g}$), and the next longest parallel to the long axis ($^1B_{3u} \leftarrow {}^1A_{1g}$); thus the order is the reverse of that found in naphthalene[53]. In azulene and phenanthrene, the first transition is polarized parallel to the short axis and the second parallel to the long axis[54]. In *p*-dimethoxybenzene, the long-wavelength transition occurs transverse to, and the next transition parallel to, the long axis[55]. In some purines and pyrimidines, the orientation of the transition at about 275 mμ was found to be approximately parallel to the N(1)–C(4) direction, and that of the transition at about 220 mμ to be perpendicular to this direction[56]. The ligand field splitting[57] of the energy levels of nickel was studied with polarized light in the complexes $Ni(NH_3)_4(NCS)_2$ and $Ni(NH_3)_4(NO_2)_2$, and was concluded to be affected by vibronic interaction[58]. A number of papers deal with the polarization of the characteristic absorption bands (CT bands)[*1] of electron donor-acceptor complexes (charge-transfer complexes). In anthracene/trinitrobenzene[59] and in quinhydrone[60], for example, the CT transition was found to be perpendicular to the plane of the molecule, as expected from the theory[61] of these transitions. In the pyrene/trichloroethylene complex, *Kuroda*[62] found two bands (510 and 830 mμ), which he interpreted as CT transitions on the basis of their polarization.

Attempts have also been made to assign the transitions in pyrene, phenanthrene, and benzil[63] on the basis of the luminescence polarization of single crystals. In the phenanthrene crystal, most of the emission occurs from molecules at lattice defects[64]. In the case of hexachlorobenzene, the polarization of the $T_1 \rightarrow S_0$ phosphorescence can be explained by assuming a threefold symmetry (in the crystal) and a spin-orbital interaction with the degenerate state $^1E_{1u}$ (components of the transition moment parallel to the plane of the molecule) and the state $^1A_{2u}$ (component of the transition moment perpendicular to the plane of the molecule)[65].

The pure vibrational transitions are also split in the crystal, owing to coupling between the molecules; the explanation of this is similar to that for splitting of the electronic levels[66]. Thus, in favorable cases, infrared bands can be assigned on the basis of their dichroic behavior[67, 68].

## E. Electric Orientation of Dipole Molecules

### 1. Electrically Induced Dichroism. Electric Fluorescence Polarization

The partial orientation by an electric field of molecules having a permanent electric dipole moment $\mu_g$ (in the ground state) was first used by *W. Kuhn*[69] to find the orientation of the transition moment in the long-wavelength absorption band, $S_1 \leftarrow S_0$. This author studied *p*-nitrosodimethylaniline ($\mu_g = 6.9$ D) in benzene solution (dielectric constant 2.28). The transition moment is parallel to $\mu_g$.

The orientation of dipolar molecules is opposed by their thermal motion. The potential energy of a permanent dipole $\mu_g$ in a field **F**, as a function of the angle $\Omega$ between $\mu_g$ and **F**, is given by Eq. (19).

$$\Delta E_g = -|\mu_g||\mathbf{F}|\cos\Omega = -\mu_g\mathbf{F} \qquad (19)$$

With Maxwell-Boltzmann statistics, the probability that a dipole will have the orientation $\Omega$ relative to the field direction is:

$$W(\Omega)d\Omega = \frac{\exp(-\Delta E_g(\Omega)/kT)}{\int \exp(-\Delta E_g(\Omega)/kT)d\Omega}\, d\Omega. \qquad (20)$$

The field strength is limited to a maximum of $10^5$ V/cm by the dielectric strength of the solvent, and $\mu_g$ is less than about 10 D. Thus $\Delta E_g/kT$ is about $10^{-2}$ and, for the solution, the

[49] *D. S. McClure*, J. chem. Physics *22*, 1668 (1954); *24*, 1 (1956).

[50] *D. P. Craig* and *G. Fischer*, Proc. chem. Soc. (London) *1964*, 176.

[51] *R. M. Hochstrasser* and *S. K. Lower*, J. chem. Physics *36*, 3505 (1962).

[52] *R. M. Hochstrasser* and *S. K. Lower*, J. chem. Physics *40*, 1041 (1964).

[53] *D. P. Craig* and *P. C. Hobbins*, J. chem. Soc. (London) *1955*, 2302, 2309.

[54] *D. S. McClure*, J. chem. Physics *22*, 1256 (1954).

[55] *A. C. Albrecht* and *W. T. Simpson*, J. chem. Physics *23*, 1480 (1955).

[56] *R. F. Stewart* and *N. Davidson*, J. chem. Physics *39*. 255 (1963).

[57] See, *e.g.*, *H. Hartmann* and *H. L. Schläfer*, Angew. Chem. *66*, 768 (1954); *70*, 155 (1958).

[58] *C. R. Hare*, J. chem. Physics *40*, 792 (1964).

[*1] CT ≡ charge transfer.

[59] *S. K. Lower*, *R. M. Hochstrasser*, and *C. Reid*, Molecular Physics *4*, 161 (1961).

[60] *K. Nakamoto*, J. Amer. chem. Soc. *74*, 1739 (1952).

[61] See, *e.g.*, *G. Briegleb*: Elektronen-Donator-Acceptor-Komplexe. Springer, Berlin-Göttingen-Heidelberg 1961.

[62] *H. Kuroda*, J. chem. Physics *40*, 3748 (1964).

[63] *S. C. Ganguly* and *N. K. Chaudhuri*, J. chem. Physics *21*, 554 (1953).

[64] *D. S. McClure*, J. chem. Physics *25*, 481 (1956).

[65] *D. W. Olds*, J. chem. Physics *35*, 2248 (1961).

[66] See, *e.g.*, *S. Krimm* in *M. Davies*: Infrared Spectroscopy and Molecular Structure. Elsevier, Amsterdam 1963.

[67] Review: *W. Vedder* and *D. F. Hornig*, Advances Spectroscopy *2*, 189 (1961).

[68] *P. Heim* and *F. Dörr*, Ber. Bunsenges. physik. Chem. *69*, 453 (1965).

[69] *W. Kuhn*, *H. Dührkopp*, and *H. Martin*, Z. physik. Chem. B *45*, 121 (1939).

relative difference of the extinctions of light polarized parallel to and perpendicular to the field is about $10^{-4}$. The measurement of this electrically induced dichroism requires very sensitive methods. Present equipment (see *e.g.* [72]) permits the study of molecules having a dipole moment above about 2 D.

In many polar molecules, the dipole moment $\mu_a$ in the excited state $S_1$ is appreciably (up to 15 D) greater than $\mu_g$ in the ground state $S_0$ [70]. During the lifetime $\tau \approx 10^{-9}$ sec in the state $S_1$, therefore, the average degree of orientation in the field is increased according to Equations (19) and (20). The dipole moment $\mu_a$ in the excited state $S_1$ can be calculated from the degree of polarization P of the fluorescence of the solution in the electric field (electric fluorescence polarization). When observed perpendicular to the field, P is defined as

$$P = \frac{I_p - I_s}{I_p + I_s} \tag{21}$$

where $I_p$ (measured with an analyser) is the component of the light intensity polarized parallel to the field, and $I_s$ is the intensity of the component perpendicular to **F**. If the equilibrium distribution [Eq. (20)] is established in a "rotational relaxation time" shorter than about $\tau/4$, it is immaterial to the result whether the fluorescence is excited with natural or with polarized light. For P we obtain the approximation (22) [71].

$$P = \frac{1}{10} \cdot \frac{3\cos^2\alpha - 1}{2} \left(\frac{\mu_a}{kT}\right)^2 F^2 \tag{22}$$

From this equation, $\mu_a$ can be found if the angle $\alpha$ between $\mu_a$ and the transition moment corresponding to $S_1 \leftarrow S_0$ is known from symmetry considerations or from other measurements. (In most cases it can be assumed that the direction of $\mu_a$ is the same as that of $\mu_g$ for the ground state.)

The use of various electro-optical effects for the determination of molecular properties has been reviewed by *Labhart* [72].

## 2. Fundamentals of the Theory

A polar molecule in a non-polar solvent having a dielectric constant $\varepsilon_r$ is acted upon, not by the externally applied electric field $\mathbf{F}_0$, but by an internal (effective) field **F**, which may be considered to consist of two components: the field $\mathbf{F}_H$ in the cavity left in the dielectric solvent if the molecule in question were removed, and the field $\mathbf{F}_U$ produced by the polarization of solvent molecules by the polar molecule. Since the geometrical form of the polar molecule is generally irregular, and since its polarizability is anisotropic, the exact expressions for $\mathbf{F}_H$ and $\mathbf{F}_U$ are very complicated. In a first approximation $\mathbf{F}_U$ is neglected, and the field in a spherical cavity is used for $F_H$. The effective field **F** is then given by

$$\mathbf{F} \approx \frac{\varepsilon_r + 2}{3} \mathbf{F}_0 \tag{23}$$

If the polarizability of the polar molecule is taken into account by means of the tensor $(\alpha_g)$, its energy in the field is given, not by Equation (19), but by

$$\Delta E_g = -\mu_g \mathbf{F} - \frac{1}{2} \mathbf{F}(\alpha_g)\mathbf{F} \tag{24}$$

The same is true of the excited state (subscript a) [Equation (25)].

$$\Delta E_a = -\mu_a \mathbf{F} - \frac{1}{2} \mathbf{F}(\alpha_a)\mathbf{F} \tag{25}$$

A more accurate calculation should also consider the change in **F** on excitation, due to the change in the field component $\mathbf{F}_U$, produced by the change in the dipole moment.

From Equations (24) and (25), we see that the electric field causes a change $\Delta\tilde{\nu}$ in the wave number of the absorption [Eq. (26)].

$$\Delta\tilde{\nu} = \frac{1}{hc}(\Delta E_a - \Delta E_g) = \tilde{\nu}_o - \tilde{\nu}_F = \\ = \frac{1}{hc}\left\{\mathbf{F}(\mu_a - \mu_g) + \frac{1}{2}\mathbf{F}[(\alpha_a) - (\alpha_g)]\mathbf{F}\right\} \tag{26}$$

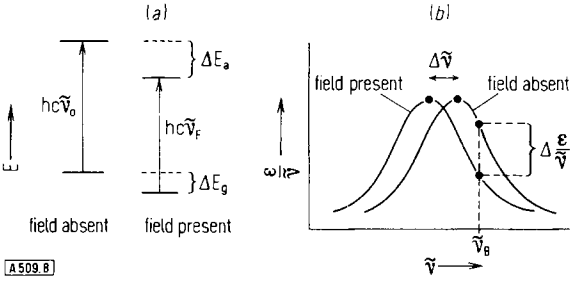



Fig. 8. Alteration of energy levels (a) and band shift (b) for the electronic excitation of a molecule in an electric field.

$\Delta E_a$ is generally greater than $\Delta E_g$ (cf. Fig. 8a). Consequently, an absorption band is displaced towards longer wavelengths in the field, with the result that the extinction coefficient $\varepsilon$ at a given observation frequency, $\tilde{\nu}_B$, changes when a field is applied, even in the case of natural light. If the field has no influence on the probability of the transition, *i.e.* on $|\mathbf{M}|^2$, then, since $|\mathbf{M}|^2 \propto \varepsilon/\tilde{\nu}$, the curve of $\varepsilon/\tilde{\nu}$ against $\tilde{\nu}$ is simply displaced parallel to itself when the field is applied (see Fig. 8b).

*Kuhn* [69] used the following assumptions in the evaluation of his measurements of electrically induced dichroism:

a) The orientation of the molecule is determined only by its permanent dipole moment $\mu_g$.

b) The anisotropy of the polarizability is neglected.

c) All transition moments are either parallel to or perpendicular to $\mu_g$.

d) The effective field is given by Equation (23).

e) The band shift of Equation (26) is not taken into account.

f) The transition probability, *i.e.* $\varepsilon/\tilde{\nu}$, is independent of the field strength.

On the basis of these restrictions, expressions were derived for the extinction coefficients $\varepsilon_p$ and $\varepsilon_s$, measured for light polarized parallel $(\varepsilon_p)$ to and perpendicular $(\varepsilon_s)$ to the field.

[70] *E. Lippert*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 962 (1957).

[71] *J. Czekalla*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 1221 (1960).

[72] *H. Labhart*, Tetrahedron *19*, Suppl. 2, 223 (1963).

The above simplifications can lead to large errors in the result (*e.g.* in the value of $\mu_a$ or in the angles between $\mu_g$ and the transition moments). *Labhart*[72–74] and *Liptay*[75–77] therefore extended the theory by a series expansion up to quadratic terms in **F**. *Liptay*[77] finally obtained very involved relationships (which cannot be discussed here) for the quantity $L_\chi$ defined in Equation (27), which can be determined experimentally.

$$L_\chi = -\frac{1}{2.303\ D_0 F^2} \cdot \frac{I_\chi - I_{\chi,0}}{I_{\chi,0}} \qquad (27)$$

In this equation, $D_0$ is the extinction at the observation frequency $\tilde{\nu}_B$ measured without an electric field; **F** is the effective field strength at the position of the molecule; $I_\chi$ is the intensity of the light having passed through the solution with an applied homogeneous field **F** when the incident light is polarized at an angle $\chi$ to the field direction; $I_{\chi,0}$ is the same quantity in the absence of the field. Depending on the symmetry of the molecules, $L_\chi$ can be used to find the angle between $\mu_g$ and the transition moments, the dipole moment $\mu_a$ in the excited state, the polarizability ($\alpha$), and other quantities.

### 3. Experimental Detection of Electric Fluorescence Polarization and Electrically Induced Dichroism

a) The degree of polarization of the luminescence of a solution in an electric field was determined by *Czekalla*[71] using the apparatus sketched in Fig. 9. The measuring cell Z is irradiated with monochromatic, unpolarized light perpendicular to the plane of the diagram. The emerging fluorescent light is partially polarized [cf. Eq. (22)]. It is modulated by a half-wave plate rotating with frequency $\omega$. An alternating current of frequency $4\omega$ is produced in the receiver, and this current vanishes when the polarization is compensated by rotation of the quartz plate compensator K. The position of K is then a measure of the degree of polarization P.

b) The double-beam arrangement described by *Labhart*[73] (see Fig. 10) has proved useful for the measurement of $L_\chi$ [Eq. (27)]. The electric field is sinusoidally modulated, but the polarity is not reversed; the angle $\chi$ is adjusted by means of the polarizer P. To obtain sufficient equations for the determination of the various quantities that are involved in $L_\chi$, the latter is measured as a function of the wave number $\tilde{\nu}$, the polarization angle $\chi$, and the temperature T.

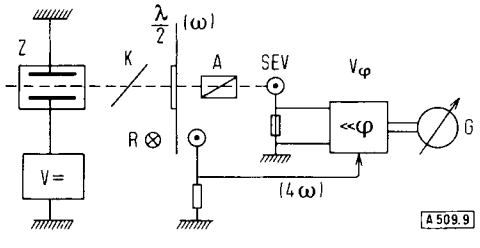



Fig. 9. Arrangement for measurement of the fluorescence polarization of solutions in an electric field [71]. (The illumination part of the apparatus is not shown).

Z condenser measuring cell; V source of high-voltage d.c.; K set of quartz plates; λ/2 rotating half-wave plate; R phase standard comprising a lamp, a rotating sector, and a photocell; A fixed analyser; SEV photomultiplier; Vφ phase-sensitive amplifier; G null detector.

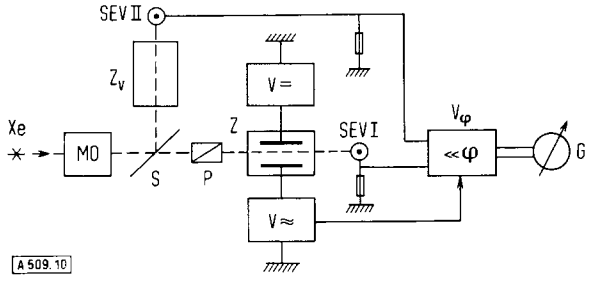



Fig. 10. Apparatus for measurement of $L_\chi$ [Eq. (27)] [73].

Xe high-pressure xenon lamp; MO monochromator; S dividing plate; P polarizer; $Z_V$ reference cell; Z condenser measuring cell; V source of 10 kV direct current; V≈ source of alternating current, peak 10 kV; SEV I and SEV II photo-multipliers; Vφ phase-sensitive symmetrical amplifier; G galvanometer.

### 4. Examples of Electric Orientation

In Fig. 11 (according to *Labhart*[72]), the total absorption $\varepsilon_{tot}$ (continuous curve) of nitrobenzene has been divided into the transitions I, II, and III by means of electrically

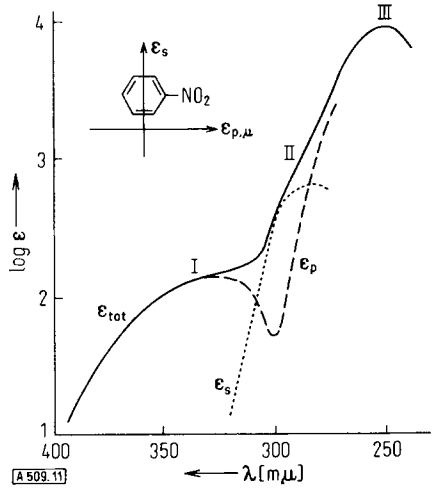



Fig. 11. Orientation of transition moments in nitrobenzene according to electrically induced dichroism [72].

$\varepsilon_p$ extinction coefficient for polarization parallel to the dipole moment; $\varepsilon_s$ that for transverse polarization.

induced dichroism. Transitions I and III are polarized parallel to the permanent dipole moment $\mu_g$ (broken curve $\varepsilon_p$), and II is polarized transverse to $\mu_g$ (dotted curve $\varepsilon_s$); $\mu_g$ is directed along the C–N axis. In spite of the transverse polarization of transition II, light absorption in this band leads to an increase of about 5 D in the dipole moment; thus the polarization of a transition may even be transverse to the net charge displacement.

In the same way *Labhart* analysed the spectra of 2,3-, 1,4-, and 1,8-dichloroanthraquinones, 2,3- and 1,4-dihydroxyanthraquinones, 2,3-, 1,4-, and 1,8-diaminoanthraquino-


[73] *H. Labhart*, Chimia *15*, 20 (1961).

[74] *H. Labhart*, Helv. chim. Acta *44*, 447 (1961).

[75] *W. Liptay* and *J. Czekalla*, Z. Naturforsch. *15a*, 1072 (1960).

[76] *W. Liptay* and *J. Czekalla*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 721 (1961).

[77] *W. Liptay*, Z. Naturforsch. *20a*, 272 (1965).

nes[73], nitrosobenzene, benzaldehyde, *p*-nitrodimethylaniline, *p*-nitrosodimethylaniline, and *p*-dimethylaminobenzaldehyde. The approximate direction of $\mu_g$ was determined theoretically for the unsymmetrical molecules[78].

According to *Czekalla*[79], the transition moments of the long-wavelength absorption bands for all the compounds listed below are parallel to $\mu_g$. The dipole moment $\mu_g$ (in debye units) in benzene solution is given alongside each compound; the dipole moment $\mu_a$ in the first excited state is shown in parentheses. In every case the polarity shows a marked increase on excitation:

4-dimethylamino-4′-nitrostilbene 7.15 (26.5); 4-amino-4′-nitrostilbene 6.50 (22); 4-dimethylamino-4′-cyanostilbene 6.95 (19); 2-amino-7-nitrofluorene 5.75 (23); 4-dimethylamino-4′-nitrobiphenyl 6.60 (24); 4-amino-4′-nitrobiphenyl 6.05 (23); *p*-dimethylamino-ω-nitrostyrene 7.65 (18), *p*-dimethylaminocinnamonitrile 6.90 (14, in hexane); *p*-nitrodimethylaniline 6.85 (15); *p*-nitroaniline 6.30 (14); *p*-nitrosodimethylaniline 6.90 (11.5).

## F. Photoselection

The electric light vector **E** vibrates perpendicular to the direction of propagation of the light. Thus the only molecules that can be optically excited are those whose transition moments have a component in the direction of **E**; *i.e.* in an isotropic solution, the light selects the suitably oriented molecules. Consequently, the excited molecules form an anisotropic entity with a definite degree of orientation, which is retained for some time after excitation in solid solution, *e.g.* in ethanol at 100 °K. The degree of orientation attainable with plane-polarized light is greater than with natural light. Fig. 12 illustrates this "photoselection" for some molecules of different orientation. The transition moment is assumed to lie along the longitudinal molecular axis[80].

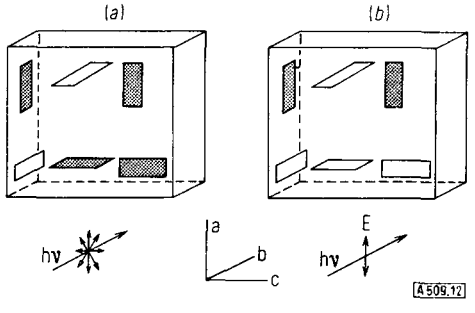



Fig. 12. Photoselection of differently oriented molecules with unpolarized (a) and with plane-polarized (b) light [80]. (The excited molecules are drawn in grey.)

If, after excitation, the molecules return to the metastable triplet state $T_1$, it is possible to measure the polarization of the $T_n \leftarrow T_1$ absorption transitions[81]. If, on the other hand, they undergo a photochemical reaction in the excited state to give a stable product, this product exhibits dichroic absorption[82–85]. The particularly important case in which the excited molecules re-emit partially polarized light ($S_1 \rightarrow S_0$ or $T_1 \rightarrow S_0$) is discussed in Section G.

### 1. Some Special Cases

By averaging over all orientations, *Albrecht* and *Simpson*[84] deduced general formulae for the dichroism, under various excitation and observation conditions, of a solid solution made anisotropic by a photochemical reaction. The most important special cases will be described below.

In Fig. 12b, letters a–c denote the axes of a coordinate system fixed in space. Suppose that the exciting light is propagated in direction b, and that it is plane-polarized along a. If the excited molecules undergo a photochemical change, but retain their positions in the solid solution, the extinctions $E_a$ and $E_b$ of the product of the photochemical reaction can be measured by means of light passing through the sample in direction c and plane-polarized along a and b, respectively. The ratio $E_a/E_b$ is characteristic of the relative orientation of the transition moment $\mathbf{M}_1$ causing the photochemical reaction in the original molecule, and of the transition moment $\mathbf{M}_2$ observed in the absorption of the reaction product.

If the excited molecules do not undergo photochemical reaction, but return to the ground state with emission of light, the emitted light is partially polarized. For observation in the b–c plane, *e.g.* in direction c, let $I_p$ be the intensity of the component of the emitted light polarized parallel to the exciting light, and $I_s$ the intensity of the perpendicularly polarized component.

For the first case above, a dichroic ratio corresponding to Equation (18) can be defined as

$$DV = \frac{E_a - E_b}{E_a + E_b} \qquad (28)$$

For the second case, the degree of polarization P is defined by Equation (21). Table 1 gives values for DV and P for a number of special positions of $\mathbf{M}_1$ and $\mathbf{M}_2$ under the experimental conditions described above.

Table 1. Limiting values of the dichroic ratio DV and the degree of polarization P for various orientations of the transition moment $\mathbf{M}_1$ corresponding to the initial absorption, and of the observed transition moment $\mathbf{M}_2$.

| Orientation of $\mathbf{M}_1$ | Orientation of $\mathbf{M}_2$ | $E_a/E_b$ or $I_a/I_b$ | DV or P |
|---|---|---|---|
| any | parallel to $\mathbf{M}_1$ | 3 | $^1/_2$ |
| any | perpendicular to $\mathbf{M}_1$ | $^1/_2$ | $-^1/_3$ |
| perpendicular to an axis of symmetry $C_n$ where $n > 2$ | parallel to $C_n$ | $^1/_2$ | $-^1/_3$ |
| perpendicular to an axis of symmetry $C_n$ where $n > 2$ | perpendicular to $C_n$ | $^4/_3$ | $^1/_7$ |


[78] *H. Labhart* and *G. Wagnière*, Helv. chim. Acta *46*, 1314 (1963).

[79] *J. Czekalla* and *G. Wick*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 727 (1961).

[80] *A. C. Albrecht*, J. molecular Spectroscopy *6*, 84 (1961).

[81] *M. A. ElSayed* and *T. Pavlopoulos*, J. chem. Physics *39*, 834 (1963).

[82] *G. N. Lewis* and *D. Lipkin*, J. Amer. chem. Soc. *64*, 2801 (1942).

[83] *G. N. Lewis* and *J. Bigeleisen*, J. Amer. chem. Soc. *66*, 520 (1943).

[84] *A. C. Albrecht* and *W. T. Simpson*, J. Amer. chem. Soc. *77*, 4454 (1955).

[85] *A. C. Albrecht*, J. Amer. chem. Soc. *82*, 3813 (1960).

It is assumed in the calculation of these values that the fraction of the molecules in the excited state is so small that the solution of the unexcited molecules can still be regarded as isotropic towards photons. This assumption is not valid under intense excitation, such as is required for the measurement of the $T_n \leftarrow T_1$ absorption, and only lower degrees of polarization are then reached [86]. It is also assumed that there is no overlapping of bands and no vibronic interaction.

The photoselection method (and hence the luminescence polarization described in Section G) gives information only about the relative orientation of the various transition moments in a molecule.

### 2. Examples

*El Sayed* and *Pavlopoulos* [77] studied the polarization of the $T_2 \leftarrow T_1$ absorption bands of perdeuterated naphthalene, phenanthrene, and chrysene by photoselection. In perdeuterated naphthalene and phenanthrene, the transition moment lies along the longitudinal molecular axis; it follows that the classification of $T_2$ for phenanthrene is $^3B_{3g}$ or $^3B_{2g}$.

*Albrecht* and *Simpson* [84] produced oriented molecules of Wurster's blue by photo-oxidation of *N,N,N',N'*-tetramethyl-*p*-phenylenediamine in solid solution. From the dichroic absorption of the dye, they deduced the positions of the transition moments: the weak band at 320 mμ, which corresponds to the long-wavelength benzene band, is polarized along the short molecular axis, and the intense band at 290 mμ along the long axis. In the short-wavelength part of the 320 mμ band, the vibrational interaction with the 290 mμ band can be recognized from the decreasing dichroism [85].

## G. Polarized Luminescence of Solid Isotropic Solutions

Of the methods mentioned so far for determining the orientation of transition moments in molecules, the measurement of luminescence polarization is the most general, since nearly all organic compounds have some symmetry and luminesce in solid solution, and since there are available polar, non-polar, acidic, and basic solvents that are transparent after solidification. The apparatus required is relatively simple, with the result that polarization spectroscopy can be developed into a routine method, which may also be of some analytical interest [87].

### 1. Definitions and Equations

Consider the absorption of monochromatic plane-polarized light of a wavelength corresponding to an isolated absorption band of the molecules in solid solution. Let the angle between the absorbing transition moment $\mathbf{M}_i$ and the emitting oscillator in the molecule be $\alpha_i$. The degree of polarization [88,89,113] of the luminescence is the same for every direction of observation in the b,c plane, which is perpendicular to the polarization direction a of the exciting light (see Fig. 12b), and is given by

$$P \equiv \frac{I_p - I_s}{I_p + I_s} = \frac{1-\rho}{1+\rho} = \frac{3\cos^2\alpha_i - 1}{\cos^2\alpha_i + 3} \qquad (29)$$

where $\rho = I_s/I_p$ is the depolarization; $I_p$ and $I_s$ are the intensities of the components polarized parallel and perpendicular to the exciting light, respectively. The limiting values are

$$-\frac{1}{3} \leqslant P \leqslant \frac{1}{2}; \quad 2 \geqslant \rho \geqslant \frac{1}{3}$$

It follows from Equation (29) that

$$\cos^2\alpha_i = \frac{3P+1}{3-P} = \frac{2I_p - I_s}{I_p + 2I_s} \qquad (30)$$

*Jablonski* calls the quantity r, defined by Equation (31), the degree of anisotropy.

$$r \equiv \frac{I_p - I_s}{I_p + 2I_s} = \frac{2P}{3-P} \qquad (31)$$

If several absorption transitions with extinction coefficients $\varepsilon_{i\lambda}$, whose oscillators include various angles $\alpha_i$ with the emitting oscillator, overlap at the exciting wavelength $\lambda$, then (still assuming excitation with plane-polarized light) we have

$$\left(\frac{2I_p - I_s}{I_p + 2I_s}\right)_\lambda \equiv B_\lambda = \frac{\sum_i \varepsilon_{i\lambda}\cos^2\alpha_i}{\sum_i \varepsilon_{i\lambda}} = \frac{\varepsilon_{1\lambda}}{\varepsilon_\lambda}\cos^2\alpha_1 + \frac{\varepsilon_{2\lambda}}{\varepsilon_\lambda}\cos^2\alpha_2 + \cdots \qquad (32)$$

The limiting values are $0 \leqslant B_\lambda \leqslant 1$.

$\sum_i \varepsilon_{i\lambda} = \varepsilon_\lambda$ is the total extinction coefficient measured at the wavelength $\lambda$.

In most cases, only two transitions overlap appreciably. If their polarizations relative to the emission are known (*e.g.* $\alpha_1 = 0°, \alpha_2 = 90°$), they can be separated according to Equation (32) if P is known. Thus for $\alpha_1 = 0°$ and $\alpha_2 = 90°$ we have:

$$\varepsilon_1 = \varepsilon\,\frac{3P+1}{3-P}; \quad \varepsilon_2 = \varepsilon - \varepsilon_1 \text{ [*]}. \qquad (33)$$

*Czekalla* and *Liptay* [90] developed the theory under very general assumptions: overlapping absorption bands, excitation and observation with high spectral bandwidths so that an average is obtained over various vibrational transitions, and no restrictions on the orientations of the oscillators. However, definite conclusions can be reached only if certain simplifications are introduced. The amount of information obtained is greatest for molecules of "medium" symmetry, particularly those of the symmetry groups $C_{2v}$, $D_2$, $D_{2h}$, $D_{3h}$, and $D_{6h}$, and for compounds whose π-electron systems

[86] *B. J. Stepanov* and *V. B. Gribkovskii*, Optics and Spectroscopy *8*, 114 (1960) [Engl. transl. of Optika i Spektroskopiya].
[87] *F. Dörr*, Z. analyt. Chem. *197*, 241 (1963).

[88] *F. Perrin*, Ann. Phys. *12*, 169 (1929).
[89] *A. Jablonski*, Z. Physik *96*, 236 (1935).
[*] The formula given in the review [1] for this case is wrong, since the factor 2 in the case of $I_s$ is neglected.
[90] *J.Czekalla*, *W. Liptay*, and *E. Döllefeld*, Ber. Bunsenges. physik. Chem. *68*, 80 (1964).

approximately have such a symmetry despite unsymmetrical substitutions.

According to *Czekalla*[90], if the bandwidth of the exciting and measuring light is sufficiently small, the degree of anisotropy [Eq. (31)] of the $S_1 \rightarrow S_0$ fluorescence, $r_f$, is proportional to that of the $T_1 \rightarrow S_0$ phosphorescence, $r_{Ph}$, for all exciting wavelengths:

$$r_f = A \cdot r_{Ph} + B. \tag{34}$$

According to Section C.2b, the phosphorescence generally consists of several components. The components of the total phosphorescence intensity $I_{Ph}$ that are polarized in various directions in the molecule can be determined from the experimental values of A and B.

For molecules with three mutually perpendicular principal axes (x is chosen perpendicular to the plane of the molecule), we have[90]:

$$\begin{aligned} I_{Ph}(x) &= \frac{A - 1 + 10\,B}{3\,A} \\ I_{Ph}(y) &= \frac{A - 1 - 5\,B}{3\,A} + \frac{I_F(y)}{A} \\ I_{Ph}(z) &= \frac{A - 1 - 5\,B}{3\,A} + \frac{I_F(z)}{A} \end{aligned} \tag{35}$$

$I_{Ph}(i)$ phosphorescence components; $I_F(i)$ fluorescence components; i = x, y, z.

It was assumed above that absorption and fluorescence are both polarized in the plane of the molecule. This is frequently not the case, *e.g.* for $\pi^* \leftarrow n$ transitions or when there is pronounced coupling with out-of-plane deformation vibrations. In any case, it is desirable to obtain the greatest possible spectral resolution. Owing to the band overlap, more information can usually be obtained from the wavelength-dependent variation of the degree of polarization than from its absolute value.

A fundamental and as yet unsolved problem is that of how to differentiate between 0,0-transitions (whose polarization is characteristic of the pure electronic states involved) and vibronic transitions.

## 2. Experimental Technique

### a) Apparatus

Several recent publications describe methods for measuring one of the quantities ρ, P [Eq. (29)], r [Eq. (31)], or $B_\lambda$ [Eq. (32)][18,90–94].

*Ainsworth* and *Winter*[95] developed a recording instrument, which forms any function of the depolarization ρ using an analogue computer. The recording instrument described by *Dehler* and *Dörr*[96] for the degree of polarization P is particularly simple in operation; this instrument is shown in Fig. 13, together with an arrangement for separate measurements of $I_p$ and $I_s$.

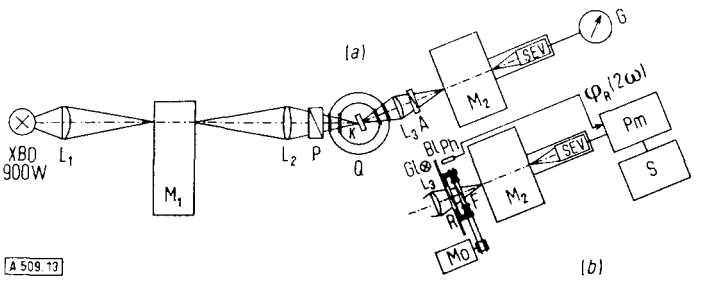



Fig. 13. Apparatus for the measurement of luminescence polarization (a) and accessory for automatic recording (b).

P Glan-Thomson-polarizer; electric vector of the transmitted light perpendicular to the plane of the drawing; K sample in a quartz Dewar vessel; A film polarizer, rotatable through 90°; $M_1$, $M_2$ monochromators; R rotating film polarizer; F fixed film polarizer, at 45° with respect to P; Gl, Bl, Ph incandescent lamp, rotating sector diaphragm, and photoresistor as phase standard; Mo motor; S pen recorder; Pm phase meter.

If the polarizer R rotates with a frequency ω, the photoelectric current consists of a direct component and two alternating components with frequencies 2ω and 4ω, respectively. The 2ω component is proportional to

$$(I_p - I_s)\cos 2\omega t + (I_p + I_s)\sin 2\omega t \approx \sin(2\omega t - \varphi)$$

where

$$\tan\varphi = \frac{I_p - I_s}{I_p + I_s} = P.$$

tan φ can be measured electrically with respect to the phase of a reference signal of frequency 2ω.

Observation at a small angle to the exciting light beam gives greater freedom in the choice of concentration than observation at right angles, since it is necessary in the latter case to match the concentration to the extinction (which depends on the wavelength), because of the strong dependence of the penetration depth on the wavelength. If ring cells or fused silica cells[96] with round bottoms and layer thicknesses of less than 3 mm are used, the stress birefringence in the sample is negligible. With high-pressure xenon lamps, the short-

Table 2. Solvents and solvent mixtures for the preparation of vitreous solid solutions for low-temperature measurements.

| Solvent | $t_G$ [°C] | Solvent | $t_G$ [°C] |
|---|---|---|---|
| $CF_3Br$ | −269 | Diethyl ether/Ethanol/Toluene 2:1:1 | −196 |
| 3-Methylpentane | −196 | Diethyl ether/Isopentane/Ethanol/Dimethylformamide 12:10:6:1 | −196 |
| Isopentane/Methylcyclohexane 5:1 | −196 | | |
| Ethanol 96% | −180 | Diethyl ether/Isopentane/Ethanol/Pyridine 12:10:6:1 | −196 |
| Ethanol/HCl 96:4 | −180 | | |
| Methanol/Ethanol 1:4 | −196 | Diethyl ether/Isopentane/Triethylamine 5:5:2 | −196 |
| Diethyl ether/Isopentane/Ethanol 5:5:2 ("EPA") | −195 | Triethylamine/Isopentane 6:1 | −148 |

[91] *E. Laffitte*, Ann. Physique *10*, 71 (1955).

[92] *M. A. ElSayed* and *R. G. Brewer*, J. chem. Physics *39*, 1623 (1963).

[93] *T. Azumi* and *S. P. McGlynn*, J. chem. Physics *37*, 2413 (1962).

[94] *W. Körber* and *V. Zanker*, Z. angew. Physik *17*, 398 (1964).

[95] *S. Ainsworth* and *E. Winter*, Appl. Optics *3*, 371 (1964).

[96] *J. Dehler* and *F. Dörr*, Z. angew. Physik *19*, 147 (1965).

[97] *M. N. McDermott* and *R. Nowick*, J. opt. Soc. America *51*, 1008 (1961).

[98] According to *M. Pestemer*: Anleitung zum Messen von Absorptionsspektren. G. Thieme Verlag, Stuttgart 1964.

wavelength excitation limit is about 220 mμ in favorable cases. The long-wavelength limit on the luminescence side is determined by the decrease in the sensitivity of the detector. A good film polarizer can be used in the range 310 to 700 mμ. Sheet polarizers for the short-wave ultraviolet have been described by *McDermott* [97]. In the polarization spectra of Fig. 14, the width at half-intensity of the exciting light and of the luminescence light is less than or equal to 2 mμ between 250 and 500 mμ.

The best solvents and solvent mixtures, which remain vitreous down to a temperature $t_G$, are listed in Table 2 [98]. The quantum yield in ethanol is generally higher than in non-polar solvents. To ensure accurate assignments, all the spectra to be compared must be recorded in the same solvent and at the same temperature.

### b) Corrections

When the measurements are carried out with an apparatus corresponding to Fig. 13a, the inherent polarization of the apparatus is included in the results. A λ-dependent correction factor is determined for the depolarization, $\rho = I_s/I_p$, by using translucent paper (instead of the sample) to produce non-polarized light. (The polarizer P is removed for these measurements). The values of P, r, or $B_\lambda$ corresponding to ρ are read off from a conversion table. The arrangement shown in Fig. 13b eliminates the polarization due to the apparatus, and is largely independent of variations in the intensity of the exciting light; it is used for the direct measurement of the degree of polarization P. Stray light causes a positive error in P. A check can be made for stray light by excitation at a slightly lower wavelength and examination of the region on the short-wavelength side of the luminescence spectrum with the receiver monochromator $M_2$; the intensity reading should then return to zero. If the transmission ranges of the two monochromators overlap then measurement becomes impossible, and for this reason single grating monochromators have not proved very useful. In practice, uncorrected P values are obtained only in the range $-0.32 \leqslant P \leqslant 0.47$; the limiting figures −0.33 and +0.5 are not reached. The main reason for this is probably the fact that depolarization due to passage through the various windows and lenses cannot be completely eliminated. In more concentrated solutions depolarization occurs as a result of energy migration (Section G.3.l); the magnitude of this effect is estimated by comparing the values obtained at various concentrations. The concentration limit at which depolarization due to energy migration becomes appreciable depends on the substance and on the solvent. It is greater than $10^{-3}$ M for aromatic compounds and ketones, and less than $10^{-4}$ M for dyes. It is often found that 1/P is linear in the concentration; cf. Section H and Fig. 21b.

## 3. Examples

The spectra in Figs. 14 to 20 were recorded using the arrangements shown in Fig. 13. In most cases it is possible to resolve the vibrational structure. Four types of polarization spectra can be recorded by the use of two monochromators:

(a) APF (absorption-polarization spectrum based on the fluorescence): the receiver is adjusted to one vibration fluorescence band (preferably the 0,0-band), and the wavelength of the exciting light is varied over the various absorption bands.

(b) APPh: as in (a), but based on the phosphorescence.

(c) FP (fluorescence polarization spectrum): A certain vibration band of the absorption spectrum (preferably the longest-wavelength 0,0-band) is excited, and the relative polarization of the various vibration bands in the fluorescence spectrum is determined.

(d) PhP: as in (c), but for the phosphorescence instead of the fluorescence.

All four types of polarization spectra are shown in Fig. 14 for phenanthrene, together with the normal absorption, fluorescence, and phosphorescence spectra.

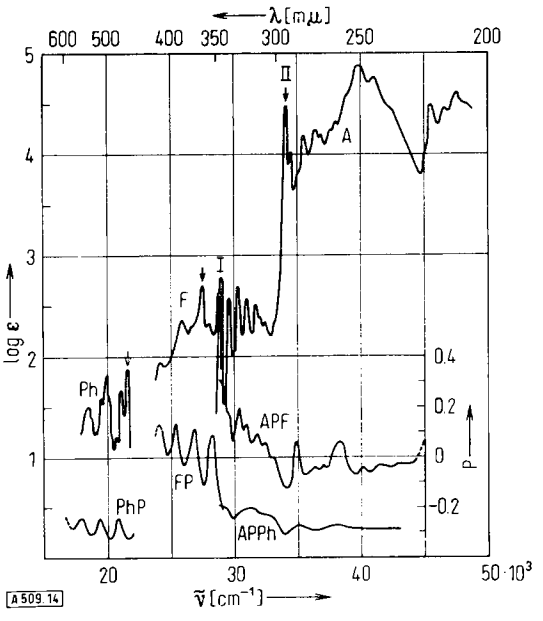



Fig. 14. Spectra of phenanthrene in $10^{-3}$ M ethanolic solution at 90 °K [96].

### a) A Simple Symmetrical Cyanine

In the simple pentamethinecyanine *(1)*, all the $S_n$–$S_0$ transition moments lie in the plane of the molecule. Theoretical considerations and measurements on stretched films indicate that the long-wavelength transition is polarized along the longitudinal axis.

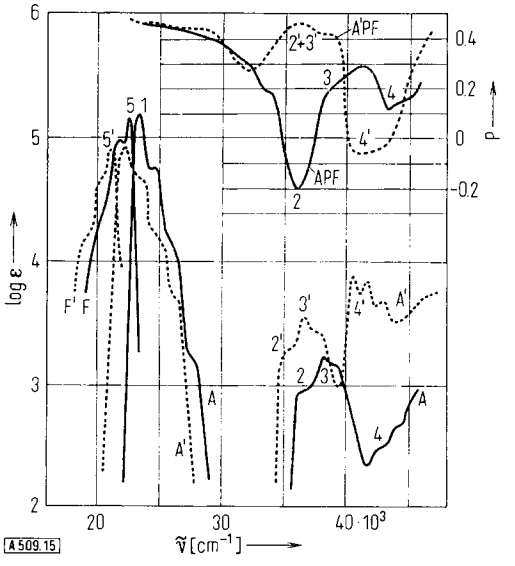
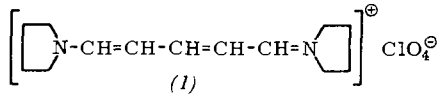



Fig. 15. Spectra of α,ω-di-(*N*-pyrrolidinyl)pentamethinecyanine in $10^{-4}$ M ethanolic solution at 90 °K [112]. *trans* (———); *cis* (– – – –); A,A′ absorption; F,F′ fluorescence.

Fig. 15 shows the absorption spectrum (A) and the APF spectrum of the all-*trans* form of *(1)*. Since the symmetry is $C_{2v}$, all the transition moments are mutually parallel



*(1)*

or perpendicular. It can be concluded from the APF curve that transitions 1 and 3 are polarized along the longitudinal axis, and transitions 2 and 4 along the transverse axis. The curves A′ and A′PF are discussed in Section G.3k.

### b) Vibronic Interactions

The maxima and minima of the curves APF, FP, and PhP in Fig. 14 coincide with (partly masked) vibration bands in the absorption spectrum A. The degree of polarization, APF, decreases in the electron band I (29000–34000 $cm^{-1}$) with excitation of higher vibrational levels, since the increase in the vibration amplitude is accompanied by an increase in the vibronic coupling with the negatively polarized transition II. In the symmetry classification, I belongs to the representation $A_1$ (polarized parallel to the short axis), and II belongs to $B_1$ (polarized along the long axis); according to Equation (9) the coupled vibration of about 700 $cm^{-1}$, which causes the minima in APF, also has symmetry $b_1$ (in-plane deformation vibration) [93,99].

### c) $T_1 \rightarrow S_0$ Phosphorescence in Aromatic Compounds

The APPh spectrum in Fig. 14 shows that the $T_1 \rightarrow S_0$ phosphorescence of phenanthrene ($C_{2v}$) consists of a strong y-component [$\Gamma(y) = B_2$] perpendicular to the plane of the molecule, and a weak z-component [$\Gamma(z) = A_1$] parallel to transition I. Assuming that only the spin-orbital coupling of $T_1$, and not that of $S_0$, is important, and that the orbital function of $T_1$ belongs to the representation $B_1$, then the intense y-component results from the interaction of $T_1$, *via* $\mathfrak{H}'_{ls}(z)$ ($A_2$), with a $B_2$ state of the type $S(\sigma\pi^*)$ [93]. The maxima in the PhP spectrum may be due to $a_2$ or $b_1$ vibrations. The $T_1 - S_0$ oscillator is also perpendicular to the plane of the molecule in many other aromatic and N-heterocyclic compounds [100–103].

### d) The Heavy-Atom Effect in Spin-Orbit Coupling

The phosphorescence of naphthalene consists of a principal component perpendicular to the plane of the molecule, and a small component parallel to $^1L_b$ (the major axis). Halogenation in position 1 leads to an increase in the intensities of the components along the long and short axes, the effect increasing with the atomic number [cf. Eq. (13)]. Substitution in position 2, on the other hand, has very little effect (cf. Table 3) [90,104].

Table 3. Change in the APPh spectrum of naphthalene as a result of monohalogenation [104].

| $T_1 \rightarrow S_0$ | Naphthalene | 1-F | 1-Cl | 1-Br | 1-I | 2-F | 2-Cl | 2-Br | 2-I |
|---|---|---|---|---|---|---|---|---|---|
| P *vs.* $^1L_b$ [*] | −0.30 | −0.22 | −0.20 | −0.04 | +0.13 | −0.26 | −0.25 | −0.22 | −0.18 |
| P *vs.* $^1L_a$ [*] | −0.32 | −0.28 | −0.17 | +0.02 | +0.15 | −0.29 | −0.24 | −0.25 | −0.24 |

[*] 0,0-Band

### e) High Symmetry

Fig. 16 shows the fluorescence (F) and phosphorescence (Ph) spectra of triphenylene (symmetry group $D_{3h}$). Similar spectra are obtained with coronene ($D_{6h}$). The fluorescence is polarized in the plane perpendicular to the threefold (or sixfold, respectively) axis of symmetry; FP has the value $+1/7$ for all absorption transitions [105] (cf. Table 1). The phosphorescence is largely polarized perpendicular to the plane of the molecule; it is coupled with non-totally symmetric vibrations. (In the case of coronene, the fluorescence and phosphorescence spectra overlap to some extent.) The APF curve of crystal violet reaches values greater than 0.4 in the long-wavelength part of the "color band" [30,91]; this is consistent with the fact that the molecule does not possess threefold symmetry owing to steric hindrance.

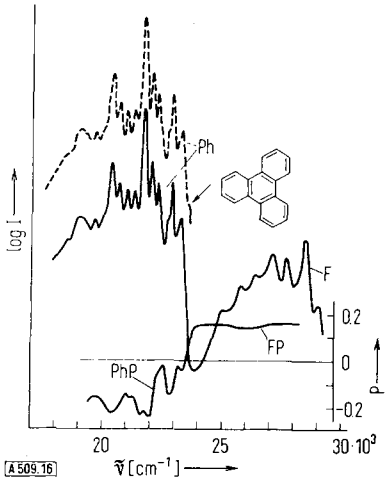



Fig. 16. Fluorescence (F) and phosphorescence (Ph) of triphenylene (example of a highly symmetrical molecule) in $10^{-3}$ M ethanolic solution at 90 °K [101].


[99] *H. Zimmermann* and *N. Joop*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 66, 342 (1961).

[100] *F. Dörr* and *H. Gropper*, Angew. Chem. *74*, 354 (1962).

[101] *F. Dörr* and *H. Gropper*, Ber. Bunsenges. physik. Chem. *67*, 46 (1963).

[102] *F. Dörr* and *H. Gropper*, Ber. Bunsenges. physik. Chem. *67*, 193 (1963).

[103] *V. G. Krishna* and *L. Goodman*, J. chem. Physics *37*, 912 (1962).

[104] *F. Dörr*, *H. Gropper*, and *N. Mika*, Z. Naturforsch. *18a*, 1025 (1963).

[105] *H. Zimmermann* and *N. Joop*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65*, 138 (1961).

### f) Aromatic Ketones

Aromatic ketones with long-wavelength $\pi^* \leftarrow n$ shoulders (cf. example in Section C.2a) do not fluoresce, but simply exhibit a $T_1(n\pi^*) \rightarrow S_0$ phosphorescence. This is probably parallel polarized to the C–O direction [20][cf. the example following Eq. (17)]. Fig. 17 shows the APPh spectrum of anthrone [106, 107]. The $\pi^* \leftarrow n$ absorption band is largely negatively polarized with respect to the C–O axis, probably in the plane of the molecule. The APF spectrum in the $\pi^* \leftarrow n$ band rises towards shorter wavelengths; the $S(n\pi^*) \leftarrow S_0$ transition can couple, by means of a non-planar $a_2$ vibration, with a $\pi^* \leftarrow \pi$ transition, resulting from the splitting of the transitions in the benzene rings, and lying in the C–O direction ($A_1$) [106–108].

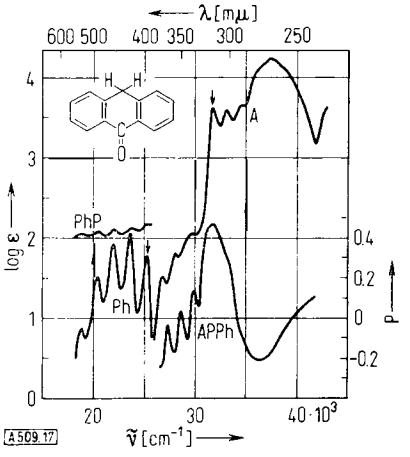



Fig. 17. Spectra of anthrone, $10^{-2}$ to $10^{-4}$ M in 2-methyltetrahydrofuran at 90 °K [108].

### g) N-Heterocycles

N-Heterocycles containing one or two rings give separate $\pi^* \leftarrow n$ transitions only if they contain two or three nitrogen atoms in the same ring. The $S(n\pi^*) \leftarrow S_0$ transition moment is perpendicular to the plane of the ring, and the $T_1 \rightarrow S_0$ emission from pyrazine and pyrimidine is polarized parallel to the N–N direction. In these compounds the $T_1$ state is of the ($n\pi^*$) type [18, 92].

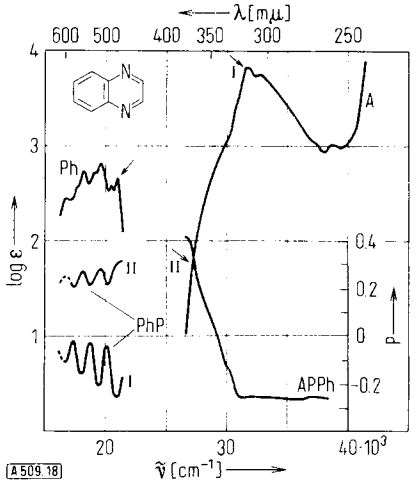



Fig. 18. Spectra of quinoxaline in $10^{-2}$ M ethanolic solution at 90 °K [110].

In quinoxaline, on the other hand, $T_1$ is of the ($\pi\pi^*$) type [109], and presumably (by analogy with the $^3L_a$ state of naphthalene) belongs to the representation $B_2$ (symmetry $C_{2v}$). The PhP and APPh spectra are positive on excitation in the $\pi^* \leftarrow n$ shoulder, and negative on irradiation in the strong $\pi^* \leftarrow \pi$ absorption bands (see Fig. 18) [92, 110].

### h) Masked Transitions

The $\pi^* \leftarrow n$ transition is not observed in the absorption spectrum of benzoquinoxaline since it is masked by the much stronger $\pi^* \leftarrow \pi$ bands. However, the $S(n\pi^*) \leftarrow S_0$ transition corresponds to the minimum in the APF spectrum and to the maximum in the APPh spectrum at 32000 $cm^{-1}$ [110]. *Zimmermann* and *Joop* [111] found an unexplained absorption band at 33900 $cm^{-1}$ in the polarization spectra of azulene. Calculation of the spectrum of azulene gives a corresponding excited state only if configuration interaction is taken into account.

### i) Hybridization State of a Heteroatom

Figs. 19 and 20 show the spectra of dibenzothiophene and its *S,S*-dioxide. These two compounds differ very markedly in their APF and APPh spectra. This must be due to the change in the hybridization of the sulfur atom.

### k) *cis-trans* Isomerism

The cyanine *(1)* (Fig. 15) undergoes a reversible photoisomerization. The absorption curve A′, the fluorescence spectrum F′, and the polarization spectrum A′PF are those of the product. The intensification of the short-axis polarized transition 4′ supports the proposed explanation, *i.e.* that light rearranges the compound to give an unstable mono-*cis* form [112].

### l) Concentration Depolarization

The radiationless transfer of excitation energy between identical molecules leads to a depolarization of the fluorescence, as can be seen from the FP spectrum, in which P tends towards zero. An example of this is shown in Fig. 21 [30]. The probability of energy migration increases with concentration [113]. The association of dye molecules is also clearly shown by the APF spectrum, sometimes at even lower concentrations than in the ab-


[106] *V. G. Krishna*, J. molecular Spectroscopy *13*, 296 (1964).

[107] *F. Dörr* and *J. Dehler*, Tetrahedron Letters *1965*, 189, 2155.

[108] *J. Dehler*, Dissertation, Technische Hochschule München, 1965.

[109] *R. Müller* and *F. Dörr*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *63*, 1150 (1959).

[110] *F. Dörr*, *H. Gropper*, and *N. Mika*, Ber. Bunsenges. physik. Chem. *67*, 202 (1963).

[111] *H. Zimmermann* and *N. Joop*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 1219 (1960).

[112] *F. Dörr*, *J. Kotschy*, and *H. Kausen*, Ber. Bunsenges. physik. Chem. *69*, 11 (1965).

[113] *Th. Förster*: Fluoreszenz organischer Verbindungen. Vandenhoeck u. Rupprecht, Göttingen 1951.

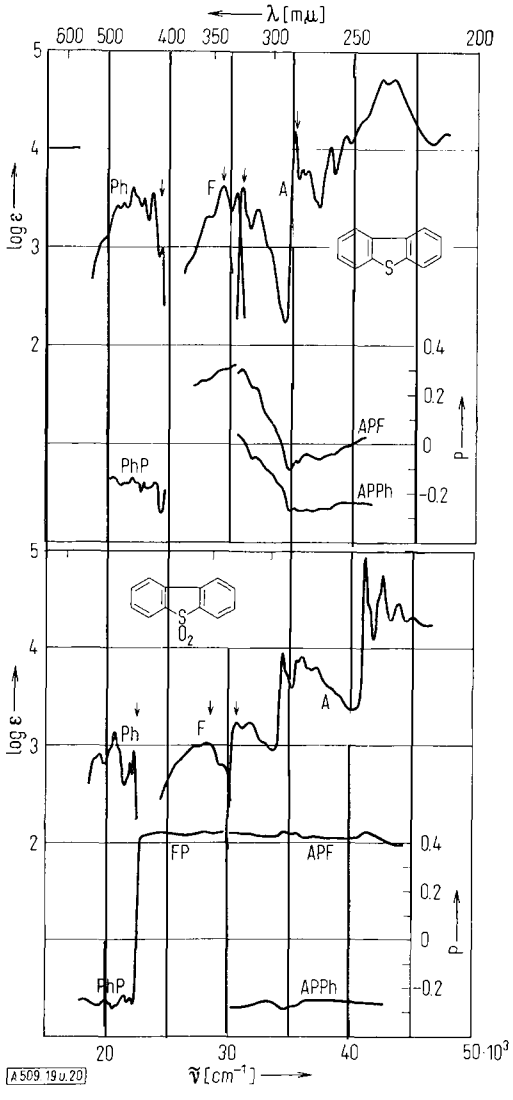



Fig. 19 (top). Spectra of dibenzothiophene in $10^{-3}$ M ethanolic solution at 90 °K.

Fig. 20 (bottom). Spectra of dibenzothiophene *S,S*-dioxide in $10^{-3}$ M ethanolic solution at 90 °K.

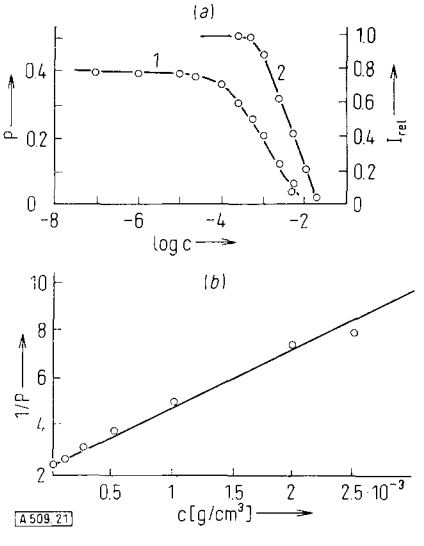



Fig. 21. Fluorescein in glycerol at 20 °C [30].

(a) Concentration depolarization (1) and concentration quenching (2) of the fluorescence; (b) linearity of 1/P with concentration; $I_{rel}$ relative fluorescence intensity.

sorption spectrum[114]. The phenomenon of association differs from depolarization due to energy migration in that the degree of polarization of the luminescence of the associates can even become negative.

### m) Polarization of Charge-Transfer Bands

*Mulliken*'s theory of electron donor-acceptor complexes (charge-transfer complexes) explains the long-wavelength, so-called CT absorption bands as resulting from electron transfer from the donor D to the acceptor A. The transition moment should lie along the line joining the electrical "centers of gravity" of A and D, *i.e.* for two planar molecules placed one above the other, the transition moment should be perpendicular to the planes of the molecules[*]. In solid solution, the $T_1 \rightarrow S_0$ phosphorescence of the donor molecule can be observed on excitation in this CT band[115].

In the cases of naphthalene (Table 3), phenanthrene (Fig. 14), and chrysene[101], the $T \rightarrow S_0$ transition is polarized perpendicular to the plane of the molecule. *Chowdhury* and *Goodman*[116] found that, in the complexes of tetrachlorophthalic anhydride with these aromatic compounds, the CT absorption band is polarized parallel to the phosphorescence band of the aromatic compound. This confirms the proposed "sandwich" structure.

### n) Fluorescence from Two Terms

Some compounds, *e.g.* indole, have a broad absorption band at long wavelengths, and a broad fluorescence band which is almost a mirror image of the absorption band. The polarization spectra show that both bands consist of two transitions, *i.e.* that two adjacent levels $S_1$ and $S_2$ with different symmetries are emitting simultaneously. The radiationless transition $S_2 \rightarrow S_1$ (cf. Fig. 1) is strongly hindered in this case[117,118].

## H. Polarization of the Luminescence of Liquid Solutions

*Perrin*[88] corrected for the depolarization in liquid solutions due to the rotation of the excited molecule (which was assumed to be spherical) by means of Equation (36). *Memming*[119] extended the theory to include non-spherical molecules.

$$\frac{1}{P} = \frac{1}{3} + \left(\frac{1}{P_0} - \frac{1}{3}\right)\left(1 + \frac{3\tau}{\rho_0}\right) \qquad (36)$$

with $\rho_0 = \eta V/kT$

[114] *V. Zanker, M. Held,* and *H. Rammensee,* Z. Naturforsch. *14b,* 789 (1959).

[115] *G. Briegleb, J. Czekalla, W. Herre,* and *R. Glier,* Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61,* 537, 1053 (1957).

[116] *M. Chowdhuri* and *L. Goodman,* J. Amer. chem. Soc. *86,* 2777 (1964).

[*] From formal selection rules, transverse polarization should also be possible in special cases.

[117] *H. Zimmermann* and *N. Joop,* Z. Elektrochem., Ber. Bunsenges. physik. Chem. *65,* 61 (1961).

[118] *V. P. Klochkow* and *B. S. Neporent,* Optics and Spectroscopy *12,* 125 (1962) [Engl. transl. of Optika i Spektroskopiya].

[119] *R. Memming,* Z. physik. Chem. *68,* 80 (1964).

P: measured degree of polarization; $P_0$: limiting degree of polarization for the frozen solution; $\tau$: lifetime of the excited state; $\eta$: viscosity of the solvent at the temperature T; V: (effective) molecular volume.

It is found experimentally that 1/P is nearly linear in $T/\eta$, provided that there is no temperature-dependent quenching to shorten the lifetime $\tau$. If $\tau$ is appreciably reduced (this can also result from the concentration-dependent action of a fluorescence quencher), then according to Equation (36), P approaches the limiting value $P_0$ for the frozen solution. The degree of polarization can therefore also be used as an indicator for quenching effects (see [30]).

If the molecular volume V is known, *e.g.* from viscosity measurements, Equation (36) provides a means of determining the lifetime $\tau$. If, on the other hand, $\tau$ is measured independently, it is then possible to determine the molecular volume V. This may be of great practical importance especially for large molecules, for example, in biochemistry. Non-fluorescent macromolecules often interact with dye molecules to form fluorescent associates, which can be used for the measurement of rotational depolarization. Any change in the molecular volume as a function of temperature or of the concentration of other solutes (*e.g.* of the pH) can be detected from the variation of the degree of polarization.

[120] *G. Weber*, Advances in Protein Chemistry *8*, 415 (1953).

The quantity $\rho_0$ in Equation (36) has the significance of a rotational relaxation time. Only for spherical molecules is there a simple definition for it. For ellipsoids of revolution or for molecules in which two parts can rotate relative to each other, $\rho_0$ consists of two components $\rho_a$ and $\rho_b$:

$$\rho_0 = \frac{2(\rho_a + \rho_b)}{\rho_a \cdot \rho_b} \qquad (37)$$

Restriction or enhancement of such internal rotations by co-solutes also lead to a change in $\rho_0$, and hence in the degree of polarization.

The effects described in this section form the bases of some interesting applications of polarization spectrometry in biochemistry. *Weber*, who introduced this method to this field, published a survey of his results and an introduction to his extended theory [120]. He listed the following advantages: low concentrations (*e.g.* $10^{-2}$ % serum albumin) can be used; P is almost independent of the salt and protein concentrations; the temperature and pH can be varied within wide limits; in mixtures, a certain protein may be labelled; the procedure is relatively simple.

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# Carbohydrates Containing Nitrogen or Sulfur in the "Hemiacetal" Ring

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*In 5-amino-5-deoxy- and 5-thioaldoses, a 6-membered hemiacetal ring can be formed by incorporation of a nitrogen or sulfur atom into the ring instead of the oxygen present in pyranoses. In the case of 5-(N-acylamido)-5-deoxyaldoses, the nucleophilic strength of the amide grouping is lowered, with the result that ring closure occurs only when sterically favored, or when a side reaction with formation of furanose is not possible. On the other hand, 5-amino-5-deoxyaldoses containing a free amino group readily form 6-membered "hemiacetal" rings. The resulting piperidinoses possess properties that are unusual in sugars, since they contain the 2-hydroxypiperidine ring system. Piperidinoses are stable to alkalis and labile to acids; they rearrange in the presence of acids to give Amadori compounds, or lose three molecules of water to give derivatives of β-hydroxypyridines. Owing to the high reactivity of the mercapto group, 5-thioaldoses form only sugars with rings containing sulfur, the behavior of which resembles that of the oxygen analogues. 4-Amino-4-deoxy- and 4-thioaldoses can form 5-membered rings containing nitrogen and sulfur.*

## I. Introduction

Free monosaccharides generally do not exist in the open-chain carbonyl form, but in the cyclic hemiacetal form, which results from the intramolecular reaction of the carbonyl group with a hydroxyl group. This reaction usually involves the hydroxyl group on C-5, and leads to the formation of a 6-membered pyranose ring. The 6-membered ring in the chair form is favored energetically, since in this form all the substituents assume the staggered position, particularly when the ring is fixed in one of the two chair forms, the C 1 or the 1 C form (see Fig. 1), by a sufficient number of bulky substituents.

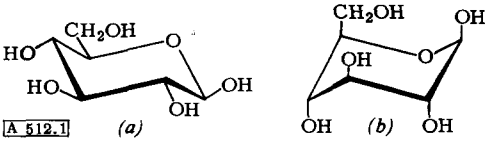


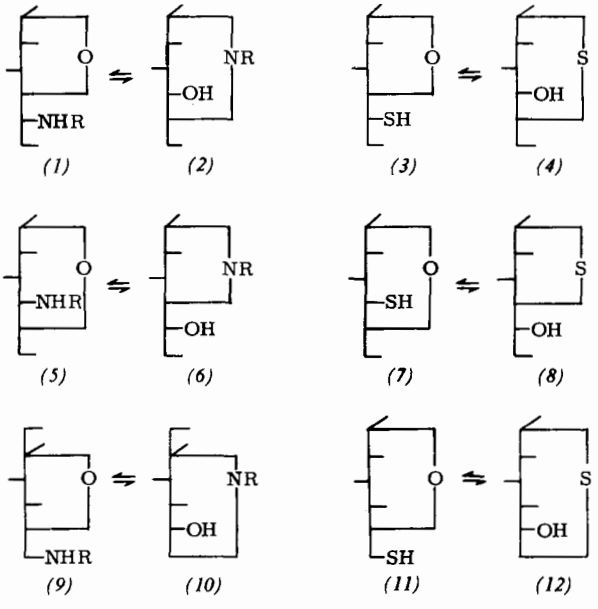

Fig. 1. β-D-Glucose: C 1 form (a) and 1 C form (b).

The hydroxyl group on C-4 can also react to give a 5-membered furanose ring. Owing to the presence of the substituents, however, the furanose ring is stereochemically unfavored and, therefore, is formed only in special cases (*e.g.* when position 5 is blocked).

It is interesting to replace the oxygen in the hemiacetal rings of sugars by other heteroatoms, particularly nitrogen and sulfur, and to study the properties and reactions of modified sugars of this type. We started with the synthesis of 5-amino-5-deoxy sugars, which were expected to form "hemiacetal" rings. In this way we obtained the first crystalline member of this class of substances, *N*-acetyl-α-D-xylopiperidinose [1]. Other sugars with rings containing sulfur or nitrogen have been prepared in recent years. These compounds are not only of chemical interest, but may also act as antimetabolites, particularly since many antibiotics contain aminodeoxy sugars with unusual structures [2].

Direct substitution of the ring oxygen, which is readily achieved in pyran chemistry, *e.g.* in the case of kojic acid [3], is not possible in the case of monosaccharides, since this is equivalent to *O*-alkyl cleavage on C-5, which does not occur in acetals. Thus the problem is to introduce a substituent containing the desired new heteroatom into position 5 of the monosaccharide, *i.e.* to synthesize a 5-amino-5-deoxy or a 5-thio sugar. Pyranose derivatives naturally cannot be used in this synthesis, which, therefore, must be carried out with furanose derivatives or derivatives of open chain forms.

Formulae *(1)* to *(12)* show a number of model schemes for the reaction of compounds substituted in this way. In the 5-amino-5-deoxy sugar *(1)* ⇌ *(2)*, the amino group competes with a hydroxyl group in the formation of the "hemiacetal" ring. If the amino group is sufficiently reactive with respect to acetal formation, a 6-membered ring *(2)* containing nitrogen is formed. If the amino group is not sufficiently reactive, the reaction leads to the formation of the energetically less favorable furanose form *(1)*. A similar situation occurs in the case of the 5-thio sugar *(3)* ⇌ *(4)*, in which there is competition between the mercapto group and a hydroxyl group.




In the compounds *(5)* ⇌ *(6)* and *(7)* ⇌ *(8)*, the positions of the substituents have been interchanged. A 5-membered ring *(6)* containing nitrogen will be formed only if the amino group is sufficiently reactive to overcome the preference for the 6-membered pyranose ring *(5)*. The same is true in the case of the derivatives *(7)* ⇌ *(8)* containing sulfur. Examples of other systems are the 6-amino-6-deoxy ketoses *(9)* ⇌ *(10)*, in which a 6-membered ring form *(10)* containing nitrogen is in equilibrium with a furanose form *(9)*. In very reactive aldoses with substituents in position 6, *e.g.* 6-thioaldose *(11)*, it is possible that a 7-membered ring *(12)* containing sulfur, which ordinarily would be energetically unfavorable, could enter into the equilibrium [3a].

The possibilities for tautomerism can be greatly increased if the positions of the heteroatoms O, N, and S (and possibly also Se) are interchanged. Though only some of these possibilities have so far been studied, it is already possible to recognize the fundamental modes of reaction of sugars containing nitrogen and sulfur in the ring.

There are two basic types of 5-amino-5-deoxy sugars, *i.e.* those containing *N*-acylated amino groups and those containing free amino groups. The amino group loses much of its basic character on acylation, owing to amide mesomerism, and it is, therefore, less able to compete with the hydroxyl group. Thus amides cannot form *N*-glycosides by direct reaction, except in the case of urea and glucose [4]. The Mannich condensation of amides [5] requires stronger acid catalysis than the corresponding reaction of amines [6]. 5-Acylamido-5-deoxy sugars, therefore, form 6-membered rings containing nitrogen only when ring formation is highly favored by steric factors, *e.g.* in the case of 5-acetamido-5-deoxy-D-xylose, or when this is the only ring that can be formed. Monosaccharides with an *N*-acylimino group in the ring behave in the same manner as the corresponding oxygen compounds, and react with alcohols to form glycosides.

5-Amino-5-deoxy sugars containing free amino groups behave quite differently. The more strongly nucleophilic amino group competes strongly with the hydroxyl group. This can be seen in the reaction of aldoses with amines, in which the glycosidic hydroxyl group readily can undergo nucleophilic substitution with formation of an *N*-glycoside. Thus 5-amino-5-deoxy sugars preferentially form a 6-membered ring containing nitrogen [*(2)*, R = H].

These piperidinoses *(2)*, R = H, exhibit properties not previously observed in carbohydrate chemistry. In contrast to all other monosaccharides, these sugar derivatives are stable only in alkaline solution; in the presence of acids they readily lose 3 moles of water to form derivatives of 3-hydroxypyridine. In alkaline media, the 2-hydroxypiperidine system is present; the sugar derivatives, therefore, possess some of the properties of this system, particularly the tendency to form piperideine. Thus it seems reasonable to name these sugar derivatives piperidinoses.

Owing to the high reactivity of the mercapto group, 5-thio sugars readily give the ring form *(4)*, in which the sulfur is built into the 6-membered ring. The mercapto group is more reactive than the amino group, since the reaction of aldoses with mercaptans always leads to cleavage of the hemiacetal ring and formation of the open-chain mercaptals; no thioglycosides are formed. The properties of the thiopyranoses [*] are similar to those of the corresponding oxygen compounds.

## II. Monosaccharides Containing Nitrogen in the Ring

### 1. Sugars with N-Acylimino Groups in the "Hemiacetal" Ring

#### a) 5-(*N*-Acylamido)-5-deoxy Sugars

The first sugar with nitrogen in the "hemiacetal" ring obtained in crystalline form was *N*-acetyl-D-xylopiperi-

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[2] *J. D. Dutcher*, Advances Carbohydrate Chem. *18*, 259 (1963).

[3] *K. Heyns* and *G. Vogelsang*, Chem. Ber. *87*, 1377, 1440 (1954).

[3a] *J. M. Cox* and *L. N. Owen*, Chem. Commun. *1965*, 513.

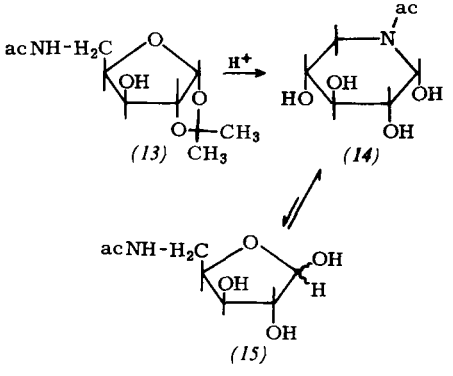
[4] *J. Goodman*, Advances Carbohydrate Chem. *13*, 215 (1958).

[5] *H. Hellmann*, Angew. Chem. *69*, 463 (1957).

[6] *H. Hellmann* and *G. Opitz*, Angew. Chem. *68*, 265 (1956).

[*] The term "thiopyranose" is used in this paper for monothiopyranoses in which the oxygen in the hemiacetal ring is replaced by sulfur (cf. also Section IIIa).

dinose *(14)* [1,7–10]. Partial acid hydrolysis of the compound *(13)* leads to a mixture of piperidinose *(14)* and furanose *(15)* in the ratio 2:1, from which the crystalline piperidinose *(14)* is obtained directly[7]. Both forms *(14)* and *(15)* are stable in neutral solution and can, therefore, be separated by column chromatography without fear of interconversion due to readjustment of the equilibrium. Equilibration occurs only with catalysis by acids or bases. Thus with *(14)* or *(15)* in the presence of 0.1 N HCl at room temperature, equilibrium is reached after about 35 h [9]. In the presence of bases, equilibration takes only a few minutes; however, side reactions also occur in this case.

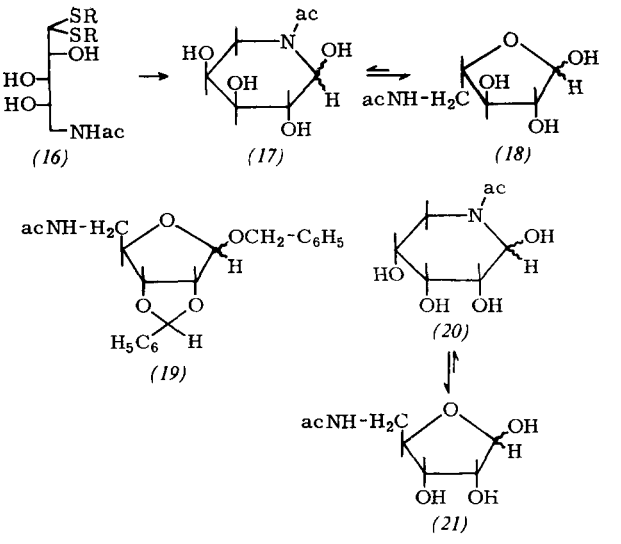



The 6-membered cyclic form of the piperidinose *(14)* is proved by the following results. The infrared spectrum of *(14)*, unlike that of *(15)*, does not contain an amide-II band due to an NH group. Peracetylation of *(14)* gives a tetraacetate, and that of *(15)* a triacetate[7]. The results obtained on cleavage of *(14)* with periodate indicate a 6-membered ring form[8], as do the differing NMR spectra of *(14)* and *(15)* [9].

The proportion of the piperidinose form can be increased by partial hydrolysis of 5-carbobenzoxyamino-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose. The product consists almost entirely of crystalline *N*-carbobenzoxy-D-xylopiperidinose, since the furanose concentration at equilibrium is small[11]. The carbobenzoxyamino group is evidently more strongly nucleophilic than the acetamido group, with the result that the 6-membered ring containing nitrogen is preferred. The behavior of *N*-benzoyl-D-xylopiperidinose is similar to that of the *N*-acetyl compound[11a].

The piperidinose *(14)* reacts readily with alcohol/hydrochloric acid to form the corresponding glycoside, in which the acetamido group is still built into the ring; this method has been used to prepare *e.g.* methyl- and benzylxylopiperidinosides[7,8], the properties of which are similar to those of the oxygen analogues.

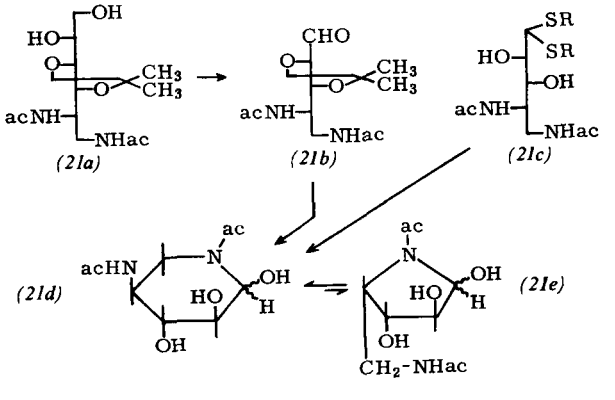
5-Acetamido-5-deoxy-L-arabinose can be prepared, like *(14)*, by hydrolysis of a suitable 1,2-isopropylidene compound[12] or by elimination of RSH from *(16)*




with $HgCl_2$–$CdCO_3$ [9]. The product is again a mixture of the 6-membered and 5-membered ring forms *(17)* ⇌ *(18)*; the equilibrium ratio of *(18)* to *(17)* is approximately 2:1, *i.e.* in contrast to the *xylo* compound, the furanose form *(18)* appears to be favored in this case. In 5-acetamido-5-deoxy-D-ribose, which can be obtained by hydrogenolysis of *(19)* [9], the proportion of piperidinose *(20)* in the equilibrium mixture is even smaller, so that the isolation of *(20)* is not easy [9].

These results show that the weakly nucleophilic acetamido group cannot form a "hemiacetal" ring containing nitrogen except under the most favorable steric conditions. Such favorable conditions exist in the *xylo* configuration in the 6-membered ring, in which all the substituents are in the equatorial position, and where there is no steric hindrance by bulky substituents on C-5. This should, therefore, be the configuration assumed by most of the piperidinose form in the equilibrium *(14)* ⇌ *(15)*. Even in the case of the *arabino* configuration, containing one axial hydroxyl group, the proportion of the piperidinose form *(17)* is smaller. Ribose itself exhibits a complex mutarotation involving the furanose form or the open-chain form[13], and this explains to some extent the fact that the smallest contribution of piperidinose *(20)* and the largest of furanose *(21)* are found in 5-acetamido-5-deoxy-D-ribose.

4,5-Diacetamido-4,5-dideoxy-L-xylose can form either a 6-membered ring or a 5-membered ring containing nitrogen. It is obtained by hydrolysis of *(21a)* with





[7] *H. Paulsen*, Liebigs Ann. Chem. *670*, 121 (1963).

[8] *J. K. N. Jones* and *W. A. Szarek*, Canad. J. Chem. *41*, 636 (1963).

[9] *S. Hanessian* and *T. H. Haskell*, J. org. Chemistry *28*, 2604 (1963).

[10] *T. H. Haskell* and *S. Hanessian*, J. org. Chemistry *28*, 2598 (1963).

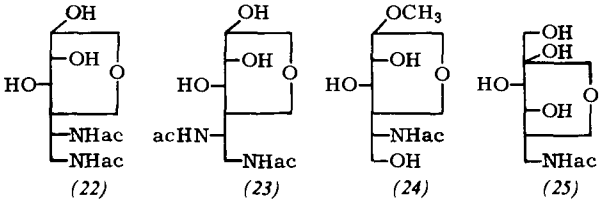
[11] *H. Paulsen, K. Todt*, and *F. Leupold*, Tetrahedron Letters *1965*, 567.

[11a] *M. S. Patel* and *J. K. N. Jones*, Canad. J. Chem. *43*, 3105 (1965).

[12] *J. K. N. Jones* and *J. C. Turner*, J. chem. Soc. (London) *1962*, 4699.

periodate followed by cleavage of *(21b)* [13a], or from *(21c)* by mercaptal cleavage [13b]. It exists in an equilibrium *(21d)* ⇌ *(21e)*, in which the piperidinose form *(21d)* greatly predominates [13a,13b]. 2,5-Diacetamido-2,5-dideoxy-D-xylose, surprisingly, forms only the furanose form [13c].

The tendency to form a 6-membered "hemiacetal" ring with an acetylimino group in the ring is even smaller in the case of 5-acetamido-5-deoxyaldohexoses. The compounds studied, *(22)* and *(23)*, when present as free sugars, always assume the furanose form [14]. Methanolysis of 5-acetamido-5-deoxy-1,2-*O*-isopropylidene-D-glucofuranose leads only to the methylfuranoside *(24)* [15]. 5-Acetamido-5-deoxy-L-idose is the only hexose with which a piperidinose form has been shown to exist. This is a special case, since the piperidinose cyclizes to give the bicyclic structure *(67)* [15a]. 6-Acetamido-6-deoxyketoses such as the *arabino* compound *(25)* also avoid forming 6-membered rings containing nitrogen, in favor of the furanose form *(25)* [16].

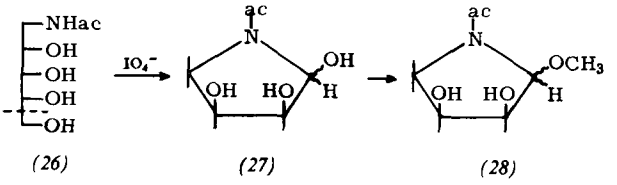



b) 4-(*N*-Acylamido)-4-deoxy Sugars

4-Acetamido-4-deoxyaldoses should be capable of forming a 5-membered "hemiacetal" ring, *i.e.* a sugar containing the pyrrolidine ring. Owing to the low reactivity of the acetamido group, a ring of this nature is to be expected mainly when no other ring can be formed, *i.e.* in 4-acetamido-4-deoxytetroses or 4-acetamido-4,5-dideoxypentoses.

Compounds of this class do, in fact, tend to form 5-membered rings. Thus, controlled cleavage of 1-acetamido-1-deoxy-D-ribitol *(26)* with periodate leads to an *erythro* compound *(27)* which, after treatment with methanol/HCl, was isolated as the methyl glycoside *(28)* of a pyrrolidine sugar [16]. As in the case of the 6-membered ring sugars, the fact that the acetamido group is built into the ring is shown by the infrared and NMR spectra and by the results obtained on cleavage with periodate [16].

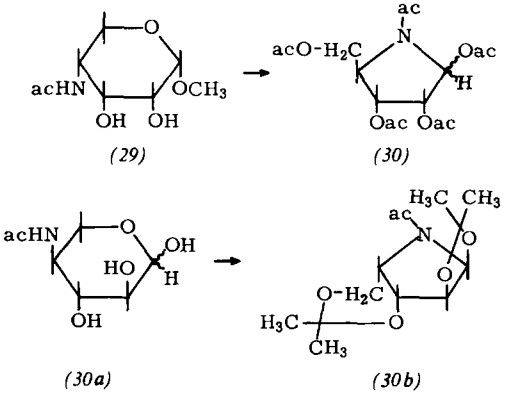
*(27)* can also be obtained by conversion of 5-acetamido-5-deoxy-D-arabinose mercaptal into the disulfone by oxidation with perpropionic acid, followed by degradation with ammonia [17]. Degradation of the sulfone of the corresponding *xylo* compound or the controlled cleavage of 6-acetamido-6-deoxy-D-galactopyranose with




*(26)* *(27)* *(28)*

periodate leads to the pyrrolidine sugar *(27)* with the *threo* configuration [18]. 4-Acetamido-4,5-dideoxy-L-xylose, too, forms only a pyrrolidine sugar, since the 6-membered cyclic form is not possible [13b, 18a].

A 4-acetamido-4-deoxypentose with a 5-membered ring containing nitrogen is most likely to occur in the *ribo* configuration, since ribose tends to form a furanose ring owing to its special configuration. Acetolysis of the ribopyranoside *(29)* does, in fact, lead surprisingly smoothly to ring contraction and formation of the peracetylated pyrrolidine sugar *(30)* [19]. It is not yet known whether free 4-acetamido-4-deoxy-D-ribose at equilibrium forms a 5-membered ring containing nitrogen. 4-Acetamido-4-deoxy-L-xylose occurs only in the pyranose form *(30a)*; it can be forced into the pyrrolidine form by conversion into the 1,2;3,5-diisopropylidene compound *(30b)* [19a].




A number of ketoses which possibly could give 5-membered "hemiacetal" rings containing nitrogen have been studied. The *xylo* compound *(31)* preferentially forms a 6-membered pyranose ring [20]. The ketoses *(32)* and *(33)*, in which ring formation would necessarily lead to a 5-membered ring containing nitrogen, exist in the open-chain keto form [21]. These examples show the low tendency for ring formation of the acetamido group in ketoses.

[13] *R. W. Jeanloz* and *H. G. Fletcher jr.*, Advances Carbohydrate Chem. *6*, 135 (1951).

[13a] *M. L. Wolfrom*, *J. L. Minor*, and *W. A. Szarek*, Carbohydrate Res. *1*, 156 (1965).

[13b] *S. Hanessian*, Carbohydrate Res. *1*, 178 (1965).

[13c] *H. Weidmann*, Liebigs Ann. Chem. *687*, 250 (1965).

[14] *H. Paulsen*, Liebigs Ann. Chem. *665*, 166 (1963).

[15] *R. L. Whistler* and *R. E. Gramera*, J. org. Chemistry *29*, 2609 (1964).

[15a] *H. Paulsen* and *K. Todt*, Chem. Ber., in press.

[16] *W. A. Szarek* and *J. K. N. Jones*, Canad. J. Chem. *42*, 20 (1964).

[17] *S. Hanessian* and *T. H. Haskell*, J. heterocyclic Chem. *1*, 57 (1964).

[18] *W. A. Szarek* and *J. K. N. Jones*, Canad. J. Chem. *43*, 2345 (1965).

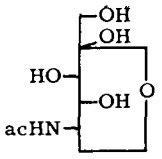
[18a] *A. E. El-Ashmawy* and *D. Horton*, Carbohydrate Res. *1*, 164 (1965).

[19] *E. J. Reist*, *D. E. Gueffroy*, and *L. Goodman*, J. Amer. chem. Soc. *87*, 677 (1965).

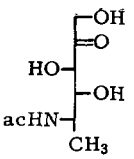
[19a] *A. J. Dick* and *J. K. N. Jones*, Canad. J. Chem. *43*, 977 (1965).

[20] *J. K. N. Jones*, *M. B. Perry*, and *J. C. Turner*, Canad. J. Chem. *39*, 965 (1961).

[21] *J. K. N. Jones*, *M. B. Perry*, and *J. C. Turner*, Canad. J. Chem. *39*, 2400 (1961); *40*, 503 (1962).



(31)



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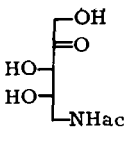


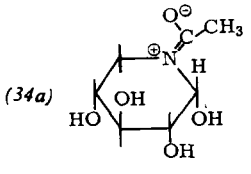
(33)

### c) Hindered Rotation in Sugars with Rings Containing an *N*-Acetylimino Group

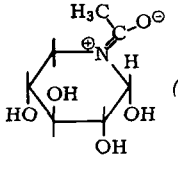
Carboxamides are generally stabilized by resonance $\rangle\overset{\oplus}{N}=\overset{|}{C}-O^{\ominus}$ in the planar form, so that rotation about the N–C bond is hindered. Thus unsymmetrically *N*-substituted carboxamides can exist in a *cis* and in a *trans* form. These forms have different NMR spectra and can, therefore, be generally detected in the presence of each other at room temperature by NMR spectroscopy [22]. At higher temperatures the rotation is generally no longer hindered. If the rotation (and hence the transition between the *cis* and *trans* forms) is sufficiently fast, an "average" NMR spectrum is obtained, the lines of which lie between those of the *cis* and the *trans* forms. Thus the spectrum of a carboxamide with restricted rotation will exhibit a characteristic temperature dependence [22].

Monosaccharides with an *N*-acetylimino group in the ring also exhibit hindered rotation. *N*-Acetyl-D-xylopiperidinose with a planar $\rangle\overset{\oplus}{N}=\overset{|}{C}-O^{\ominus}$ grouping can exist as the isomers *(34a)* and *(34b)* [23, 24].

The NMR spectrum of this compound at room temperature contains two doublets in the region of the anomeric protons.



(34a)



(34b)

The relationships are clearest in the NMR spectrum of the tetra-*O*-methyl compound of *(34a)* + *(34b)* (Fig. 2) [25]. The two widely separated signals due to the anomeric proton $H^1$ of the *trans* and *cis* forms ($\tau \approx 4.2$ and $\tau \approx 5.1$) can be seen at very low field. At 110 °C (upper curve), the lines converge because of rapid rotation of the amide group.

The signal due to the protons on C-5 also shows splitting. The left-hand quartet for the equatorial proton $H^5_e$ occurs at $\tau \approx 5.5$, while the corresponding right-hand quartet is masked by the multiplet between $\tau \approx 6$ and $\tau \approx 7$. At higher temperatures these quartets coalesce to give a single diffuse quartet ($H^5_e$ above). In the case of the axial proton $H^5_a$, only the right-hand quartet is visible ($\tau \approx 7.7$); this, too, migrates into the multiplet at higher temperatures. The signals due to the $OCH_3$ groups ($\tau \approx 6.6$ to 6.8) are also split at room temperature and coalesce at higher temperatures, as can be seen by comparison of the upper and lower spectra. Similar

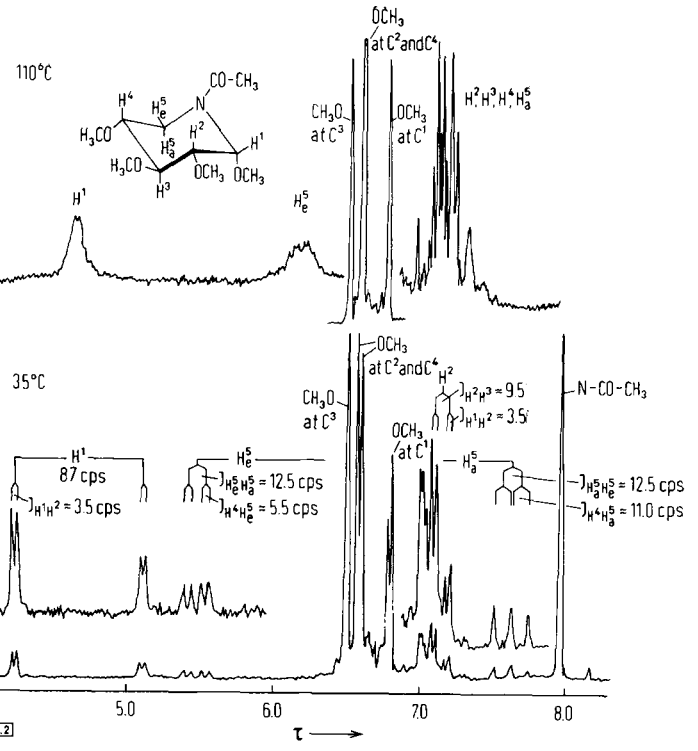



Fig. 2. NMR spectra of methyl 2,3,4-tri-*O*-methyl-*N*-acetyl-α-D-piperidinoside (100 Mc/s; in tetrachloroethylene, tetramethylsilane (TMS) as internal standard).

relationships are found with other *N*-acetylpiperidinoses and *N*-acetylpyrrolidine sugars [16, 18].

### d) Conformation of *N*-Acylpiperidinoses and their Configuration at C-1

The NMR spectrum of *N*-acetyl-D-xylopiperidinose shows slight splitting for the anomeric proton, giving a coupling constant $J_{H^1H^2} \approx 3.5$ cps. This small constant corresponds to an equatorial-axial coupling, and it was, therefore, concluded that the compound exists in the α-form, though this is contrary to the evidence of the negative optical rotation. No mutarotation is observed, so that only one anomeric form is present.

The configuration at C-1 can be found from the coupling constant $J_{H^1H^2}$ only if the conformation of the piperidinose ring is known. A complete conformational analysis was, therefore, carried out with the aid of NMR spectroscopy [25].

1,2,3,4-Tetra-*O*-acetyl-*N*-carbobenzoxy-D-xylopiperidinose *(35)* was found to be a suitable object for this study. This compound does not exhibit hindered rotation, so that there is no duplication of signals and the spectrum is consequently simplified. Accordingly, Fig. 3 contains only one line for the anomeric proton $H^1$. Fig. 3 shows a complete first-order analysis of the spectrum. The couplings were assigned by the double resonance technique. The oblique lines indicate that the irradiation frequencies used are the resonance frequencies of the protons $H^1$, $H^2$, and $H^4$. The upper series gives the corresponding signals which experience spin decoupling [25]. The results of this analysis are summarized in Fig. 4, which gives the positions of all the protons and their mutual coupling constants, together with the dihedral angle calculated from a modified Karplus relationship [25a]. The table

[22] *H. S. Gutowsky* and *C. H. Holm*, J. chem. Physics *25*, 1228 (1956).

[23] *H. Paulsen*, International Carbohydrate Symposium, Münster (Germany) 1964.

[24] *W. A. Szarek*, *S. Wolfe*, and *J. K. N. Jones*, Tetrahedron Letters *1964*, 2743.

[25] *H. Paulsen* and *F. Leupold*, Carbohydrate Res., in press.

[25a] *R. J. Abraham*, *H. Gottschalck*, *H. Paulsen*, and *W. A. Thomas*, J. chem. Soc. (London) *1965*, 6268.

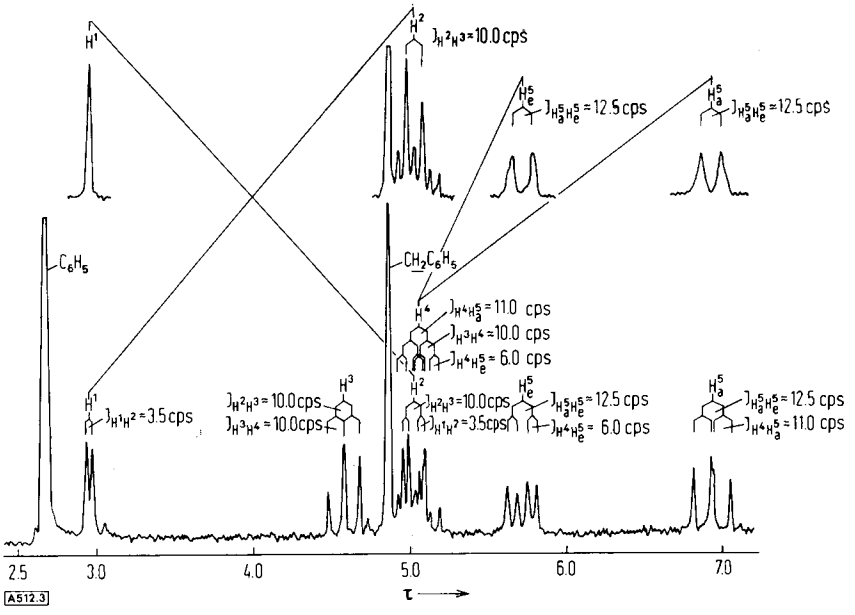
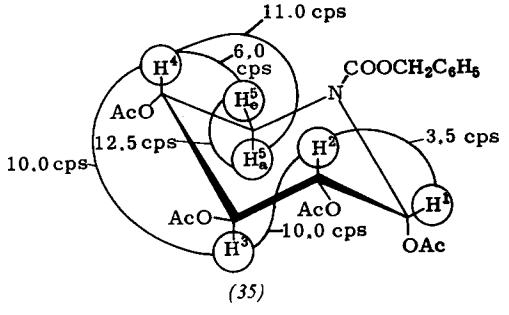



Fig. 3. NMR spectrum of 1,2,3,4-tetra-*O*-acetyl-*N*-carbobenzoxy-α-D-xylopiperidinose *(35)*. (100 Mc/s; in $DCCl_3$, TMS as internal standard). Upper curves: Spin decoupling of the $H^1$, $H^2$, $H^5_e$, and $H^5_a$ signals with the resonance frequencies of $H^2$, $H^1$, and $H^4$.




*(35)*

| | $H^1H^2$ | $H^2H^3$ | $H^3H^4$ | $H^4H^5_e$ | $H^4H^5_a$ | $H^5_aH^5_e$ |
|---|---|---|---|---|---|---|
| J, cps (approx.) | 3.5 | 10.0 | 10.0 | 6.0 | 11.0 | 12.5 |
| Dihedral angle Φ, deg. (approx.) | 56 | 163 | 163 | 42 | 180 | — |

Fig. 4. Coupling constants J and the corresponding conformation of 1,2,3,4-tetra-*O*-acetyl-*N*-carbobenzoxy-α-D-xylopiperidinose *(35)* according to *Karplus* [*] ($J = 11 \cos^2 \Phi$) [25a].

shows definitely that the piperidinose must exist in the chair form. This is shown by the large diaxial couplings between $H^2$, $H^3$, $H^4$, and $H^5_a$. The small coupling constant $J_{H^1H^2}$, therefore, indicates the presence of the α form.

Comparison with the NMR spectra of other *N*-acylpiperidinoses and of the *N*-acylpiperidinosides shows that all known compounds of the *xylo* series exist only in the α form. The unfavorable steric situation in the β-anomer (the equatorial substituent in eclipsed position with respect to the amide group) is proposed as the cause of the pronounced anomeric effect.

[*] It should be emphasized that the Karplus equation gives only approximate values of the dihedral angle; critical appraisal shows, however, that these are suitable for comparison with the theoretically expected values for an ideal chair form. The vicinal coupling constants are influenced, apart from the dihedral angle, by factors such as electronegativities, bond distances, and bond angles, although to a lesser degree. These factors are not considered in the simple Karplus equation; they are not yet amenable to quantitative treatment.

For a discussion see *M. Karplus*, J. Amer. chem. Soc. *85*, 2870 (1963); *R. U. Lemieux* and *J. D. Stevens*, Canad. J. Chem. *44*, 249 (1966); *B. Coxon*, Tetrahedron *21*, 3481 (1965).

In an attempt to explain the anomalous optical rotation of the *N*-acylpiperidinoses, optical rotatory dispersion curves were recorded (Fig. 5) [25]. In normal monosaccharides of the D-series, in accordance with Hudson's rules, α-glycosides always give positive plain curves, β-glycosides always negative plain curves, as shown in Fig. 5b for the D-xylosides. The *N*-acyl-α-D-xylopiperidinoses and their α-glycosides, on the other hand, give negative plain curves, contrary to the predictions of Hudson's rule (Fig. 5).

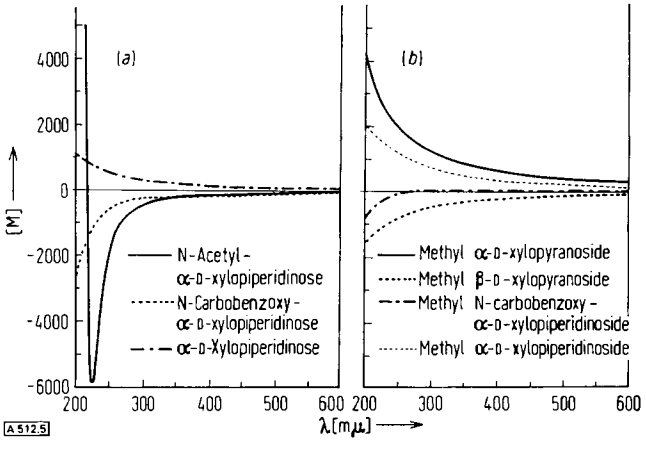



Fig. 5. Rotatory dispersion curves of some piperidinoses (a) and of some piperidinosides and pyranosides (b); [M] = molecular rotation.

## 2. Sugars Containing an Unsubstituted Imino Group in the "Hemiacetal" Ring

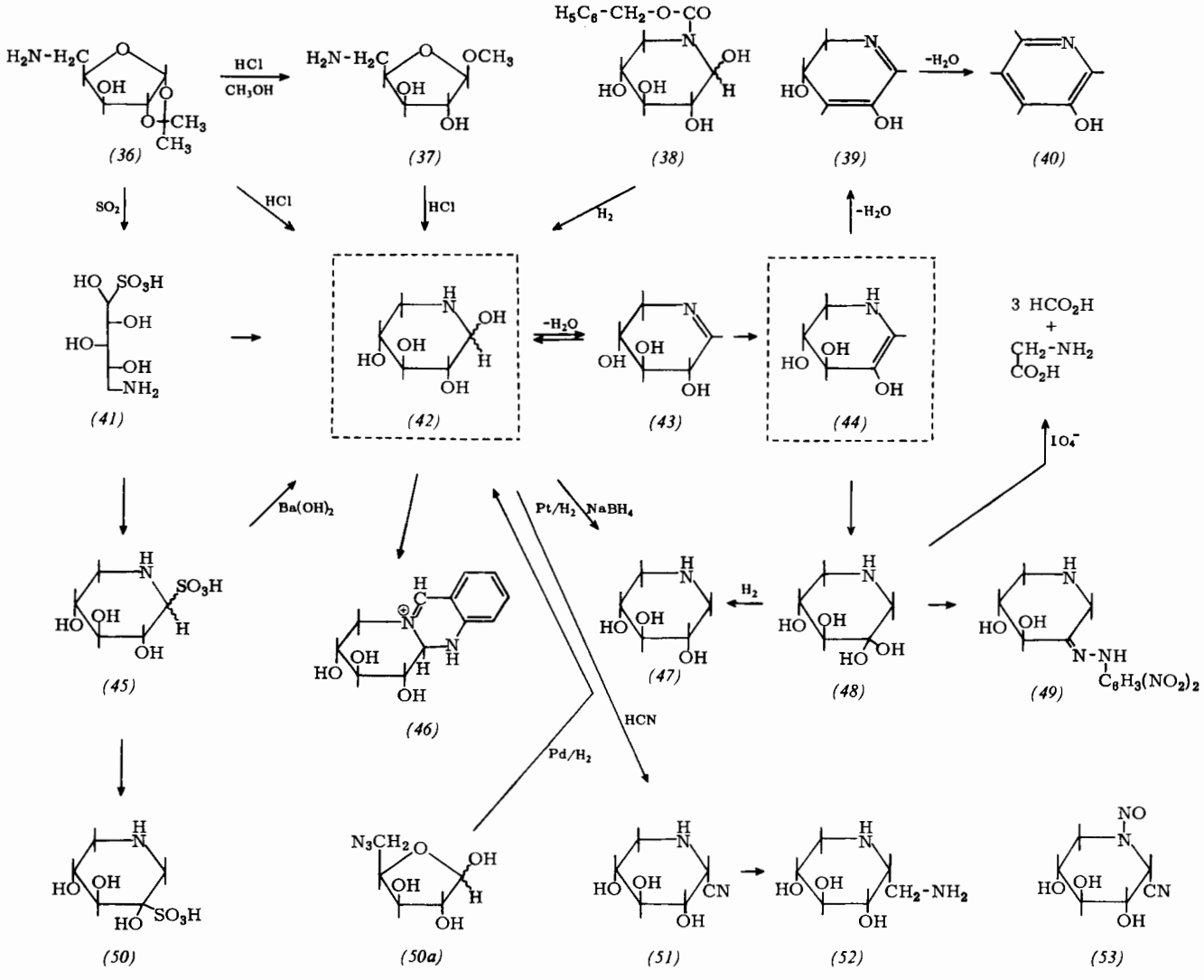
### a) 5-Amino-5-deoxypentoses

5-Amino-5-deoxy sugars with free amino groups are a more interesting class of compounds, since the reactivity of the free amino group in hemiacetal formation is sufficiently high to enable this group to compete successfully with the hydroxyl group. The resulting piperidinoses can enter into a series of fast secondary

reactions. The compound we have studied most is 5-amino-5-deoxy-D-xylose [26, 27], which will be used as a prototype for the detailed discussion.

The 1,2-*O*-isopropylidene *(36)* or cyclohexylidene derivative of 5-amino-5-deoxy-D-xylose was used as the starting material. Reaction of *(36)* with methanol/HCl in the absence of water leads to the methyl-β-furanoside *(37)*. Thus the furanose liberated on methanolysis reacts to form the furanoside before rearrangement of the 5-membered ring to the 6-membered ring can occur. Neither a methylpiperidinoside nor 3-hydroxypyridine (expected as a by-product) have been detected [27].

The compound *(48)* is a product of Amadori rearrangement of the assumed piperidinose intermediate *(42)*. The structure *(48)* is supported by NMR and mass spectroscopy [27]. In particular, the mass spectrum shows the expected fragments CO and $\cdot CH_2-\overset{\oplus}{N}H=CH_2$. Compound *(48)* gives all the color reactions of a strongly reducing Amadori compound; cleavage with periodate leads to glycine, and catalytic hydrogenation gives the optically inactive xylitol derivative *(47)*, the *N*-acetyl derivative of which again gives the expected fragments on reaction with periodate. Rather surprisingly, the Amadori compound *(48)* can only be




An entirely different course is followed by the hydrolysis of *(36)* with aqueous HCl. The products obtained are 3-hydroxypyridine *(40)* and 1,5-dideoxy-1,5-imino-D-threopentulose *(48)* in the form of the crystalline hydrochloride. The ratio of the two products depends on the reaction conditions, *(40)* being the main product of hydrolysis at 70 °C, while *(48)* is the main product at room temperature. The same products *(40)* and *(48)* are also obtained by acid cleavage of the furanoside *(37)*.

obtained as the hydrate. The water of hydration cannot be removed without decomposition of the compound; the carbonyl group can be detected by preparation of a dinitrophenylhydrazone *(49)*. The conversion of the piperidinose *(42)* into *(48)* is the first example of a cyclic Amadori rearrangement [27].

The formation of the Amadori compound *(48)* and of 3-hydroxypyridine *(40)* on hydrolysis of *(36)* demands some consideration. It appears that the 5-amino-5-deoxy-D-xylose liberated from *(36)* can readily assume a piperidinose form *(42)*, which spontaneously loses one mole of $H_2O$ in acidic solution to form the piperideine

[26] *H. Paulsen*, Tetrahedron Letters *1964*, 451.
[27] *H. Paulsen*, Liebigs Ann. Chem. *683*, 187 (1965).

*(43)*. A similar carbinolamine dehydration occurs in the case of the parent compound, α-hydroxypiperidine, and with many alkaloids [28].

The piperideine *(43)* is a cyclic Schiff's base of an α-ketol, and as such enolizes to give the enaminol *(44)* [29]; this latter compound is the central intermediate which can react further by one of two routes. Protonation of *(44)* on C-1 leads to completion of the Amadori rearrangement and formation of *(48)*; this rearrangement is irreversible, since *(48)* cannot be converted into 3-hydroxypyridine *(40)* by treatment with alkalis and subsequent acidification. The second route by which *(44)* can react leads to proton-catalysed elimination of $OH^{\ominus}$ from C-3 to form the dehydration product *(39)*, which then undergoes aromatization, with loss of a further mole of $H_2O$, to form 3-hydroxypyridine *(40)*. The formation of the aromatic pyridine system undoubtedly is an essential driving force for the second reaction route [27].

If cold sulfurous acid is used instead of hydrochloric acid for the hydrolysis of 5-amino-5-deoxy-1,2-*O*-isopropylidene-D-xylose *(36)*, the 5-amino-5-deoxy-D-xylose liberated is intercepted as the bisulfite adduct before the secondary reaction can occur; the product obtained is the open-chain sulfonic acid *(41)* [30]. When heated in water, *(41)* cyclizes to form D-xylopiperidinosyl-1-sulfonic acid *(45)*, which is a bisulfite adduct of the piperidinose *(42)* [11, 30a, 30a]

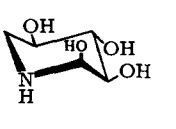
On prolonged heating, *(45)* is smoothly converted into the sulfonic acid *(50)*, which is a bisulfite adduct of the Amadori compound *(48)*. It is thought that *(45)* first loses $SO_2$, and that the resulting piperidinose *(42)* immediately rearranges *via (43)* and *(44)* to give *(48)*, which then adds sulfurous acid to form *(50)*. *(50)* can also be obtained by the reaction of the pure Amadori rearrangement product *(48)* with $SO_2$.

Cleavage of the sulfonic acids *(41)* or *(45)* with $Ba(OH)_2$ in alkaline solution gives D-xylopiperidinose *(42)*, the parent compound of this class [30a]. The piperidinose *(42)* is relatively stable in alkaline solution, but is extremely sensitive to acids, by which it is rearranged to *(48)* and *(40)*. Thus the behavior of piperidinoses is opposite to that of all other monosaccharides. Proof that *(42)* exists only in the form of a 6-membered ring containing nitrogen is found in the fact that *N*-acetylation of *(42)* leads to *(14)*, while hydrogenation leads to *(47)* [30a].

The piperideine *(43)* could also be detected as a further intermediate. This compound contains a C=N chromophore in an asymmetric environment. Its weak absorption due to the n → π* transition should, therefore, give a Cotton effect. Piperidinose solutions, in fact, give a negative Cotton effect at 300 mμ, which can be readily detected by measurement of the circular dichroism, and which must be assigned to the piperideine *(43)*, since *(42)* and *(48)* do not give a Cotton effect [30a].

Measurement of the circular dichroism is an excellent and extremely sensitive method for the study of the reactions of the piperidinose *(42)* [30a]. Freshly prepared solutions of *(42)* (pH 7.8) do not contain *(43)* or *(48)*; a Cotton effect is observed after a few hours and reaches a maximum after two days. An equilibrium piperidinose *(42)* ⇌ piperideine *(43)* is then established. This equilibrium is pH-dependent, the content of *(43)* being about 3 to 5 % at pH 7.8. On acidification with $CO_2$ to pH 6.8, the Cotton effect is immediately reduced, since the acid-catalysed Amadori rearrangement *(43)* → *(48)* is accelerated. However, the product *(48)* is a secondary amine and is, therefore, a stronger base than *(42)* and *(43)*, so that as *(48)* accumulates in the system, the pH rises once more. This retards the Amadori rearrangement *(43)* → *(48)* to such an extent that the equilibrium *(42)* ⇌ *(43)* with its high Cotton effect can be re-established. This reaction sequence can be repeated until all the *(42)* has been converted into *(48)*. When the solution of *(42)* is acidified to pH 5.8 with acetic acid, the Amadori rearrangement proceeds so rapidly that *(43)* cannot accumulate, and hence no Cotton effect occurs.

The sign of the Cotton effect is interesting. According to the theory [30c], C-3 and substituents on C-2 and C-5 in piperideines in the half-chair conformation *(53b)* do not contribute to the Cotton effect, the sign of which is determined by C-4; thus the Cotton effect should be positive if, C-4 lies above the plane of the ring, and negative if C-4 lies below the ring. The most favorable conformation for the piperideine formed from *(53a)* is undoubtedly *(53b)*; this should theoretically give a negative Cotton effect, as was actually found [30a].

*(53a)*  *(53b)*

A piperidinose with a free imino group, such as *(42)*, can generally also be prepared by hydrogenation of a 5-azido-5-deoxy sugar, *e.g. (50a)* [30d], or by hydrogenation of the *N*-carbobenzoxypiperidinose *(38)* [30a]. *(42)* cannot be isolated in pure form, since the product always contains *(43)* and *(48)*; it is, however stable enough in solution for derivatives to be isolated. Thus *(42)*, which is a 2-hydroxypiperidine, has the structure of a reactive Mannich base [5] and, therefore, can enter into condensations, provided that these are carried out in alkaline solution (rearrangement to *(48)* occurs in acidic solution). *(42)* reacts with *o*-aminobenzaldehyde and picric acid to form a red, crystalline 1,2-dihydroquinazolinium picrate *(46)*. *(42)* reacts particularly readily with HCN to form 2,6-dideoxy-2,6-imino-D-idononitrile *(51)*, which is an in-

[28] *C. Schöpf, A. Komzak, F. Braun,* and *E. Jacobi,* Liebigs Ann. Chem. *559*, 1 (1948).

[29] *K. Heyns* and *W. Stumme,* Chem.Ber.*89*, 2833, 2844 (1956).

[30] *D. L. Ingles,* Chem. and Ind. *1964*, 451.

[30a] *H. Paulsen, F. Leupold,* and *K. Todt,* Liebigs Ann. Chem. *692*, 200 (1966)

[30b] *D. L. Ingles,* Tetrahedron Letters *1965*, 1317.

[30c] *H. Ripperger, K. Schreiber,* and *G. Snatzke,* Tetrahedron *21*, 1027 (1965).

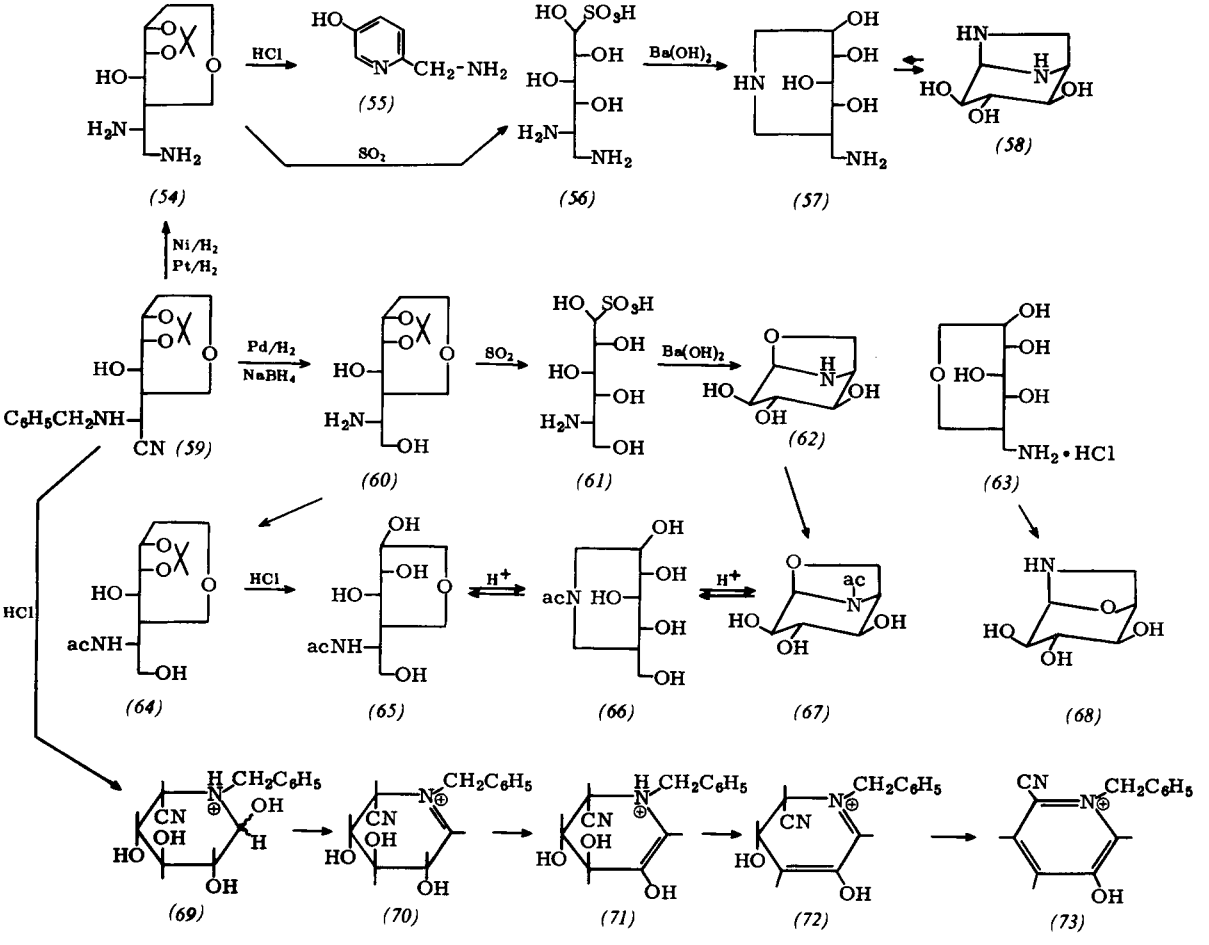
[30d] *S. Hanessian,* Chem. and Ind. *1965*, 1296.

teresting starting material for further syntheses; for example, hydrogenation of *(51)* yields the amine *(52)*, and nitrosation leads to the nitroso compound *(53)* [31]. The methyl glycoside of *(42)* is very readily cleaved even by water. In methanol, it exists in equilibrium with the piperideine *(43)* formed by elimination of methanol [25].

### b) 5-Amino-5-deoxyhexoses

Hydrolysis of 5-amino-5-deoxyhexoses with aqueous hydrochloric acid also leads to elimination of three molecules of water to form hydroxypyridine derivatives. Thus the idose derivative *(54)*, which can be pyridinium salt *(73)* *via* the piperidinose *(69)* and *(70)* to *(72)*. Thus the pyridine formation is not blocked by *N*-alkylation of the 5-amino group. The reaction sequence *(69)* → *(73)* shows that protonation of the piperidinose *(69)* is essential, since the initial elimination of water to form the piperideine *(70)* otherwise cannot take place [34].

Hydrolysis of *(54)* with sulfurous acid leads to the sulfonic acid *(56)*. Alkaline cleavage of *(56)* leads immediately to the piperidinose *(57)*, which spontaneously loses water with quantitative conversion into *(58)* [15a, 34a]. The 1,6-anhydro compound *(58)* is an idosan derivative in which two oxygen atoms have been replaced by nitrogen; it can be obtained in crystalline




obtained by hydrogenation of the idurononitrile *(59)*, gives 2-aminomethyl-5-hydroxypyridine *(55)* [32]. Cleavage with methanol/hydrochloric acid generally leads to the methyl furanosides [33].

The dehydration in acidic solution proceeds particularly readily in the case of 5-*N*-alkylamino-5-deoxy sugars [34]. Thus on hydrolysis with HCl, the idurononitrile *(59)* is converted almost quantitatively into the *N*-benzyl-form and is the first known stable monosaccharide containing a free amino group in the ring.

Hydrogenation of *(59)* leads to the 5-amino-5-deoxyidose derivative *(60)*, which gives *(61)* on cleavage with $SO_2$. Alkaline hydrolysis of *(61)* again leads to cyclization of the intermediate piperidinose to give *(62)* [15a, 34a].

An interesting reaction in this connection is the selective hydrolysis of the 5-acetamido-5-deoxyidose derivative *(64)* with aqueous HCl. The crystalline bicyclic compound *(67)*, which can also be prepared from *(62)*, is obtained in 23 % yield from the reaction mixture [15a]. In this case there is, evidently, an equilibrium between

[31] *H. Paulsen* and *K. Todt*, unpublished work.

[32] *H. Paulsen*, Angew. Chem. *74*, 585 (1962), Angew. Chem. internat. Edit. *1*, 454 (1962).

[33] *R. E. Gramera*, *R. M. Bruce*, *S. Hirase*, and *R. L. Whistler*, J. org. Chemistry *28*, 1401 (1963).

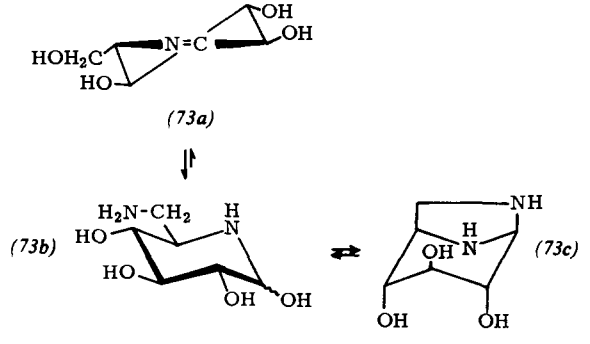
[34] *H. Paulsen*, *K. Todt*, and *K. Heyns*, Liebigs Ann. Chem. *679*, 168 (1964).

[34a] *H. Paulsen* and *K. Todt*, Angew. Chem. *77*, 589 (1965), Angew. Chem. internat. Edit. *4*, 592 (1965).

the furanose *(65)* and piperidinose *(66)* and the bicyclic form *(67)*. This is the only 5-acetamido-5-deoxyhexose in which a piperidinose form has been detected. The piperidinose formation is favored in this case by the secondary reaction to form the bicyclic compound *(67)*.

The third idosan derivative with nitrogen in the 5-membered ring, *i.e. (68)*, can be prepared from *(63)*. 6-Amino-6-deoxy-L-idose *(63)* has long been known as the hydrochloride [34b]; when this is converted into the free base, crystalline *(68)* is formed in quantitative yield [15a, 34a].

The tendency towards formation of the 1,6-anhydro compound is evidently greatly increased in the hexopiperidinoses. Thus *(62)* exists entirely in the anhydro form, while L-idose forms 75 % of the anhydro compound at equilibrium [35]. This becomes even clearer in the case of the glucopiperidinose *(73b)*, which can be obtained from the corresponding sulfonic acid. At equilibrium, this compound contains 20 to 40 % of the sterically highly unfavorable cyclic form *(73c)* [15a]. Glucose itself gives only 0.3 % of the 1,6-anhydro form on treatment with acid [35]. A small quantity of the piperideine *(73a)* is also present in equilibrium with *(73b)*, as is shown by the weak negative Cotton effect of the solution.



*(73a)* ⇌ *(73b)* ⇌ *(73c)*

The *N*-acetyl derivatives of *(58)*, *(62)*, and *(68)* all contain amido groupings with hindered rotation [15a]. The *N,N'*-diacetyl derivative of *(58)* is particularly interesting. It contains two amido groupings with hindered rotation in the same molecule, so that this compound can exist in four isomeric forms, the structures of which are shown in Fig. 6. In these formulae, which differ only in the conformation of the amido groups, the 6-membered ring is shown behind the 5-membered ring.

The NMR spectrum of the compound in Fig. 6 shows that all four isomeric forms are present at low temperatures, and that the two amido groups have quite different coalescence temperatures [15a]. Fig. 7 shows the NMR spectra at different temperatures. At 15 °C, three signals are found for the anomeric proton (top); the left-hand and right-hand signals are due to the *trans,trans* or *cis,cis*, and the strong middle signal to the *trans-cis* and *cis-trans* compounds. The splitting of all three signals is caused by slight spin coupling between $H^1$ and $H^2$. The *N*-acetyl signals (bottom) are more complicated.

At 35 °C the signals begin to coalesce. At 40 °C the amido group in the piperidinose ring exhibits free rotation, while rotation of the amido group in the 1,6-anhydro ring still

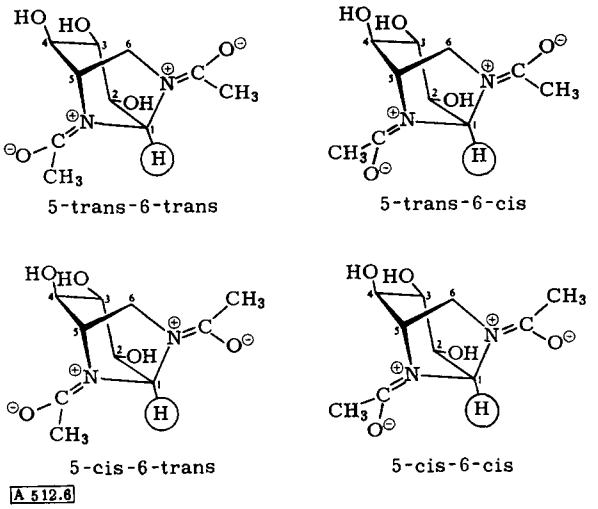
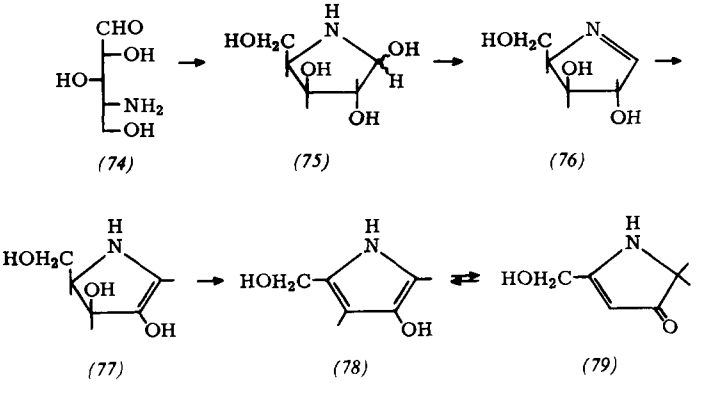



Fig. 6. Four isomeric forms of 1,6-acetylimino-*N*-acetyl-6-deoxy-L-idopiperidinose.

remains hindered. This is particularly obvious at 50 °C, when only two anomeric proton signals are obtained, corresponding to the remaining *cis* and *trans* forms. The corresponding *N*-acetyl signal (bottom) still shows the wide splitting corresponding to a 5-membered ring amide; the middle line is the signal of the amide in the 6-membered ring. At 65 °C the signals are closer together; at 96 °C the amide in the 5-membered ring also exhibits free rotation, and the anomeric proton and the *N*-acetyl groups now give only one signal each [15a].

### c) 4-Amino-4-deoxy Sugars

4-Amino-4-deoxy sugars with free amino groups, *e.g.(74)*, should be able to form 5-membered "hemiacetal" rings, in which the nitrogen is built into the ring to give sugars of the pyrrolidine type *(75)*. Since the tendency towards acetal formation is stronger for the amino group than for the hydroxyl group, the 5-membered pyrrolidine ring *(75)* should be favored; the 6-membered pyranose ring, on the other hand, is favored on steric grounds. Nevertheless, the amino group should compete successfully with the hydroxyl group.



*(74)* *(75)* *(76)*



*(77)* *(78)* *(79)*

The "pyrrolidine sugar" *(75)* is a carbinol base, and as such it should lose water in acidic solution to form the pyrroline *(76)*. This reaction is well known from model compounds, *e.g.* derivatives of γ-aminobutyraldehyde or of the 2-hydroxypyrrolidine present at equilibrium [36]. If a secondary reaction similar to that occuring in the conversion of piperidinoses into pyridine derivatives is

[34b] *H. O. L. Fischer*, J. Amer. chem. Soc. *70*, 1476 (1948).

[35] *N. K. Richtmyer*, Arch. Biochem. Biophysics *78*, 376 (1958).

[36] *F. Galinovsky, A. Wagner*, and *R. Weiser*, Mh. Chem. *82*, 551 (1951).

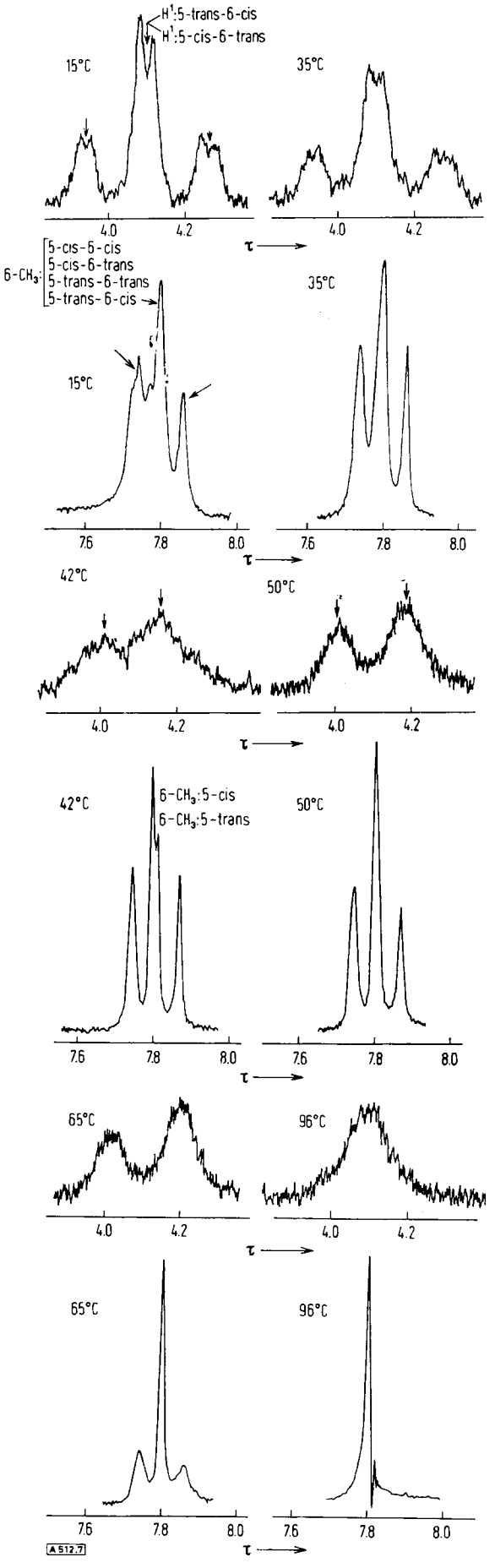
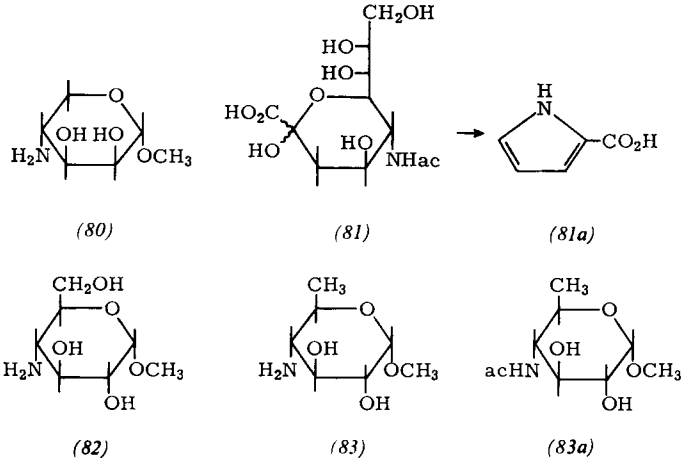



Fig. 7. Sections of the NMR spectrum of 1,6-acetylimino-*N*-acetyl-6-deoxy-L-idopiperidinose at various temperatures (cf. Fig. 6).
Top row: Anomeric proton signals.
Bottom row: Signals due to the *N*-acetyl $CH_3$ groups.

assumed to take place, the pyrroline *(76)*, which is a cyclic Schiff's base of a ketol, should rearrange into the enaminol *(77)*; this in turn loses water, with formation of derivatives of 3-hydroxypyrrole *(78)* and of 4-oxo-$\Delta^2$-pyrroline *(79)* [37]. No derivatives of 3-hydroxypyrrole have so far been detected on hydrolysis of 4-amino-4-deoxy sugars, but certain observations suggest that the reaction sequence described is feasible. The derivatives of 3-hydroxypyrrole are unstable [38], and readily polymerize in a complex manner to give dark products [39]. When an attempt is made to obtain the free 4-amino-4-deoxy sugar by acid hydrolysis of methyl 4-amino-4-deoxy-α-D-lyxopyranoside *(80)*, the solution begins to darken within a few minutes, and black polymeric material separates out [40].




The long known *N*-acetylneuraminic acid *(81)* may be regarded as a 4-amino-4-deoxy-sugar, since the amino group is in position 4 with respect to the keto group. Under the action of mineral acids, *N*-acetylneuraminic acid *(81)* readily forms insoluble dark polymers of unknown structure [41]. Intensive alkali degradation of *(81)* gave pyrrol-2-carboxylic acid *(81a)* as a fragment [42].

Considerable difficulties were also encountered in attempts to obtain free 4-amino-4-deoxyhexoses by hydrolysis. The 4-amino-*gluco* compound *(82)* cannot be hydrolysed without decomposition [43]. Despite all efforts, attempts to liberate 4-amino-4-deoxy-D-glucose from other derivatives have so far been unsuccessful [44]. The 4-amino-4-deoxy sugar cannot be obtained by direct hydrolysis of the 6-deoxy-*gluco* compound *(83)* or of the corresponding *galacto* compound, since decomposition occurs instead [45]. However, hydrolysis of

[37] *R. S. Atkinson* and *E. Bullock*, Canad.J.Chem. *41*, 625 (1963).
[38] *A. Treibs* and *A. Ohrodnik*, LiebigsAnn.Chem. *611*, 149 (1958).
[39] *R. Kuhn* and *G. Osswald*, Chem. Ber. *89*, 1423 (1956).
[40] *W. G. Overend*, *A. C. White*, and *N. R. Williams*, Chem. and Ind. *1963*, 1840.
[41] *F. Zilliken* and *M. W. Whitehouse*, Advances Carbohydrate Chem. *13*, 237 (1958).
[42] *A. Gottschalk*, Nature (London) *170*, 662 (1952).
[43] *E. J. Reist*, *R. R. Spencer*, *B. R. Baker*, and *L. Goodman*, Chem. and Ind. *1962*, 1794.
[44] *E. J. Reist*, *R. R. Spencer*, *D. F. Calkins*, *B. R. Baker*, and *L. Goodman*, J. org. Chemistry *30*, 2312 (1965).
[45] *C. L. Stevens*, *P. Blumbergs*, *F. A. Daniher*, *R. W. Wheat*, *A. Kujomoto*, and *E. L. Rollins*, J. Amer. chem. Soc. *85*, 3061 (1963); *C. L. Stevens*, *P. Blumbergs*, *D. H. Otterbach*, *L. J. Strominger*, *M. Matsuhashi*, and *D. N. Dietzler*, *ibid. 86*, 2937 (1964).

methyl 4-acetamido-4-deoxyglucoside *(83a)* leads to the 4-amino-4-deoxy-*gluco*-pyranose hydrochloride, without formation of a "pyrrolidine sugar" [45].

### d) 6-Amino-6-deoxyketohexoses

In 6-amino-6-deoxyhexuloses, there is again competition between the 6-membered N-ring, and the 5-membered O-ring. On hydrolysis of the sorbose derivative *(87)* with strong aqueous hydrochloric acid, it is possible to isolate a crystalline furanose hydrochloride *(84)*, which is stable only in strongly acidic solutions. A solution of *(84)* in water (pH $\approx$ 6) leads quantitatively, in four days at room temperature, to 3-hydroxy-2-hydroxymethylpyridine *(89a)* [46].

In neutral solution, the salt *(84)* evidently is hydrolysed to such an extent that some of the base can change into the piperidinose *(85)*. Under the conditions of the reaction, *(85)* immediately loses one molecule of water to give *(88)*, which loses a further two molecules of water and is converted *via (88a)* and *(89b)* into the pyridine *(89a)*. On heating, this reaction is completed within a few minutes [46].

In alkaline solution, the furanose hydrochloride *(84)* is immediately converted into the free piperidinose *(85)*, which is so stable that it can be hydrogenated to the piperidine derivative *(86)* [46]. Thus 6-amino-6-deoxy-L-sorbose is a sugar that assumes the furanose form in acidic solution, and the piperidinose form in alkaline solution, while in neutral solution it spontaneously loses water with formation of *(89a)*.

only in alkaline solution. The most important secondary reactions in acidic solution are the cyclic Amadori rearrangement and the elimination of three molecules of water, under mild conditions, to form 3-hydroxypyridines. An interesting parallel to the latter reaction has been found in the fragmentations occurring in the mass spectrometer on ionization in the gas phase. Trihydroxypiperidine derivatives undergo a succession of cleavages which again lead to 3-hydroxypyridinium ions with mass number (MN) 96 as a principal fragment [27].

As an example, consider the mass spectrum of 1,5-(*N*-acetylimino)-2,3,4-tri-*O*-acetyl-1,5-dideoxyxylitol. This compound was obtained by hydrogenation and acetylation of the piperidinose *(42)*. Its mass spectrum is shown in Fig. 8; Fig. 9 shows reaction schemes for the various fragmentation processes.

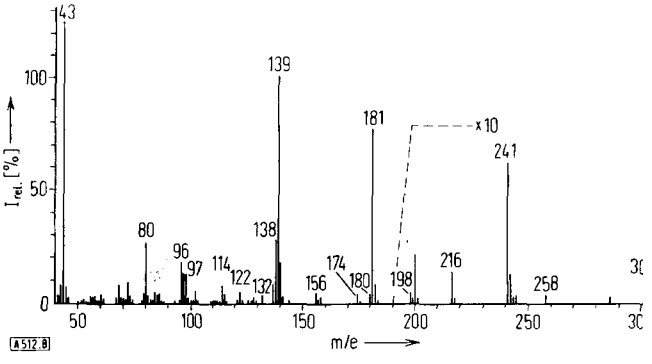
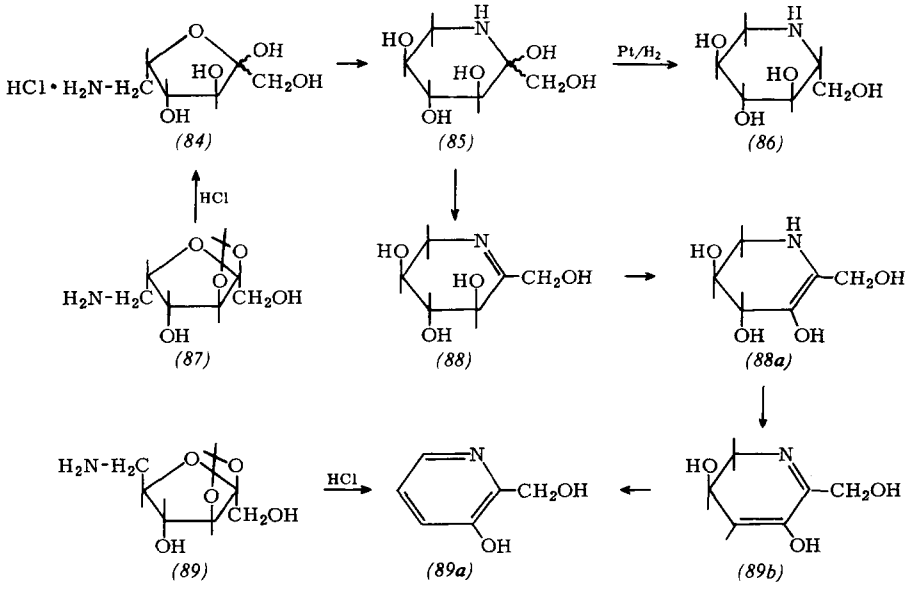



Fig. 8. Mass spectrum of 1,5-(*N*-acetylimino)-2,3,4-tri-*O*-acetyl-1,5-dideoxy-xylitol. (The relative intensity $I_{rel}$ of the ion with mass 139 was taken as 100 %).




The fructose derivative *(89)* also forms *(89a)* on acid hydrolysis [46,46a]. 1,6-Diamino-1,6-dideoxy-2,3-*O*-isopropylidene-a-L-sorbofuranose reacts with aqueous hydrochloric acid in a similar reaction sequence to yield 2-aminomethyl-3-hydroxypyridine [46].

### e) Mass Spectra of 5-Amino-5-deoxy Sugars

As was shown in the case of the 5-amino-5-deoxyxyloses, piperidinose forms are readily formed, and are stable

The compound gives a molecule ion of MN 301. The principal route involves elimination of acetic acid to form the allyl radical ion with MN 241; this also loses acetic acid to form the ion with MN 181, which splits off ketene to give the ion with MN 139. This fragment is converted by two routes into the 3-hydroxypyridinium ion with MN 96, and also forms a pyridinium ion of MN 80 [27].

A second, less important route leads *via* the ion with MN 258, which loses several molecules of ketene and of water to give the 3-hydroxypyridinium ion with MN 96, as shown in Fig. 9 [27]. The formation of pyridine derivatives from piperidinoses and hydroxypiperidines, both in acidic solution and in the gas phase, illustrates the preference for eliminations leading to this aromatic ring system.

[46] *H. Paulsen, I. Sangster,* and *K. Heyns,* unpublished work.
[46a] *S. Hanessian,* personal communication.

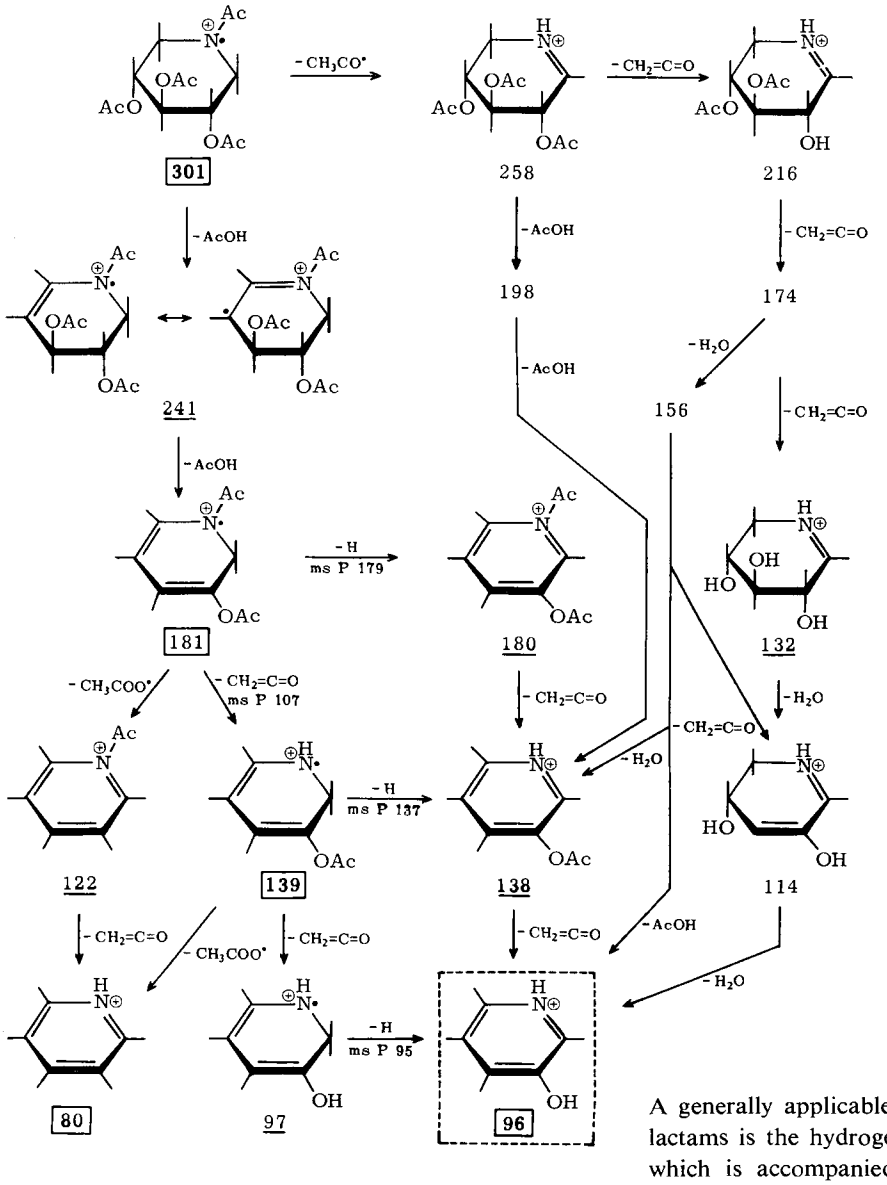


Fig. 9. Degradation routes for 1,5-(*N*-acetylimino)-2,3,4-tri-*O*-acetyl-1,5-dideoxyxylitol in mass-spectroscopic studies (ms P = metastable ion).

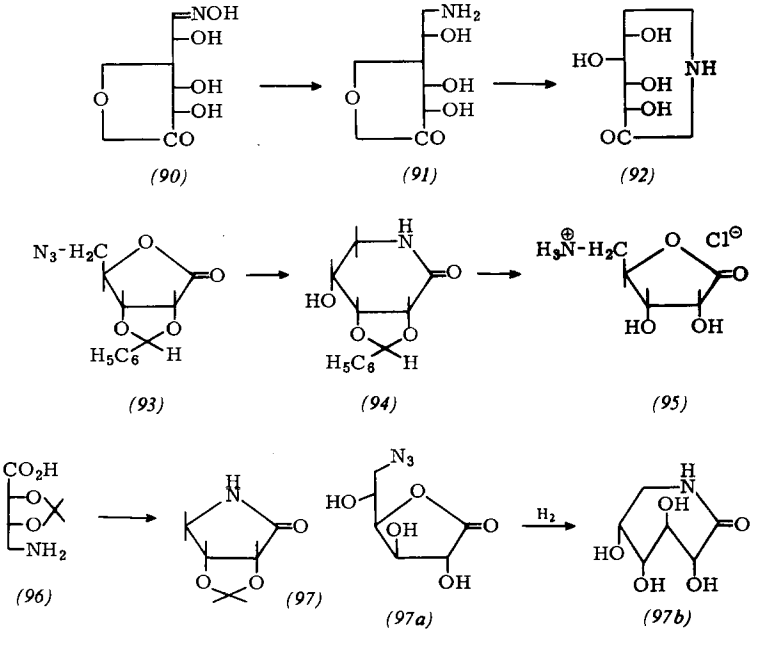
A detailed fragmentation scheme has also been published for methyl *N*-acetyl-2,3,4-tri-*O*-methyl-α-D-xylopiperidinoside [46b]. The so-called primary cleavage B in this case leads to the methoxypyridinium ion with MN 110. The precise fragmentation routes for the peracetylated bicyclic idosan derivatives *(58)*, *(62)*, and *(68)* have also been determined [46c].

## f) Sugars Containing a Lactam Ring

When carboxyl, hydroxyl, and amino groups are present simultaneously in sugar derivatives, competitive reactions can occur in the formation of cyclic ester and amide linkages. Since ester linkages can generally be cleaved by amines with formation of amides, the introduction of an amino group into an existing lactone will lead to rearrangement to the lactam, if this is sterically possible.

Thus hydrogenation of the lactone of D-glucuronic acid oxime *(90)* gives the amine *(91)*. This can be rearranged by treatment with alkali to give the gulonolactam *(92)*, a stable ε-lactam with a 7-membered ring [47].

A generally applicable method for the preparation of lactams is the hydrogenation of azido lactones *(93)*, which is accompanied by ring expansion. Thus the lactam *(97b)* is obtained from 6-azido-6-deoxygluconolactone *(97a)*. All the pentonolactams have been prepared in this way [46a]. Hydrogenation of the ribono-



[46b] *K. Heyns* and *D. Müller*, Tetrahedron *21*, 3151 (1965).

[46c] *K. Heyns* and *H. Scharmann*, Chem. Ber., in press.

[47] *H. Weidmann* and *E. Fauland*, Liebigs Ann. Chem. *679*, 192 (1964).

lactone azide *(93)*, for example, leads directly to a ribonolactam *(94)* [48]. However, acid hydrolysis of *(94)* leads to ring contraction, the product again being a ribonolactone *(95)* [48]. The 4-amino-4-deoxyerythronic acid *(96)* yields an erythronolactam *(97)* on sublimation at 150 °C [17].

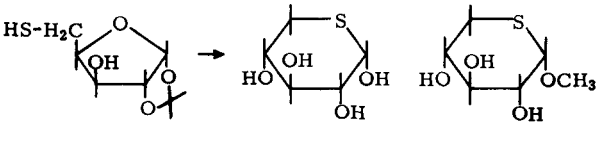
## III. Monosaccharides with "Hemiacetal" Rings Containing Sulfur

### a) 5-Thio Sugars

Mercaptans are much more reactive than alcohols in "acetal" formation. 5-Thio sugars therefore, should form only a 6-membered "hemiacetal" ring containing sulfur, since the furanose ring containing oxygen is also less favorable on steric grounds. Experimental results indicate, in fact, that free 5-thio sugars give only 6-membered S-rings and that no furanose form is detectable at equilibrium [49-51].

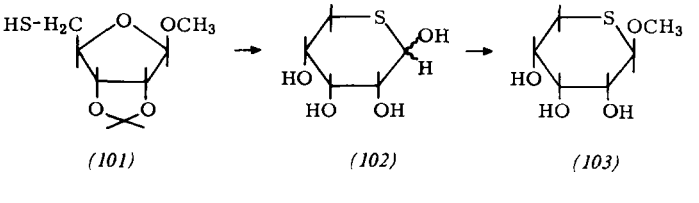
Thio sugars are usually prepared by nucleophilic displacement of *O*-tosyl groups with sodium benzyl mercaptide, sodium thioacetate, or sodium thiocyanate. Subsequent reductive cleavage or hydrolysis yields the desired sugar with a free SH group. Owing to the ease of oxidation to disulfides, strict exclusion of oxidizing agents is essential.

Acid hydrolysis of the 5-thioxylofuranose derivative *(98)* yields a free xylothiopyranose *(99)* as stable colorless crystals [49,50]. None of the reactions of free SH groups, such as oxidation with $I_2$ or dichloroindophenol, are given by *(99)*, making evident that the sulfur is stably bound in a mercaptal linkage in the 6-membered ring. The properties of the xylothiopyranose *(99)* are similar to those of normal xylose. The compound responds to the typical reduction tests for sugars, and exhibits a mutarotation of $[\alpha]_D = +202 \rightarrow [\alpha]_D = +178°$, which indicates the presence of the α form in the crystalline state [49,50]. Cleavage of *(98)* with methanol/HCl leads directly to methyl α-D-xylothiopyranoside *(100)* [51,52]. Thus in contrast to the behavior of compounds containing nitrogen, this methanolysis is accompanied by ring expansion to form the 6-membered S-ring.

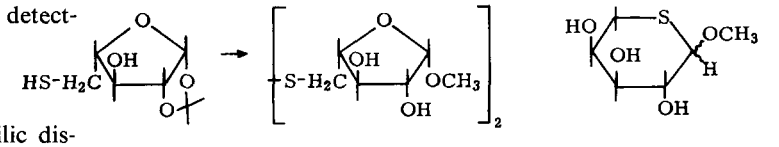


*(98)* *(99)* *(100)*

Acid hydrolysis of the *ribo* compound *(101)* leads to a syrupy ribothiopyranose *(102)*, which reacts only very slowly with $I_2$ and, therefore, must exist as the 6-membered ring [53]. Methanolysis of *(101)* proceeds with ring expansion and yields the stable methyl β-D-ribothiopyranoside *(103)* [52]. An interfering disulfide formation, which is noticeable even during the preparation of *(103)*, is particularly pronounced in the methanolysis of the *arabino* compound *(104)*, whereby, in addition to the methyl arabinothiopyranoside *(106)*, the principal product is the disulfide *(105)* [54].

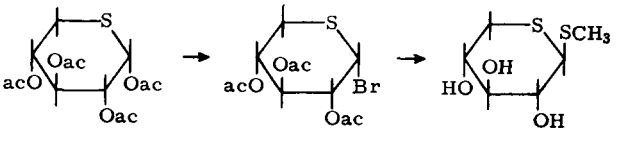


*(101)* *(102)* *(103)*



*(104)* *(105)* *(106)*

The properties and reactions of xylothiopyranose have been studied in detail by *Whistler*. It was found that the normal reactions of carbohydrate chemistry can be carried out, in the same manner, with sugars containing an S-ring. Thus the tetraacetate of the xylothiopyranose *(107)* reacts readily with HBr/glacial acetic acid to give the acetobromo compound *(108)* [55], from which methyl β-D-xylothiopyranoside [55], methyl-1-thio-β-D-xylothiopyranoside *(109)* [56], and *N*-glycosides [57] can be prepared by the Königs-Knorr synthesis.



*(107)* *(108)* *(109)*

Comparison of the NMR spectra of methyl-α-D-xylothiopyranosides and methyl-β-D-xylothiopyranosides with those of the corresponding α- and β-D-xylopyranosides shows that the sulfur compounds and the oxygen compounds scarcely differ in their conformations, and that all exist in the C 1 conformation. The same is true of free xylothiopyranose and xylopyranose [58].

The kinetics of hydrolysis of various xylothiopyranosides have been compared with those of the corresponding

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[49] *J. C. P. Schwarz* and *K. C. Yule*, Proc. chem. Soc. (London) *1961*, 417.

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[54] *R. L. Whistler* and *R. M. Rowell*, J. org. Chemistry *29*, 1259 (1964).

[55] *R. L. Whistler* and *T. van Es*, J. org. Chemistry *28*, 2303 (1963).

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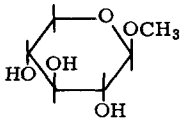
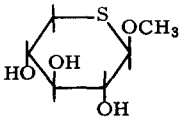
[57] *D. L. Ingles*, Chem. and Ind. *1963*, 1901.

[58] *V. S. R. Rao*, *J. F. Foster*, and *R. L. Whistler*, J. org. Chemistry *28*, 1730 (1963).

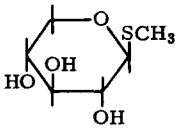
oxygen compounds[55,56]. It was found that glycosides containing S-rings generally are hydrolysed 10 to 20 times faster than their oxygen analogue[55].



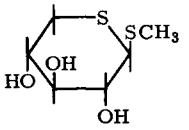
*(110)* $k = 1.8 \cdot 10^{-3}\ min^{-1}$



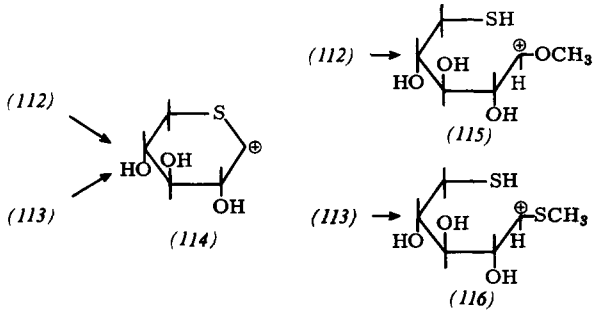
*(112)* $k = 26.1 \cdot 10^{-3}\ min^{-1}$



*(111)* $k = 0.9 \cdot 10^{-3}\ min^{-1}$



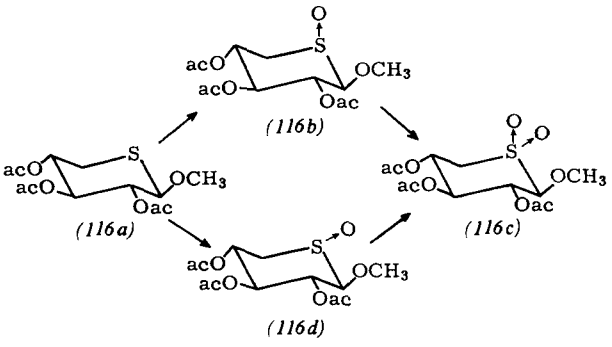
*(113)* $k = 18.3 \cdot 10^{-3}\ min^{-1}$



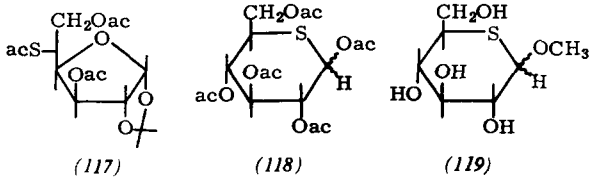
Of the compounds studied, *(110)* to *(113)*, two pairs with similar hydrolysis rates can be compared: *(110)* and *(111)* are hydrolysed slowly, while *(112)* and *(113)*, which contain S-rings, are hydrolysed 15 to 20 times faster[56]. It follows that the rate of hydrolysis is strongly affected by the heteroatom in the ring, but not by the glycosidic heteroatom. Thus the hydrolysis is assumed to proceed by a slow rate-determining initial step leading to a cyclic carbonium ion *(114)* since this is the only mechanism by which *(112)* and *(113)* would give the same transition state. If the mechanism were acyclic, *(112)* and *(113)* would give different transition states *(115)* and *(116)*, and this cannot easily be reconciled with the fact that the reaction rates are roughly the same[56].

Xylothiopyranose *(99)*, like normal sugars, reacts with aromatic amines to form *N*-glycosides, a large number of which have already been synthesized with various arylamines[57,59]. An attempt to rearrange *N*-*p*-tolyl-D-xylothiopyranosylamine yielded a substance with all the properties of an Amadori rearrangement product, but which is not crystalline and does not form crystalline derivatives[59].

The α-and β-xylothiopyranose tetraacetates *(107)* can be converted into sulfones by oxidation with $H_2O_2$[60]. Mild oxidation of methyl tri-*O*-acetyl-β-D-xylothiopyranoside *(116a)* with periodate yields a mixture of β-sulfoxide *(116b)* (sulfoxide group *endo* to the ring) and α-sulfoxide *(116d)* (*exo*)[60]. Both of these give the sulfone *(116c)* on further oxidation. Partial oxidation of methyl tri-*O*-acetyl-α-D-xylothiopyranoside gives only a β-sulfoxide, for steric reasons[60].



5-Thiohexoses, like 5-thiopentoses, preferentially form 6-membered rings, and the behavior of the two classes of compounds is similar. Acetolysis of the 5-thioglucofuranose derivative *(117)* gives a glucothiopyranose *(118)*; methanolysis of *(117)* gives a methyl glucothiopyranoside *(119)*[61]. A similar series of reactions has been carried out with 5-thioidose[50]. 6-Acetamido-6-deoxy-5-thio-L-idose also forms a 6-membered ring containing sulfur on acetylation[62].



b) 4-Thio Sugars

4-Thio sugars should also preferentially form a 5-membered S-ring, though the stability of this ring is expected to be lower than that of the 6-membered S-ring.

Methanolysis of the ribothiopyranose derivative *(120)* gives a methyl ribothiofuranoside *(121)*[63], while acetolysis leads to the tetraacetate *(122)*[64,65]. Neither *(121)* nor *(122)* gives the reactions of the SH group; the sulfur must, therefore, be stably bound in the 5-membered ring. Hydrolysis of *(122)* gives free ribothiofuranose *(123)*[65]. The spectroscopic data show that the free sugar is also almost entirely in the form of the thiofuranose *(123)*. This is supported by the fact that glycoside formation with *(123)* gives *(121)*, and acetylation of *(123)* gives *(122)*[65].

However, ribothiofuranose *(123)* gives positive reactions for SH groups. It is quickly and quantitatively oxidized by $I_2$ at room temperature to the disulfide *(125)*[65]. It must, therefore, be assumed that in contrast

[59] *T. van Es* and *R.L.Whistler*, J. org.Chemistry*29*, 1087 (1964).

[60] *R.L.Whistler, T.van Es*, and *R.M.Rowell*, J. org. Chemistry *30*, 2719 (1965).

[61] *M. S. Feather* and *R. L.Whistler*, Tetrahedron Letters *1962*, 667.

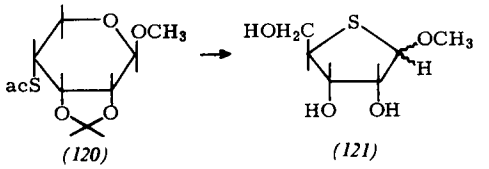
[62] *L. Goodman* and *J. E. Christensen*, J. org. Chemistry *29*, 1787 (1964).

[63] *R. L.Whistler, W. E. Dick, T. R. Ingle, R. M. Rowell*, and *B. Urbas*, J. org. Chemistry *29*, 3723 (1964).

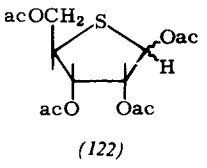
[64] *E. J. Reist, D. E. Gueffroy*, and *L. Goodman*, J. Amer. chem. Soc. *85*, 3715 (1963).

[65] *E. J. Reist, D. E. Gueffroy*, and *L. Goodman*, J. Amer. chem. Soc. *86*, 5658 (1964); Chem. and Ind. *1964*, 1364.

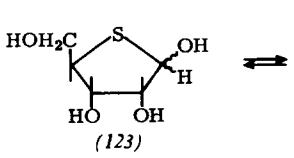
to the case of xylothiopyranose, an equilibrium is rapidly reached between ribothiofuranose *(123)* and 4-thiopyranose *(124)* The latter is readily oxidized to the disulfide *(125)* and is, therefore, continuously



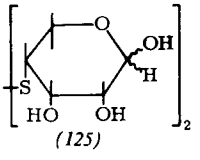
*(120)* *(121)*



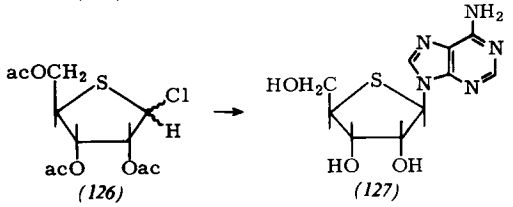
*(122)*



*(123)* *(124)*



*(125)*



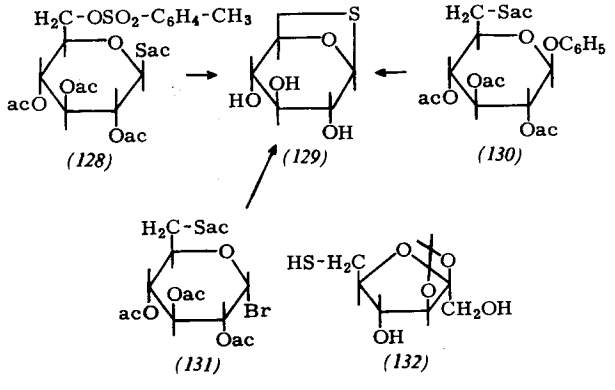
*(126)* *(127)*

removed from the equilibrium [65]. Thus the thiofuranose ring is much less stable than the thiopyranose ring.

The tetraacetate *(122)* reacts with HCl in ether to form the thiofuranosyl chloride *(126)*, from which the interesting modified nucleoside 4'-thioadenosine *(127)* has been prepared by condensation with 6-benzamido-9-(chloromercuri)purine [65].

### c) 6-Thio Sugars

1,6-Anhydropyranoses with sulfur in the 1,6-anhydro ring have been prepared in the form of the so-called "thiolaevoglucosan" *(129)*. The 1,6-anhydro ring can be closed from C-1 by treatment of *(128)* with alkali [66], while the ring is closed from C-6 by treatment of *(130)* and *(131)* with alkali [67].



*(128)* *(129)* *(130)*

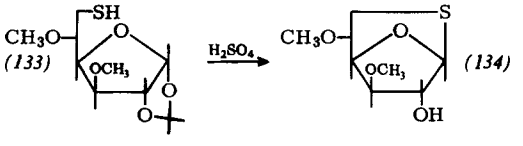


*(131)* *(132)*

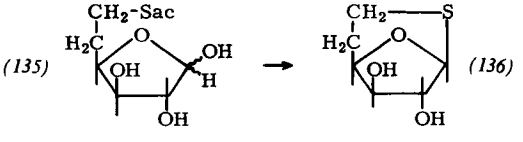
Attempts have also been made to detect a 6-thiopyranose form in 6-thiofructose [68]; however, the hydrolysis of the 6-thiofructofuranose derivative *(132)* did not yield conclusive results.

1,6-Anhydrofuranose derivatives with sulfur in the 1,6-anhydro ring have also been prepared from *(133)* and *(135)*. Position 5 is blocked by a methoxy group in *(133)*, and by the presence of the 5-deoxy group in *(135)*, so that cleavage of *(133)* and *(135)* [3a] yields *(134)* [3a] and *(136)* [69], respectively.

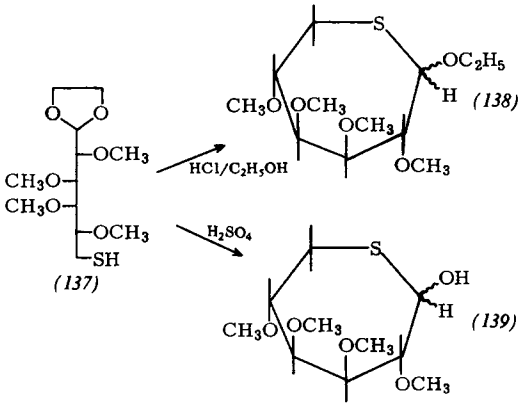
A heptanose derivative with sulfur in the 7-membered ring can be obtained by acetal cleavage of the 2,3,4,5-tetramethyl thiol *(137)* [3a]. Reaction with ethanol/hydrochloric acid gives the ethylthioheptanoside *(138)*, and hydrolysis with sulfuric acid yields the free thioheptanose *(139)*. The 7-membered S-ring is less stable than a thiopyranose ring [3a].



*(133)* *(134)*



*(135)* *(136)*



*(137)* *(138)* *(139)*

*I am grateful to my co-workers K. Todt, I. Sangster, D. Stoye, and F. Leupold for their enthusiastic assistance in the work on sugars containing N-rings. Thanks are also due to Prof. Dr. K. Heyns for his constant support of these investigations.*

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German version: Angew. Chem. *78*, 501 (1966)
Translated by Express Translation Service, London

[66] *M. Akaji, S. Tejima*, and *M. Haga*, Chem. pharmac. Bull. (Japan) *11*, 58 (1963).

[67] *P. A. Seib* and *R. L. Whistler*, 148th Meeting Amer. chem. Soc. *1964*, Abstracts of Papers, 18 D.

[68] *M. S. Feather* and *R. L. Whistler*, J. org. Chemistry *28*, 1567 (1963).

[69] *R. L. Whistler* and *B. Urbas*, J. org. Chemistry *30*, 2721 (1965)

## Errata

Specification of Molecular Chirality, by *R. S. Cahn, C. K. Ingold,* and *V. Prelog*, Angew. Chem. internat. Edit. *5*, 385 (1966).

Page 391, left-hand column: (i) In the definition of "Ligancy Complementation", line 4, insert "they" after "which". (ii) In the Standard Sub-rule (4), replace *p* by *r*.

Page 397, left-hand column, footnote: (i) For $X(ab)_{10}$ read $(Xab)_{10}$. (iii) The sequence-rule symbols ascribed to *(30a)* refer to *(30b)*, and *vice versa*.

Page 402, right-hand column, line 9: Delete "chiral".

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"Automation of Structure Analysis II: Automation of the Evaluation" by *W. Hoppe*, Angew. Chem. internat. Edit. *5*, 267 (1966):

Fig. 15 (p. 280) of this review should be turned through 180° for proper comparison with Fig. 14.

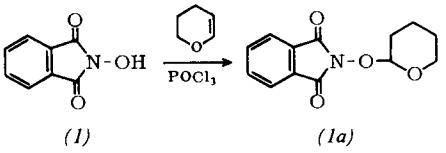
# COMMUNICATIONS

## Synthesis of 1-Hydroxy-2-thiouracil

By Dr. R. N. Warrener and E. N. Cain

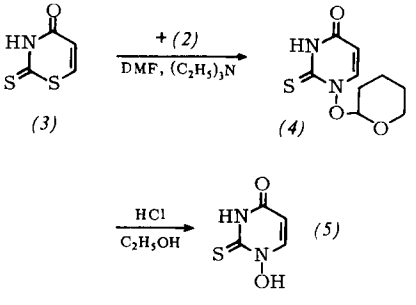
Department of Chemistry, Australian National University, Canberra, A.C.T. (Australia)

For the synthesis of 1-hydroxy-2-thiouracil, *O*-tetrahydropyran-2-ylhydroxylamine *(2)* was first prepared by the reaction:




Reaction of *(1)* [1] with 1.5 equivalents of 2,3-dihydro-4*H*-pyran and a few drops of phosphorus oxide chloride in tetrahydrofuran at 25 °C for 3 hours agave *(1a)*, m.p. 123 °C, which on heating with an equivalent of hydrazine hydrate in benzene for 3 hours, afforded *(2)* in 50% yield. It was obtained as a colorless liquid, b.p. 83 °C/23 mm (benzoyl derivatives: m.p. 150 °C, *(1a)*: m.p. 123 °C).

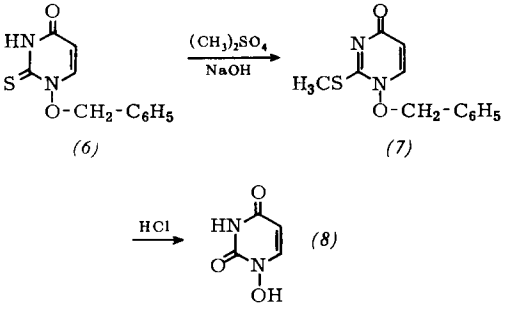
Reaction of *(2)* with the 1,3-thiazine *(3)* [2] in dimethylformamide containing one equivalent of triethylamine for 12 h at room temperature gives 1-tetrahydropyran-2-yloxy-2-thiouracil *(4)*, m.p. 208 °C (yield 21 %). The protecting group was readily removed by heating in ethanolic hydrochloric acid (10 %) to afford 1-hydroxy-2-thiouracil *(5)*, m.p. 203 °C and 275–277 °C, in 82 % yield. (Ultraviolet spectrum at pH 1: $\lambda_{max}$ = 217, 264, 297; log ε = 4.12, 4.08, 3.98; at pH 13: $\lambda_{max}$ = 244, 274, 320; log ε = 4.41, 4.15, 3.87).




Compound *(5)* gives an intense deep violet color with ferric chloride in ethanol, and like 1-hydroxy-uracil [3] liberates carbon dioxide from saturated sodium hydrogen carbonate solution.

Reaction between *O*-benzylhydroxylamine and *(3)* in boiling ethanol gives 1-benzyloxy-2-thiouracil *(6)*, m.p. 226 °C (yield 28 %). Removal of the *O*-benzyl group with hydrogen bromide in acetic acid is more difficult and gives inferior yields of *(5)*.

Treatment of *(6)* with alkaline dimethyl sulfate gives 1-benzyloxy-*S*-methyl-2-thiouracil *(7)*, m.p. 149 °C, yield 97 %, which on boiling with concentrated hydrochloric acid gives 1-hydroxyuracil *(8)* (50 %), m.p. 280–281 °C.




Received: February 1st, 1966 [Z 148/981 IE]
German version: Angew. Chem. *78*, 491 (1966)

[1] *G. H. L. Nefkens* and *G. J. Tesser*, J. Amer. chem. Soc. *83*, 1263 (1961).

[2] *R. N. Warrener* and *E. N. Cain*, Chem. and Ind. *1964*, 1989.

[3] *W. Klötzer*, Mh. Chem. *95*, 1729 (1964).

## Preparation of Saturated and Unsaturated Ketocarboxylic Acids from Dicarboxylic Anhydrides and Alkylaluminum Compounds [1]

By Dr. H. Reinheckel and Dr. K. Haage

Institut für Fettchemie der Deutschen Akademie der Wissenschaften, Berlin-Adlershof (Germany)

Reaction of organo-magnesium, -cadmium, and -zinc compounds with anhydrides of dicarboxylic acids to give keto acids occurs to a significant extent only when one of the reactants contains an aromatic group [2]. However, use of alkylaluminum compounds always leads to keto acids.

Succinic anhydride and $(C_2H_5)_3\,Al_2\,Cl_3$ (mole ratio 1:1) in methylene chloride at 40 °C give aluminum salts of 4-oxohexanoic acid, from which the free keto acid is obtained in 60 % yield on treatment with dilute $H_2SO_4$. Glutaric anhydride and $(C_2H_5)_3Al_2Cl_3$ (1:1) afford 5-oxoheptanoic acid in 44 % yield.

The reaction can be effected with higher alkylaluminum compounds, but it is then advantageous to use alkylaluminum dichlorides. The molar ratio of aluminum to anhydride should be 2:1 because of the resulting complex-formation.

The excess of alkylaluminum compound may be replaced by anhydrous $AlCl_3$. A solution of the anhydride and $AlCl_3$ in methylene chloride is allowed to react with the alkylaluminum compound, *e.g.* trialkylaluminum.

Maleic anhydride (as a suspension in methylene chloride) gives the corresponding α,β-unsaturated γ-keto acids, *e.g.* with $(C_2H_5)_3Al_2Cl_3$ (mole ratio 1:1) at −10 °C it gives 4-oxo-2-hexenoic acid in 47 % yield.

Lactones are by-products in all the reactions of cyclic anhydrides. Diketones and dicarboxylic acids are formed in addition to keto acids from acyclic anhydrides because of the statistical attack on the CO–O–CO group.

| Anhydride + alkylating agent | Molar ratio | Keto acid | Yield [%] |
|---|---|---|---|
| Succinic anhydride + $(C_2H_5)_3Al_2Cl_3$ | 1:1 | 4-Oxohexanoic | 60 |
| $AlCl_3$ + $(C_2H_5)_3Al$ | 1:1:0.4 | 4-Oxohexanoic | 69 |
| $C_6H_{13}AlCl_2$ | 1:1.7 | 4-Oxodecanoic | 49 |
| $AlCl_3$ + $C_8H_{17}AlCl_2$ | 1:1:1 | 4-Oxododecanoic | 56 |
| $AlCl_3$ + $C_{12}H_{25}AlCl_2$ | 1:1:1.3 | 4-Oxohexadecanoic | 38 |
| Glutaric anhydride + $(C_2H_5)_3Al_2Cl_3$ | 1:1 | 5-Oxoheptanoic | 44 |
| Maleic anhydride + $(C_2H_5)_3Al_2Cl_3$ | 1:1 | 4-Oxo-2-hexenoic | 47 |
| $AlCl_3$ + $C_8H_{17}AlCl_2$ | 1:1.5:1 | 4-Oxo-2-dodecenoic | 17 |
| Decanedioic anhydride + $(C_2H_5)_3Al_2Cl_3$ | 1:1.2 | 10-Oxododecanoic | 42 |
| Phthalic anhydride + $AlCl_3$ + $(C_2H_5)_3Al_2Cl_3$ | 1:1:0.5 | *o*-Propionylbenzoic | 95 |

a) *Saturated keto acids*: 89 g (0.36 mole) of $(C_2H_5)_3Al_2Cl_3$ is dropped, with stirring, into a solution of 35.6 g (0.36 mole) of succinic anhydride in 250 ml of $CH_2Cl_2$ at 20 °C. The mixture is boiled for 2 hours and then hydrolysed with 15 % $H_2SO_4$. Fractional distillation of the organic phase gives 28 g (60 %) of pure 4-oxohexanoic acid, b.p. 98–100 °C/0.1 mm, m.p. 34–36 °C.

b) *Unsaturated keto acids*: Reactions with maleic anhydride are carried out at −10 °C (suspension in $CH_2Cl_2$); hydrolysis is effected at −10 to −15 °C. 32.7 g (0.33 mole) of maleic anhydride and 83 g (0.33 mole) of $(C_2H_5)_3Al_2Cl_3$ afford 20 g (47 %) of 4-oxo-2-hexenoic acid, m.p. 110 °C, on evaporation of the solvent and recrystallization of the residue from light petroleum.

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German version: Angew. Chem. *78*, 491 (1966)

[1] Communication VII on Reactions with Aluminum Alkyls. – Communication VI: *H. Reinheckel* and *D. Jahnke*, Chem. Ber., in press.

[2] For a summary see *M. S. Kharasch* and *O. Reinmuth*: Grignard Reactions of Non-metallic Substances, Prentice-Hall. New York 1954.

## Conformations of trans-1,2-Dicyclopropylethylene and Vinylcyclopropane

By Prof. Dr. W. Lüttke and Dipl.-Chem. A. de Meijere

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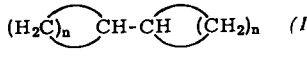
der Universität Göttingen (Germany)

In the course of our systematic studies[1] of the rotational isomerism of 1,3-butadiene and the lower bicycloalkyls *(1)* we were interested in the conformational behavior of vinylcyclopropane, which is intermediate between 1,3-butadiene [*(1)*, n = 1] and bicyclopropyl [*(1)*, n = 2].




*(1)*, n = 1, 2 . . . 5

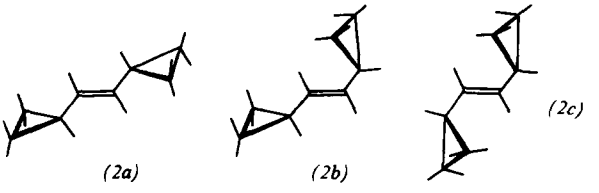
Vinylcyclopropane itself is not a suitable case for study of this problem by vibration spectroscopy since the conceivable conformers of this molecule (s-*trans*, s-*cis*, and *gauche* forms) do not differ sufficiently in symmetry and thus in the relevant selection rules (point groups: $C_s$, $C_s$, and $C_1$, respectively).

We have therefore measured the infrared spectrum of *trans*-1,2-dicyclopropylethylene *(2)* in the liquid and in the crystalline state; this compound may be considered to represent a vinylcyclopropane system with a potential symmetry center.

The most important result was the appearance of a C=C stretching vibration band at 1660 $cm^{-1}$ and two intense bands at 952 and 960 $cm^{-1}$ (C–H out-of-plane deformation of *trans*-1,2-substituted ethylenes[2]) in the spectrum of the liquid, whereas the bands at 1660 and 952 $cm^{-1}$ do not occur in the spectrum of the crystals.

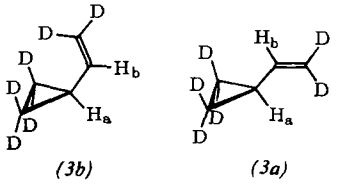
According both to experimental findings[3] and theoretical calculations[4] cyclopropanecarbaldehyde has a two-fold torsional potential, with minima at φ = 0 ° and φ = 180 ° (φ = torsion angle). It is thus to be assumed that only the s-*trans*- and the s-*cis*-conformation (φ = 180 and 0 °, respectively) of the isoelectronic vinylcyclopropane are stable, because only in these is the additional nonbonded interaction between hydrogen atoms minimal[5]. This fundamental difference from bicyclopropyl[1] follows from the differing geometry of the molecule.

On such considerations crystalline *trans*-1,2-dicyclopropylethylene consists exclusively of one of the two centrosymmetric conformers, s-*trans*-s-*trans* *(2a)* or s-*cis*-s-*cis*- *(2c)*, whereas the s-*cis*-s-*trans*-conformer *(2b)* also occurs in the equilibrium mixture in the liquid state.



*(2a)* *(2b)* *(2c)*

We have been able to prove, by NMR spectroscopy, that the s-*trans*-conformation of vinylcyclopropane is energetically more favored than the s-*cis*-conformation. For this purpose we measured the temperature-dependence of the vicinal H,H coupling constant $J_{ab}$ in hexadeuteriovinylcyclopropane *(3)*.




*(3b)* *(3a)*

Interconversion of the s-*trans*- *(3a)* and the s-*cis*-form *(3b)* is very fast in the temperature range studied. Thus a mean coupling constant (see table, second column) is observed, the following equation being valid ($x_{trans}$ and $x_{cis}$ = mole fractions of the s-*trans*- and the s-*cis*-form, respectively):

$$J_{ab}^{obs} = x_{trans} \cdot J_{ab}^{trans} + x_{cis} \cdot J_{ab}^{cis} \qquad (a)$$

$J_{ab}^{trans}$ is certainly larger than $J_{ab}^{cis}$[6]. It therefore follows from the fact that $J_{ab}^{obs}$ increases with decreasing temperature that the concentration of the *trans*-conformer increases. The s-*trans*-conformation is thus energy-poorer.

| Temp. [°C] | $J_{ab}^{obs}$ [cps] | $x_{trans}$ | $x_{cis}$ |
|---|---|---|---|
| −30 | 9.13 | 0.69 | 0.31 |
| −10 | 9.05 | 0.68 | 0.32 |
| +60 | 8.38 | 0.56 | 0.44 |
| +80 | 8.15 | 0.53 | 0.47 |

If we assume that $J_{ab}^{trans}$ lies between 11 and 12 cps[7] and $J_{ab}^{cis}$ between 4.5 and 6 cps[8], we can obtain the equilibrium concentrations $x_{trans}$ and $x_{cis}$ from Equation (a). (In the table, columns 3 and 4 give the values of $x_{trans}$ and $x_{cis}$ that result from the values $J_{ab}^{trans} = 11.0$ cps and $J_{ab}^{cis} = 5.0$ cps.

From the temperature-dependence of the equilibrium constants

$$K = x_{trans}/x_{cis}$$

the energy difference between the *trans*- and the *cis*-conformer has been estimated graphically to be 1.1 ± 0.2 kcal/mole.

Received: February 10th, 1966 [Z 171/3 IE]
German version: Angew. Chem. 78, 544 (1966)

[1] *W. Lüttke, A. de Meijere, H. Wolff, H. Ludwig,* and *H. W. Schrötter,* Angew. Chem. *78*, 141 (1966); Angew. Chem. internat. Edit. *5*, 123 (1966).

[2] *L. J. Bellamy*: The IR-Spectra of Complex Molecules. Methuen, London 1960, p. 45.

[3] *L. S. Bartell* and *J. P. Guillory*, J. chem. Physics *43*, 647 (1965).

[4] *R. Hoffmann*, Tetrahedron Letters *1965*, 3819.

[5] In a recent publication [Angew. Chem. *78*, 266 (1966); Angew. Chem. internat. Edit. *5*, 251 (1966)] *H. Günther* and *D. Wendisch* support the view that for vinylcyclopropane derivatives a *trans* ($\varphi = 180°$) and two *gauche* forms ($\varphi \approx 40°$) are the stable conformers. – Consideration of a molecular model of cyclopropane, like calculation of the sum of all the H···H interactions as a function of the torsion angle $\varphi$ [potential according to *L. S. Bartell*, J. chem. Physics, *32*, 827 (1960)], shows a narrow minimum at the *cis*-position ($\varphi = 0°$) and a broad minimum region for the *trans*-position ($\varphi = 180 \pm 100°$). The two maxima of the torsional potential curve lie at $\varphi \approx 40°$ and 320°.

[6] *H. Suhr*: Anwendungen der kernmagnetischen Resonanz in der organischen Chemie. Springer, Berlin 1965, p. 53.

[7] *A. A. Bothner-By, C. Naar-Colin,* and *H. Günther*, J. Amer. chem. Soc. *84*, 2748 (1962).

[8] *J. B. Lambert, L. J. Durham, P. Lepoutere,* and *J. D. Roberts*, J. Amer. chem. Soc. *87*, 3896 (1965).

## Proton Activity in the 1,2-Dithiolium System

By Prof. Dr. H. Prinzbach, Dr. E. Futterer, and Prof. Dr. A. Lüttringhaus

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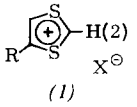
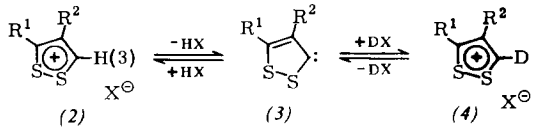
As with analogous 1,3-dihetero cations, the acidity of the H atom at position 2 of 1,3-dithiolium salts *(1)* is considerable[1]. In concordance with the results of quantum-mechanical studies [2] and with the weak electronic shielding shown by low τ-values [3], the H atoms at positions 3 and 5 of the 1,2-dithiolium system *(2)*, $R^1{=}R^2{=}H$ (the C atoms to which they are attached have only one S atom as neighbor) undergo readily measurable H/D exchange even in 10% (v/v) $F_3CCOOD/D_2O$ (74 ± 2 °C; 0.5 mole/l). By NMR-spectroscopic measurements we have determined the effective exchange half-lives $t_{1/2}$ listed in the Table.



*(1)*

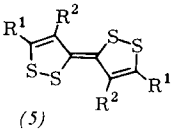


*(2)* *(3)* *(4)*

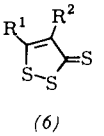
| | | | |
|---|---|---|---|
| *(a)*: | $R^1 = (CH_3)_3C$ | $R^2 = H$ | $X = ClO_4$ |
| *(b)*: | $R^1 = C_6H_5$ | $R^2 = H$ | $X = Br$ |
| *(c)*: | $R^1 = p\text{-}CH_3O\text{–}C_6H_4$ | $R^2 = H$ | $X = Cl$ |
| *(d)*: | $R^1 = H$ | $R^2 = C_6H_5$ | $X = Cl$ |

| | $t_{1/2}$ [min] | τH(3) ($F_3CCO_2D$) |
|---|---|---|
| *(2a)* | 522 ± 60 | −0.57 |
| *(2b)* | 120 ± 10 | −0.30 |
| *(2c)* | 200 ± 20 | 0.01 |
| *(2d)* | 11.6 ± 1 | −0.50 |

As expected from the acid-base equilibrium *(2)* ⇄ *(3)* the rate of H/D exchange decreases with increasing concentration of $F_3CCOOD$.



*(5)*



*(6)*

In contrast to 1,3-dithiolium salts *(1)*, the 1,2-dithiolium salts (in acetonitrile) do not give the dimers *(5)* when treated with *N*-ethyldiisopropylamine, but instead give the dithiole-3-thione *(6)* (yield *ca.* 50 %). In view of the easy scission of the disulfide linkage by carbenes[4], attack of the carbene *(3)* on the disulfide bridge in *(2)* or *(3)* is not excluded. The yields of *(6)* can be increased substantially (up to 97 %) by addition of elemental sulfur[5].

Received: February 14th, 1966 [Z 163/995 IE]
German version: Angew. Chem. 78, 492 (1966)

[1] *H. Prinzbach, H. Berger,* and *A. Lüttringhaus*, Angew. Chem. *77*, 453 (1965); Angew. Chem. internat. Edit. *4*, 435 (1965).

[2] *R. Zahradník* and *J. Koutecky*, Coll. czechoslov. chem. Commun. *28*, 1117 (1963); *G. Bergson*, Arkiv Kemi *19*, 181 (1962).

[3] *H. Prinzbach* and *E. Futterer*, Adv. heterocyclic Chem. *7*, in press (1966).

[4] *A. Schönberg, O. Schütz,* and *J. Peter*, Ber. dtsch. chem. Ges. *62*, 440 (1929); *J. H. Hartenstein*, Diploma Thesis, Universität Freiburg, 1961; *U. Schmidt* and *Ch. Osterroht*, Angew. Chem. *77*, 455 (1965); Angew. Chem. internat. Edit. *4*, 437 (1965).

[5] *E. Klingsberg*, J. org. Chemistry *28*, 529 (1963).

## Preparation and Rearrangement of Allylalanes

By Dr. H. Hoberg

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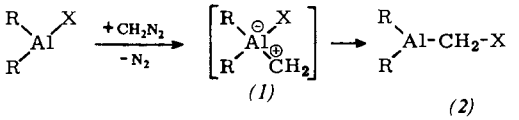
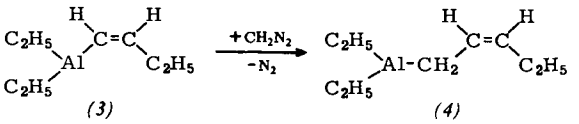
Diazomethane reacts with organic derivatives of aluminum hydrides in toluene at −78 °C, giving, by way of Al ylides *(1)*, products *(2)* in which a residue attached to the Al atom has been lengthened by a $CH_2$ group[1]. The $CH_2$ group is



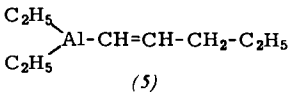
*(1)* *(2)*

X = Halogen, H, or organic group
R = $C_2H_5$

inserted preferentially between Al and the most electronegative ligand. Thus alkenyldialkylalanes *(3)* (prepared from triethylalane and acetylene[2]) reacts with equimolar amounts of diazomethane in toluene/anisole (4:1 v/v) at −78 °C predominantly at the Al–$C_{(alkenyl)}$bond, for hydrolysis of the product gives pentene as well as ethane. However,



*(3)* *(4)*

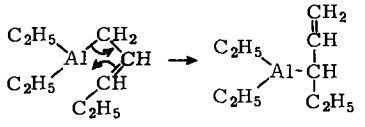


*(5)*

the product does not have the structure *(4)*, for the hydrolysis gives 1-pentene and not *cis*-2-pentene. This appears to indicate structure *(5)*, but hydrolysis with $D_2O$ gives a monodeuterio-1-pentene in which a saturated C atom has been deuterated, as is shown by the position of the C–D stretching vibration ($\tilde{\nu}$ = 2140 $cm^{-1}$) on comparison with the spectra of alkenes deuterated at known positions[3].

If an excess of diazomethane is used with compound *(3)*, insertion of a second $CH_2$ group per alane molecule occurs, so that subsequent hydrolysis gives propane and, above all, 3-methyl-1-pentene, but no hexene, as well as ethane and 1-pentene. Thus an isomerization *(4)* → *(5)* is excluded.

The formation of 3-methyl-1-pentene on alcoholysis after reaction of compound *(3)* with an excess of diazomethane throws light on the nature of the rearrangement. The 3-methyl group results from the second $CH_2$ insertion, so after the first insertion an allyl rearrangement onto aluminum according to *(4)* → *(6)* must have occurred.



*(4)* *(6)*

A recent paper on allyl rearrangements on addition of dialkylalanes to substituted 1,3-dienes[4] supports our formulations.

Received: February 16th, 1966 [Z 172/4 IE]
German version: Angew. Chem. *78*, 492 (1966)

[1] *H. Hoberg*, Liebigs Ann. Chem., in press.

[2] *G. Wilke* and *H. Müller*, Liebigs Ann. Chem. *629*, 222 (1960); *G. Wilke* and *W. Schneider*, Bull. Soc. chim. France *1963*, 1462.

[3] *E. G. Hoffmann*, Liebigs Ann. Chem. *618*, 276 (1958); *H. W. Schrötter* and *E. G. Hoffmann*, *ibid.* *672*, 44 (1964).

[4] *J. J. Eisch* and *G. R. Husk*, J. organomet. Chem. *4*, 415 (1965).

## New Synthesis of 1,2,5-Thiadiazole and Some of its Derivatives

By Dr. V. Bertini and Prof. Dr. P. Pino

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Hitherto the only synthesis of 1,2,5-thiadiazole has been a five-stage one affording poor yields[1].

In continuation of our study of the use of $S_4N_4$ for synthesis of thiadiazole derivatives we have prepared 1,2,5-thiadiazole (b.p. 94 °C, $n_D^{25}$ = 1.5151, ultraviolet spectrum: $\lambda_{max}$ = 254 mμ, log ε = 3.94) in 70 % yield by heating 0.0434 mole of ethylenediamine with 0.0109 mole of $S_4N_4$ in 45 ml of a mixture of *o*-, *m*-, and *p*-xylene for 2–3 hr[2,3]. The 1,2,5-thiadiazole was isolated and purified by distillation of the reaction mixture, followed by precipitation as Cd salt, decomposition of the latter in steam, and salting out of the aqueous solution with $Na_2SO_4$. Under similar conditions 0.0326 mole of propylenediamine and 0.0109 mole of $S_4N_4$ yielded 3-methyl-1,2,5-thiadiazole[4] (b.p. 121 °C; $n_D^{25}$ = 1.5053; $\lambda_{max}$ = 259 mμ, log ε = 3.94) in 97 % yield.

Synthesis of mono- and di-aryl derivatives of 1,2,5-thiadiazole, which can be obtained in low yield by reaction of $S_4N_4$ with alkylaromatic hydrocarbons of the type $R-CH_2-CH_2-R'$ (with R = $C_6H_5$, $C_{10}H_7$; R′ = H, $C_6H_5$)[5], is accomplished in much higher yield and more conveniently from the more readily accessible monoamines[6] $C_6H_5-CH_2-CH(NH_2)-R'$ (R′ = H or $C_6H_5$). In this way, boiling 0.0325 mole of phenethylamine with 0.0163 mole of $S_4N_4$ in the xylene mixture gives a 20 % yield of 3-phenyl-1,2,5-thiadiazole (m.p. and mixed m.p. 43–44 °C); and 0.0163 mole of α-phenylphenethylamine and 0.0165 mole of $S_4N_4$ give a 60 % yield of 3,4-diphenyl-1,2,5-thiadiazole (m.p. and mixed m.p. 85–86 °C)

Received: February 23rd, 1966 [Z 169/1000 IE]
German version: Angew. Chem. *78*, 493 (1966)

[1] *L. M. Weinstock*, Ph.D. Thesis, University of Indiana, 1958; Univ. Microfilms (Ann Arbor, Mich.) Mic 58-2974.

[2] Ital. Patent Appln. 2204/66 (Feb. 1st, 1966).

[3] Although the possibility of obtaining benzo-1,2,5-thiadiazole by reaction of *o*-phenylenediamine with $S_4N_4$ has been briefly mentioned in the literature [1], the reaction of $S_4N_4$ with vicinal diamines containing amino groups bound to aliphatic carbon has not been described.

[4] *G. M. Gill*, Ph.D. Thesis, University of Indiana (1963); Univ. Microfilms (Ann Arbor, Mich.) 64-468.

[5] *V. Bertini* and *P. Pino*, Angew. Chem. *77*, 262 (1965); Angew. Chem. internat. Edit. *4*, 239 (1965).

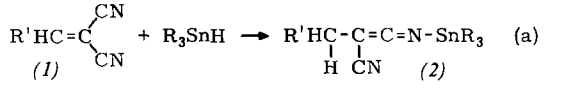
[6] Ital. Patent Appln. 2203/66 (Feb. 1st, 1966).

## Preparation of N-Stannylketenimines and Ketene Ethyl Stannyl Acetals by 1,4-Hydrostannation of Conjugated Systems

By Prof. Dr. W. P. Neumann, Dr. R. Sommer, and cand. chem. E. Müller

Institut für Organische Chemie der Universität Gießen (Germany)

In the presence of catalysts at 60–80 °C conjugated dienes, *e.g.* 1,3-butadiene, add organotin hydrides preponderatingly at the 1,4-positions in a radical reaction[1]. We now report a polar 1,4-hydrostannation of conjugated unsaturated systems whose C=C group is sufficiently polarized, *e.g.* of alkylidenemalononitriles *(1)*. *N*-Stannylketenimines *(2)* are thus formed, usually even at 20 °C and without a catalyst, in a strongly exothermic reaction. This is surprising because previous attempts to bring about reaction between organotin hydrides and CN groups failed[2] and cinnamonitrile and acrylnitrile react exclusively at their C=C groups[3].



*(1)* *(2)* (a)

R′ = *e.g.* $CH_3$, $C_2H_5O$, $C_6H_5$, *p*-$(CH_3)_2N-C_6H_4$, *p*-$CH_3O-C_6H_4$, *p*-$Cl-C_6H_4$, *p*-$O_2N-C_6H_4$, Furyl

R = $C_2H_5$, $C_4H_9$

Compounds $R'_2C=C(CN)_2$ (R′ = *e.g.* $CH_3$, $C_6H_5$) react analogously to *(1)*.

The *N*-stannylketenimines *(2)* are very reactive[4]. Their structure follows, *inter alia*, from the NMR spectra and the very intense ketene imine bands at 2060–2110 $cm^{-1}$ in their infrared spectra (C≡N absorption at 2180 $cm^{-1}$ is also present). They are readily soluble in hydrocarbons and ethers, sensitive to moisture, and stable only up to about 50 °C. The average molecular weight of these viscous, undistillable liquids in benzene increases rapidly with concentration, which indicates association by means of pentacoordinated tin.

Reaction is slower the less polarized is the C=C group. Electron-donating substituents R′ decrease the reaction velocity, as does replacement of CN by the more weakly electron-attracting ester group: alkylidenecyanoacetates *(3a)* and alkylidenemalonic esters *(3b)* also react with organotin hydrides by 1,4-addition, giving ketene ethyl stannyl acetals *(4)*, but sometimes so slowly that 1,2-hydrostannation of the C=C bond also occurs.

$$R^1HC{=}C(X)CO_2C_2H_5 + R_3SnH \longrightarrow R^1CH{-}C(X){=}C(OC_2H_5)(OSnR_3) \quad (b)$$

(3) (4)

*(3a)*, X = NC; R′ = $CH_3$, $C_6H_5$, *p*-$CH_3O$–$C_6H_4$, *p*-Cl–$C_6H_4$
*(3b)*, X = $C_2H_5CO_2$; R′ = $CH_3$, $C_6H_5$

The analogous vinyl ketones *(5)* [5] react exclusively by 1,4-addition, giving enol ethers *(6)* (characterized by, *inter alia*, NMR and infrared spectra). These are crystalline compounds, which in contrast to *(2)* and *(4)* are not sensitive to moisture.

$$R^1HC{=}C(CN){-}C(=O){-}R^2 + R_3SnH \longrightarrow R^1H_2C{-}C(CN){=}C(R^2)(OSnR_3) \quad (c)$$

(5) (6)

$R^1$ = *e.g.* *p*-$CH_3O$–$C_6H_4$, $C_6H_5$, *p*-$O_2N$–$C_6H_4$, Furyl
$R^2$ = *e.g.* $C_6H_5$

Reactions (a) and (b) also occur analogously and smoothly with dialkyltin dihydrides and organolead hydrides [6].

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[1] *W. P. Neumann* and *R. Sommer*, Angew. Chem. *76*, 52 (1964); Angew. Chem. internat. Edit. *3*, 133 (1964).

[2] *W. P. Neumann* and *E. Heymann*, Liebigs Ann. Chem. *683*, 24 (1965), where further references are cited.

[3] *G. J. M. van der Kerk*, *J. G. Noltes*, and *J. G. A. Luijten*, J. appl. Chem. *7*, 356 (1957); *G. J. M. van der Kerk* and *J. G. Noltes*, *ibid.* *9*, 106 (1959).

[4] *R. Sommer* and *W. P. Neumann*, Angew. Chem. *78*, 546 (1966); Angew. Chem. internat. Edit. *5*, 515 (1966).

[5] *R. Sommer*, Dissertation, Universität Gießen 1964; *M. Pereyre* and *J. Valade* [C. R. hebd. Séances Acad. Sci. *260*, 581 (1965); Bull. Soc. chim. France *1965*, 2420] recently described 1,4-hydrostannation of other vinyl ketones.

[6] *W. P. Neumann* and *K. Kühlein*, unpublished work.

## Syntheses with N-Stannylketenimines and Ketene Ethyl Stannyl Acetals

By Dr. R. Sommer and Prof. Dr. W. P. Neumann

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der Universität Gießen (Germany)

*N*-Stannylketenimines *(1)* and ketene ethyl stannyl acetals *(9)* have recently become known and easily accessible [1]. Some of the reactions of ketene imines and acetals [2] lead one to expect that compounds *(1)* and *(9)* would be particularly suitable for the synthesis of substituted malonic acid derivatives. This is in fact the case: compounds *(2)*–*(4)* are formed smoothly when the components are heated 6–10 hr to 60–80 °C, and compounds *(5)*–*(8)* are formed instantaneously at 0–20 °C, some of them exothermally. The by-product, trialkyltin halide or alkoxide, can be easily separated by destillation and reconverted into the organotin hydride from which compounds *(1)* and *(9)* are obtained.

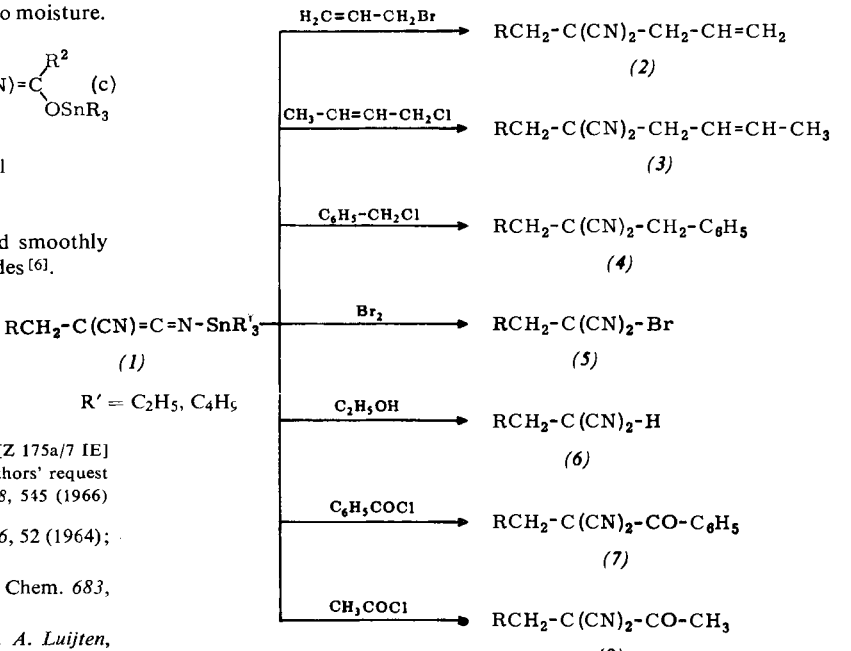
From the ketene stannyl acetals *(9)* [1]

$R{-}CH_2{-}C(X){=}C(OC_2H_5){-}OSnR'_3$ *(9a)*, X = CN
*(9b)*, X = $CO_2C_2H_5$

we obtained the following compounds similarly and in good yield:

$C_6H_5{-}CH_2{-}CH(CN){-}CO_2C_2H_5$ B.p. 160–165 °C/11 mm
$C_6H_5{-}CH_2{-}C(CN)(CO_2C_2H_5){-}CH_2{-}CH{=}CH_2$ B.p. 130–132 °C/$10^{-3}$ mm
*p*-$CH_3O$–$C_6H_4$–$CH_2$–$C(CN)(CO_2C_2H_5)$–Br B.p. 148–150 °C/$10^{-4}$ mm
*p*-Cl–$C_6H_4$–$CH_2$–$C(CN)(CO_2C_2H_5)$–$CH_2$–$CH{=}CH_2$ B.p. 135–136 °C/0.2 mm
$C_6H_5{-}CH_2{-}C(CO_2C_2H_5)_2{-}CO{-}C_6H_5$ B.p. 166–168 °C/$10^{-4}$ mm

Most of these compounds, like *(2)*–*(8)*, were previously unknown or were accessible only by complicated methods or in poor yields.




| | R | M.p. [°C] | B.p. [°C/mm Hg] | Yield [%] |
|---|---|---|---|---|
| *(2)* | $CH_3$ | | 85–86/10 | 82 |
| | $C_6H_5$ | 55 | 98–100/0.01 | 94 |
| | *m*-$NO_2$–$C_6H_4$ | 76 | | 81 |
| | 2-Furyl | 35 | 92–93/$10^{-4}$ | 86 |
| *(3)* | $C_6H_5$ | 78 | 116–118/$10^{-4}$ | 80 |
| | *p*-Cl–$C_6H_4$ | | 130–135/$10^{-4}$ | 81 |
| *(4)* | $C_6H_5$ | 131 | | 85 |
| | *p*-$CH_3O$–$C_6H_4$ | 110 | | 77 |
| | *p*-Cl–$C_6H_4$ | 127 | | 96 |
| | 2-Furyl | 104 | | 69 |
| *(5)* | $C_6H_5$ | 119 | | 90 |
| | *p*-$CH_3O$–$C_6H_4$ | 59 | | 73 |
| | *p*-$NO_2$–$C_6H_4$ | 138 | | 90 |
| | *p*-Cl–$C_6H_4$ | 124 | | 70 |
| *(6)* | $CH_3$ | | 96/21 | 83 |
| | $C_6H_5$ | 92 | | 68 |
| | *p*-$CH_3O$–$C_6H_4$ | 88 | | 96 |
| | *p*-$NO_2$–$C_6H_4$ | 154 | | 93 |
| | *m*-$NO_2$–$C_6H_4$ | 132 | | 87 |
| | *p*-Cl–$C_6H_4$ | 95 | | 67 |
| | 2-Furyl | | 88–90/$10^{-4}$ | 86 |
| *(7)* | $C_6H_5$ | 101 | 140–144/$10^{-4}$ | 58 |
| *(8)* | $C_6H_5$ | 102 | 115–120/0.6 | 66 |
| | 2-Furyl | 55 | 98–100/0.02 | 73 |

The acyl groups are removed from compounds *(7)* and *(8)*, with scission of the C–C bond, as acids by atmospheric moisture or faster as esters by means of alcohols.

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[1] *W. P. Neumann*, *R. Sommer*, and *E. Müller*, Angew. Chem. *78*, 545 (1966); Angew. Chem. internat. Edit. *5*, 514 (1966).

[2] For a review of ketene acetals see *S. M. McElvain*, Chem. Rev. *45*, 453 (1949).

## Azuleno[5,6,7-cd]phenalene, a New Quasiaromatic System

By Doz. Dr. Ch. Jutz and Dipl.-Chem. R. Kirchlechner

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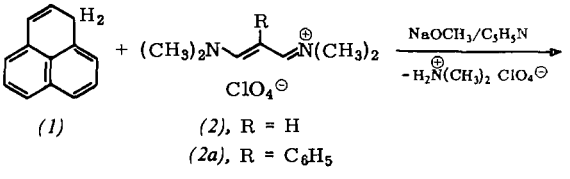
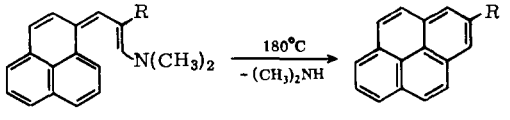
Phenalene *(1)* [1] condenses with the azacyanine perchlorates *(2)* and *(2a)* in presence of sodium methoxide in pyridine under nitrogen, giving the deeply collred "phenafulvenes" *(3)* and *(3a)* in more than 90 % yield [*(3)*: lustrous green needles, m.p. 150–151 °C; $\lambda_{max}$ = 496 mμ (log ε = 4.53) in $CH_3CN$].

Compound *(3a)* undergoes ring closure to give 2-phenylpyrene *(4a)*, m.p. 166 °C, already during isolation; compound *(3)* affords pyrene *(4)* in 80 % yield, with loss of dimethylamine, when heated in quinoline or sublimed in the presence of copper powder.

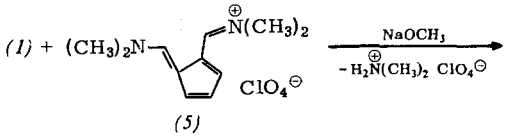


*(1)* *(2)*, R = H; *(2a)*, R = $C_6H_5$

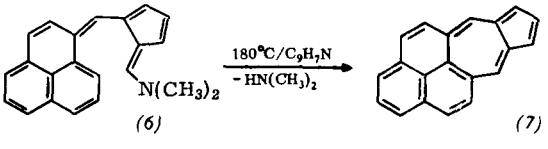


*(3)*, R = H; *(3a)*, R = $C_6H_5$ *(4)*, R = H; *(4a)*, R = $C_6H_5$

Reaction of phenalene *(1)* with *N,N*-dimethyl-(6-dimethylaminofulvenylmethylene)ammonium perchorate *(5)* [2] affords the violet "phenafulvalene" derivative *(6)*, which is converted into azuleno[5,6,7-*cd*]phenalene *(7)* (isomeric with 1,2-benzopyrene) in 60 % yield when heated in quinoline.



*(5)*



*(6)* *(7)*

The mass spectrum and elemental analysis confirm the composition. This compound *(7)* has a many-banded ultraviolet spectrum: $\lambda_{max}$ (in hexane) = 741 mμ (log ε = (3.21), 702 (3.04), 666 (3.08), 633 (2.87), 614 (2.77), 451 (5.10), 426 (4.60), 316 (5.29).

Maleic anhydride does not undergo Diels-Alder addition to compound *(7)*. Although significantly more basic, the green compound *(7)* (leaflets, m.p. 184 °C) shows many resemblances to azulene. Thus it is substituted at position 1 by dimethylformamide and phosphorus oxide chloride, affording a violet-red formimidium salt; with acetone in alcoholic mineral acid solution it forms a carmine-red carbonium ion having an intense green fluorescence.

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German version: Angew. Chem. *78*, 493 (1966)

[1] *V. Boekelheide* and *C. E. Larrabee*, J. Amer. chem. Soc. *72*, 1245 (1950).

[2] *K. Hafner, K. H. Vöpel, G. Ploss*, and *C. König*, Liebigs Ann. Chem. *661*, 52 (1963).

## Preparation of Tetramethylzirconium, $Zr(CH_3)_4$

By Priv.-Doz. Dr. H. J. Berthold and Dipl.-Chem. G. Groh

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After having isolated crystalline tetramethyltitanium and trimethyltitanium iodide some time ago [1], we have now prepared tetramethylzirconium.

Sublimed $ZrCl_4$ was dissolved in boiling ether/toluene (2:3) under reflux in the absence of moisture. After the solution had been cooled to −78 °C an etheral solution of methyl-lithium in stoichiometric proportion was added under nitrogen. No reaction occurred at this stage. When the mixture was warmed with stirring to about −45 °C, the $ZrCl_4$-ether adduct that had partly crystallized at −78 °C, as well as any $LiCH_3$ that may have separated, dissolved. The beginning of the methylation could be recognized by appearance of a yellow color and separation of LiCl. Stirring for 4 hr at −45 °C led finally to a dark reddish-brown solution, from which a small yield of a red distillate was obtained by distillation in a closed vacuum at −30 to −15 °C. Sometimes red crystals separated during the distillation on the end of the condenser; they could be transferred to the collecting vessel without decomposition by aslight increase in the temperature of the coolant.

After hydrolysis of the chlorine-free distillate, analysis gave a Zr:$CH_4$ ratio of 1:3.998. It has not yet been established whether the red crystals are pure $Zr(CH_3)_4$ or an ether adduct thereof.

Solid $Zr(CH_3)_4$ as well as its solution is unstable and decomposes even below *ca.* −15 °C with blackening and loss of methane.

In experiments with a molar ratio $ZrCl_4$:$LiCH_3$ = 1:6, precipitation with hexane and redissolution in toluene gave chlorine-free, yellow solutions containing according to analysis the complex $Li_2[Zr(CH_3)_6]$. These solutions were thermally more stable than those of $Zr(CH_3)_4$; they decomposed at about 0 °C.

Received: March 10th, 1966 [Z 174/6 IE]
German version: Angew. Chem. *78*, 495 (1966)

[1] *H. J. Berthold* and *G. Groh*, Z. anorg. allg. Chem. *319*, 230 (1963); Angew. Chem. *75*, 576 (1963).

## A Spiroheterocyclic Nickel Carbonyl [1]

By Dr. J. Ellermann and Dipl.-Chem. K. Dorn

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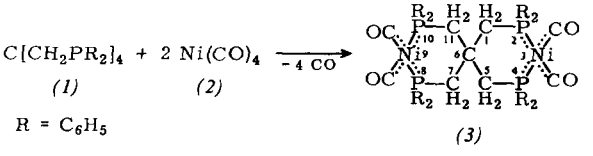
der Universität Erlangen (Germany)

The quadridentate complex ligand tetrakis(diphenylphosphinomethyl)methane *(1)* [2] usually reacts as a doubly bidentate reagent and is thus suitable for use in synthesis of spiroheterocyclic metal [1, 3] and non-metal compounds [4]. When the phosphine *(1)* is treated with tetracarbonylnickel *(2)* in the molar ratio 1:2 or with an excess of $Ni(CO)_4$ in benzene at room temperature with exclusion of air and moisture, then 3,3,9,9 - tetracarbonyl - 2,2,4,4,8,8,10,10 - octaphenyl-2,4,8,10-tetraphospha-3,9-dinickelaspiro[5.5]undecane *(3)* is formed, with elimination of 2 moles o CO per mole of $Ni(CO)_4$ in *ca.* 15 hours.



*(1)* *(2)* *(3)*

R = $C_6H_5$

Unchanged carbonyl *(2)* and benzene are distilled off in a high vacuum and the inhomogeneous dirty-white residue is

heated under reflux for 20 min with anhydrous, $N_2$-saturated ethanol. The ethanolic suspension is filtered and the small crystals of colorless residue are washed with a little alcohol and dried in a vacuum. Elemental analysis and molecular-weight determination confirm the constitution *(3)*. The compound is readily soluble in trichloroethylene, acetone, or benzene, less soluble in $CCl_4$, and almost insoluble in cyclohexane, light petroleum, ethanol, or ether. Decomposition occurs in $CS_2$. When heated, the compound discolors from 140 °C onwards and melts with decomposition at 205 °C. Its infrared spectrum (in $CCl_4$) shows, besides the bands of the spirocyclic ring system and the phenyl substituents, two intense CO stretching vibrations at 2008 ($A_1$) and 1952 ($B_2$) $cm^{-1}$ (point group $C_{2v}$), as are found also for other diphosphine-nickel carbonyl derivatives[5]. From the occurrence of only two CO stretching vibrations it follows that the two $P_2Ni(CO)_2$ groups do not couple with each other, which is to be expected for a non-planar spiroundecane system. The nickel is covalently bound in the rings; a considerable $\pi$-bond contribution is to be assumed for the N–P and Ni–C bonds[5,6].

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German version: Angew. Chem. *78*, 547 (1966)

[1] Part 4 of Spiroheterocyclic Compounds. – Part 3: *J. Ellermann* and *K. Dorn*, J. organomet. Chemistry *5* (1966), in press.
[2] *J. Ellermann* and *K. Dorn*, Chem. Ber. *99*, 653 (1966).
[3] *J. Ellermann* and *K. Dorn*, Z. Naturforsch. *20b*, 920 (1965).
[4] *J. Ellermann et al.*, unpublished work.
[5] *J. Chatt* and *F. A. Hart*, J. chem. Soc. (London) *1960*, 1378.
[6] Cf. *M. Bigorgne*, J. organomet. Chemistry *2*, 68 (1964).

## Mass Spectra of Weakly Excited Molecules [1]

By Prof. Dr. G. Spiteller and Dr. Margot Spiteller-Friedmann

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We have recently shown[2] that mass-spectrometric fragmentations can be halted at the stage of primary or secondary degradation products by decrease of the electron energy and simultaneous limitation of the thermal excitation energy of the molecules to be analysed.

This procedure has now been applied to steroids (cf. Fig. 1). Whereas the spectra of steroids and terpenes, obtained with electron energies of 70 eV and hot ion sources (about 250 °C), are characterized by the formation of many, generally non-specific fragments, spectra obtained at 12–20 eV and with "cold" ion sources (about 70 °C) generally show only a few key fragments and often are as characteristic as those of alkaloids. During the determination of the mass spectra of such weakly excited molecules, the nonspecific hydrogen shifts otherwise frequently observed for steroids are absent or substantially reduced. Small hydrocarbon fragments that greatly complicate the interpretation of other spectra are not formed. The different rates of decrease in the intensities of various ions with decreasing electron energy in the range 20–12 eV yield valuable information on the energy requirements of the corresponding fragmentation.

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German version: Angew. Chem. *78*, 494 (1966)

[1] Communication 2. – Communication 1: *G. Spiteller, M. Spiteller-Friedmann*, and *R. Houriet*, Mh. Chem. *97*, 121 (1966). We thank the Deutsche Forschungsgemeinschaft for support of this work.
[2] *G. Spiteller* and *M. Spiteller-Friedmann*, Liebigs Ann. Chem. *690*, 1 (1966).

## Reactions of α,α-Disubstituted Benzyl Anions with Carbonium Ions. Synthesis of p-Quinodimethanes

By Prof. Dr. R. Gompper, Dr. E. Kutter, and
Dipl.-Chem. H.-U. Wagner

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Benzyl anions are ambifunctional nucleophilic systems in which the exocyclic α-carbon atom and the nuclear *ortho*- and *para*-carbon atoms are reactive centers. According to MO calculations[1] the α-carbon atom carries most of the negative charge (see, *e.g.*, the deuteration of α,α-dimethylbenzylpotassium[2]).

With a view to obtaining thermodynamic control, and thus nuclear substitution, by the use of stable cations (cf. analogous reactions of phenols[3]), we studied the reaction of

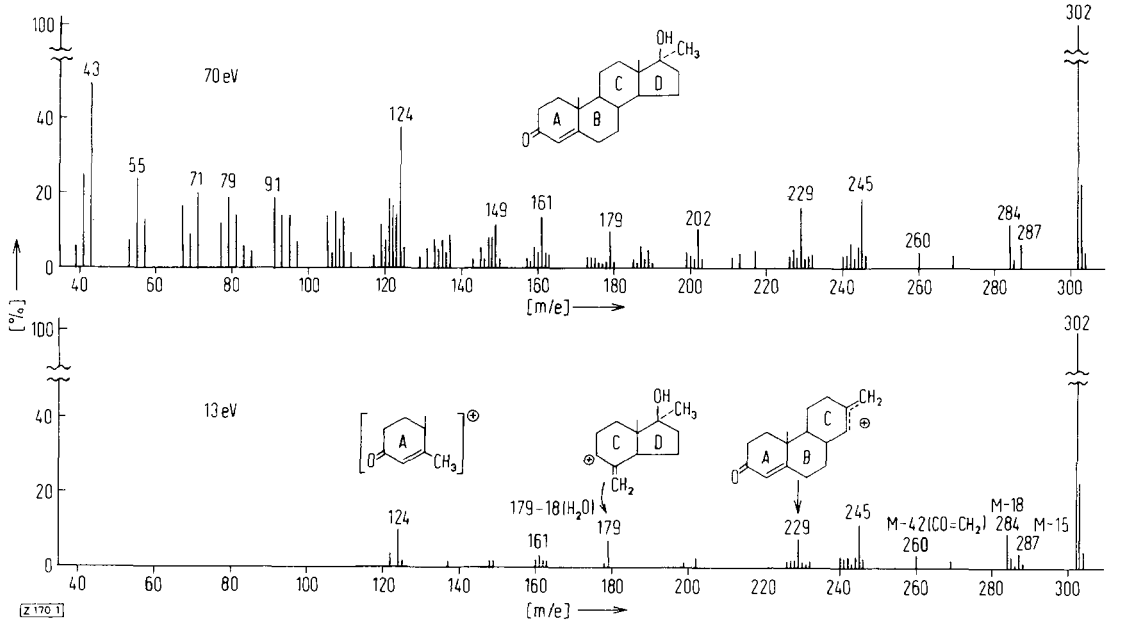
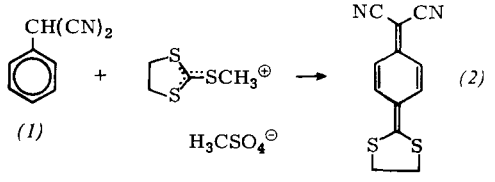


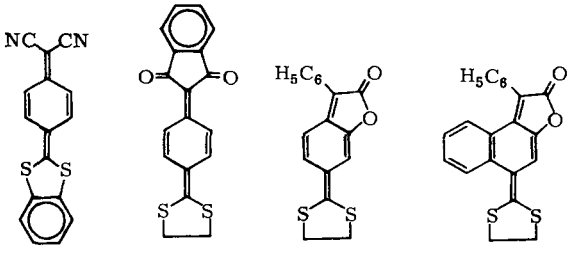

Fig. 1. Mass spectra of 17α-methyltestosterone at an ion-source temsperature of 70 °C (direct introduction of the sample into the ion source). Top: at 70 eV; bottom: at 13 eV. Increase in source temperature coniderably enhances fragmentation, making the spectra difficult to interpret. The fragment at m/e = 245 corresponds to loss of a 2-hydroxy-2-propenyl radical.

benzyl anions with carbonium ions and found that quinodimethanes can be synthesized in this way.

When benzylidene dicyanide *(1)* is heated with 2-methylthio-1,3-dithiolanium methyl sulfate in boiling glacial acetic acid/pyridine for *ca.* 112 hr, the deep blue, stable quinodimethane *(2)* results in approximately 50 % yield; it can be isolated by filtration. We have also obtained compounds *(3)* to *(6)* by analogous procedures; these products are also stable [compounds *(2)* to *(6)* decompose above 200 °C].



*(1)* *(2)*



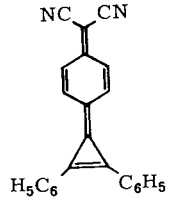
*(3)* *(4)* *(5)* *(6)*

The structure of compound *(2)* is derived from its NMR spectrum. The quinodimethanes *(2)*–*(4)* show a negative, and *(5)* and *(6)* a positive, halochromism (see Table).

| | Ultraviolet spectrum [a] in | | | |
|---|---|---|---|---|
| | $CHCl_3$ | | $CF_3CO_2H$ | |
| | $\lambda_{max}$ [mμ] | log ε | $\lambda_{max}$ [mμ] | log ε |
| *(2)* | 595 | 4.51 | 576 | 3.09 |
| | 550 | 4.69 | 535 | 3.02 |
| | 512 | 4.61 | 500 | 2.75 (S) |
| *(3)* | 638 | 4.75 | 612 | 1.70 |
| | 590 | 4.79 | 570 | 1.49 |
| | 547 | 4.57 | 540 | 1.18 (S) |
| *(4)* | 638 | 4.93 | 505 | 3.34 |
| | 585 | 4.89 | | |
| | 545 | 4.45 | | |
| | 512 | 4.22 (S) | | |
| *(5)* | 505 | 4.58 | 540 | 3.54 |
| *(6)* | 470 | 4.40 | 482 | 4.04 |

[a] Only the bands and groups of bands of longest wavelength are given. (S) = shoulder.

The generality of the reaction is illustrated by the preparation of the methylenecyclopropenes *(7)* by treatment of *(1)* with ethoxydiphenylcyclopropenylium tetrafluoroborate (in hot glacial acetic acid/pyridine). Infrared and NMR spectra are in accordance with the indicated structure. 2-Phenyl-1,3-indanedione appears to react analogously; however, we could isolate the corresponding quinodimethane only as a yellow perchlorate [$\lambda_{max}(CH_3CN)$ = 374, 320, 259 mμ; log ε = 4.50, 4.30, 4.21].



*(7)*

$\lambda_{max}(CHCl_3)$

509 mμ (log ε = 4.59)
309 mμ (log ε = 4.11)
294 mμ (log ε = 4.15)
282 mμ (log ε = 4.13)

Preliminary experiments have shown that *(1)* reacts also with amide acetals (which constitute potential carbonium ions) and related compounds.

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German version: Angew. Chem. 78, 545 (1966)

[1] *R. Waack* and *M. A. Doran*, J. physic. Chem. *68*, 1150 (1964).
[2] *G. Russell*, J. Amer. chem. Soc. *81*, 2017 (1959).
[3] *R. Gompper* and *E. Kutter*, Chem. Ber. *98*, 1365 (1965).

## Tricarbonyl-(1,6-methanocyclodecapentaene)-chromium

By Prof. Dr. E. O. Fischer and Dipl.-Chem. H. Rühle

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and

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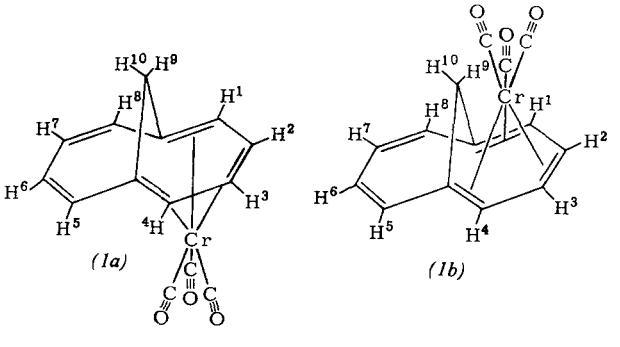
Cyclodecapentaenes substituted by a 1,6-bridge ($CH_2$, O, or NH) have recently become known and it has been deduced, chiefly from NMR-spectroscopic investigations, that they contain a delocalized 10 π-electron system [1–3]. In agreement therewith, an X-ray structure analysis [4] of 1,6-methanocyclodecapentaene-2-carboxylic acid showed that this compound contains an approximately planar $C_{10}$ perimeter, and that, in contrast to those in cyclooctatetraene, the lengths of the C–C bonds do not appreciably alternate. We have, therefore, studied the π-complex formation by such systems.

Irradiation [*] of a solution of 1,6-methanocyclodecapentaene and hexacarbonylchromium in octane under purified nitrogen for 87 hours, filtration of the dark red solution obtained, and concentration led to a solid red residue that, on recrystallization from benzene/pentane (1:1), gave dark reddish-violet, monomeric tricarbonyl - (1,6 - methanocyclodecapentaene) - chromium *(1)* (sinters above 126 °C with decomposition; soluble in benzene) in 65 % yield.

The carbonyl region of the infrared spectrum (in hexane) includes three strong ν-CO bands at 1976, 1919, and 1892 $cm^{-1}$. The NMR spectrum [at 60 Mc working frequency, chemical shift positive towards lower fields, tetramethylsilane as internal standard] is particularly informative [5]: In agreement with studies of tricarbonylnaphthalenechromium complexes [6], the $A_2B_2$ system of the half-ring not bound to the metal is shifted, in comparison with that of the free ligand, only by 26 cps to higher field, at 410 cps (H–5, H–8) and 389 cps (H–6, H–7). The protons of the half-ring bound to the metal form an $A_2B_2$ system with its center shifted by 110 cps at 374 cps (H–1, H–4) and 262 cps (H–2, H–3).



*(1a)* *(1b)*

The complex formation is particularly evident in the shift and splitting of the signals of the methylene protons: in the free ligand they are equivalent and lie at −25 cps; the equivalence disappears on complex formation, so that two doublets appear at −66 cps (H–10) and −104 cps (H–9),

with a coupling constant J = 8.8 cps; *i.e.* the tricarbonylchromium group must be asymmetrically bound to the ligand. We consider structures *(1a)* and *(1b)* to be compatible with these findings.

However, particularly in view of the molecular structure of dicarbonylnorbornadienecyclopentadienylmanganese, $C_5H_5Mn(CO)_2C_7H_8$ [8], which was originally deduced from NMR data [7] and subsequently confirmed by X-ray studies, the very large shift of the methylene protons of compound *(1)* to higher field makes structure *(1b)* appear the more probable. An X-ray analysis is in progress.

Reaction of 1,6-methanocyclodecapantaene with hexacarbonylmolybdenum gave two pale red complexes, one of which is apparently analogous to compound *(1)*.

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German version: Angew. Chem. *78*, 548 (1966)

[1] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964); *E. Vogel* and *W. A. Böll*, Angew. Chem. *76*, 784 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964); *E. Vogel*, *M. Biskup*, *W. Pretzer*, and *W. A. Böll*, Angew. Chem. *76*, 785 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964); *E. Vogel*, *W. Pretzer*, and *W. A. Böll*, Tetrahedron Letters *1965*, 3613.

[2] *F. Sondheimer* and *A. Shani*, J. Amer. chem. Soc. *86*, 3168 (1964).

[3] *H. Günther*, Z. Naturforsch. *20b*, 948 (1965).

[4] *M. Dobler* and *J. D. Dunitz*, Helv. chim. Acta *48*, 1429 (1965).

[5] We thank Drs. *C. G. Kreiter* and *K. E. Schwarzhans* for numerous discussions.

[*] High-pressure Hg lamp Q 81, Quarzlampen GmbH, Hanau (Germany).

[6] *C. G. Kreiter*, Dissertation, Universität München, 1964.

[7] *H. P. Fritz* and *H. Keller*, Chem. Ber. *96*, 1676 (1963).

[8] *E. O. Fischer* and *M. Herberhold*: Essays in Coordination Chemistry. Experientia Supplementum IX, Birkhäuser, Basel 1964, p. 275.

## β-Hetero-Substituted Lithium Alkyls and Alkenyls

By Dr. M. Schlosser and Dr. V. Ladenberger [*]

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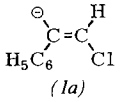
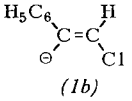
der Universität Heidelberg (Germany)

Results of H–D exchange experiments with styryl chlorides [1] indicated that the carbanions *(1a)* and *(1b)* can exist.



*(1a)*



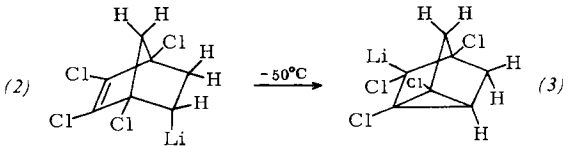
*(1b)*

Accordingly, organometallic compounds of the type 2-chlorovinyl- and 2-chloroethyl-lithium should also occur, at least transiently. However, in the only β-hetero-substituted organolithium compounds hitherto isolated the C–Li bond is part of a ring system, or is stabilized by an α-substituent capable of mesomerism or by an accumulation of neighboring fluorine atoms.

We have treated some β-hetero-substituted alkyl and alkenyl iodides with butyl-lithium in a solvent mixture of methylal, tetrahydrofuran, ether, and pentane (2:2:1:1) at −130 °C [2]. The "vicinal counter-polarized" compounds listed in the table were formed by iodine-lithium exchange; for characterization they were carboxylated, the resulting acids were esterified with diazomethane, and the methyl esters either separated and analysed or identified by gas-chromatography.

| β-Hetero-substituted lithium compound | Methyl ester, yield [%] |
|---|---|
| Cl–CH=CH–Li (*trans*) | 0 |
| Cl–CH=CH–Li (*cis*) | 0.2 |
| $Cl–CH_2–CH_2–Li$ | 5.0 |
| $F–CH_2–CH_2–Li$ | 8.0 |
| $H_3CO–CH_2–CH_2–Li$ | 5.3 |
| *(2)* | 42 |

At −50 °C 1,4,5,6-tetrachlorobicyclo[2.2.1]-5-hepten-2-yl-lithium *(2)* rearranges to the tricyclene derivative *(3)* [3]. On carboxylation and treatment with diazomethane the compounds *(2)* and *(3)* give methyl esters of m.p. 86–88 °C and 63–65 °C, respectively; hydrolysis leads to chlorinated hydrocarbons: from *(2)* to crystals of m.p. 38–40 °C [4]; from *(3)* to a colorless liquid. C–H analyses and infrared, NMR, and mass spectra prove the structures.

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German version: Angew. Chem. *78*, 547 (1966)

[*] We thank the Deutsche Forschungsgemeinschaft for generous support.

[1] *M. Schlosser* and *V. Ladenberger*, unpublished work.

[2] For the preparation and stability of "geminal counter-polarized" compounds in THF at low temperatures see *G. Köbrich*, Angew. Chem. *77*, 75 (1965); Angew. Chem. internat. Edit. *4*, 49 (1965).

[3] *G. Wittig* and *E. Hahn*, Angew. Chem. *72*, 781 (1960); *G. Wittig* and *J. Otten*, Tetrahedron Letters *1963*, 601; *G. Wittig* and *G. Klumpp*, *ibid. 1963*, 607.

[4] *C. F. Wilcox* and *J. G. Zajacek*, J. org. Chemistry *29*, 2209 (1964).

## Octamethyltetracyclo[2.2.0.0$^{2,6}$.0$^{3,5}$]hexane-1,4-dimethanol, a New Derivative of Prismane

By Prof. Dr. R. Criegee and Dr. R. Askani

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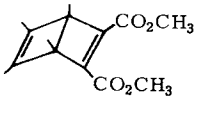
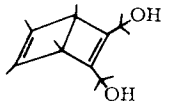
der Technischen Hochschule Karlsruhe (Germany)

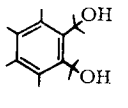
With an excess of methylmagnesium iodide at −30 °C, the dimethyl ester *(1)* [1] of "Dewar phthalic acid" (dimethyl 1,4,5,6 - tetramethylbicyclo[2.2.0]hexa - 2,5 - diene - 2,3-dicarboxylate) gives in 69% yield octamethylbicyclo[2.2.0]-hexa-2,5-diene-2,3-dimethanol *(2)*, m.p. 136–137 °C (on rapid heating). This product is almost unchanged when heated for 5 min at 200 °C; when heated for several hours at 200 °C it affords 1,3-dihydrooctamethylisobenzobenzofuran *(4)* by dehydration of the expected aromatic compound *(3)*. Only the less hindered double bond of compound *(2)* reacts on catalytic hydrogenation ($Pt/H_2$) in methanol or on treatment with ozone in methanol at −78 °C. On being boiled with *p*-toluenesulfonic acid in benzene, compound *(2)* is converted into heptamethylindene *(5)*.



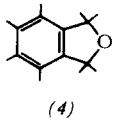
*(1)*



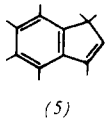
*(2)*



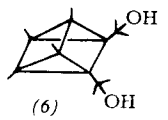
*(3)*



*(4)*



*(5)*

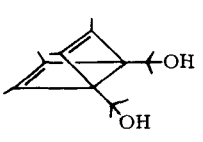


*(6)*

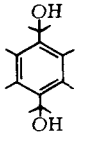
Irradiation (100 watt low-pressure mercury lamp; Messrs. Gräntzel, Karlsruhe) of a 1% solution of compound *(2)* in ether leads to at least three isomers: the aromatic compound *(3)* (20–25%; slightly soluble in ether), the prismane

derivative octamethyltetracyclo[2.2.0.0$^{2,6}$0$^{3,5}$]hexane-1,4-dimethanol *(6)* (22%), and octamethylbicyclo[2.2.0]hexa-2,5-diene-1,4-dimethanol *(7)* (6%).

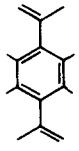
Compound *(6)* can be purified by recrystallization from ethyl acetate (m.p. ≈ 130 °C). It is extremely sensitive to acids, which reconvert it into *(2)* rapidly and exothermally even in the cold. However, when heated in pyridine at 100 °C it isomerizes predominantly to the diol *(7)* [isomeric with *(2)*], which is purified by recrystallization from ethyl acetate and itself isomerizes at 170 °C to the diol *(8)*. When *(7)* is boiled with *p*-toluenesulfonic acid in benzene, 1,4-diisopropenyl-2,3,5,6-tetramethylbenzene *(9)* is formed. Irradiation of *(7)*, under the conditions used for *(2)*, also leads to the prismane derivative *(6)*. The compound *(6)* is the second known example of this highly strained ring system, the first being 1,2,5-tri-t-butylprismane[2].




*(7)*




*(8)*



*(9)*

Appropriate elemental analyses have been obtained for compounds *(2)* to *(9)*; ultraviolet and infrared spectra agree with the structures assigned. The NMR data on which the structures are based are given in the table.

NMR spectra of compounds *(2)* to *(9)* in $CCl_4$ (tetramethylsilane as internal standard; τ values in ppm; d = doublet; q = quadruplet; m = multiplet; other signals are singlets).

| Compound | $CH_3$ on: C sat. | $(CH_3)_2COH$ | C=C | C arom. | H on C=C | Intensity ratio |
|---|---|---|---|---|---|---|
| *(2)* | 8.96 | 8.83<br>8.77 | 8.48 | | | 1:1:1:1 |
| *(3)* [*] | | 8.06 | | 7.91<br>7.70 | | 2:1:1 |
| *(4)* | | 8.53 | | 7.86<br>7.82 | | 2:1:1 |
| *(5)* | 8.67 | | 7.76 (d) | 7.82<br>7.66<br>7.60 | 4.22 (q) | 6:3:6:3:3:1 |
| *(6)* | 8.85 | 8.80 | | | | 1:1 |
| *(7)* | | 8.63 | 8.30 | | | 1:1 |
| *(8)* [*] | | 8.10 | | 7.54 | | 1:1 |
| *(9)* | | | 8.11 (m) | 7.89 | 5.35 (m)<br>4.82 (m) | 3:6:1:1 |

[*] In pyridine solution.

Received: March 18th, 1966 [Z 187/12 IE]
German version: Angew. Chem. *78*, 494 (1966)

[1] *R. Criegee* and *F. Zanker*, Angew. Chem. *76*, 716 (1964), Angew. Chem. internat. Edit. *3*, 695 (1964); Chem. Ber. *98*, 3838 (1965).

[2] *K. E. Wilzbach* and *L. Kaplan*, J. Amer. chem. Soc. *87*, 4004 (1965).

## C-Azido-N-sulfonylformamidines and their Rearrangement to 5-(N-Sulfonylamino)tetrazoles

By Doz. Dr. R. Neidlein and E. Heukelbach

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We have obtained the (to our knowledge new) *C*-azido-*N*-sulfonylformamidines *(2)*[1] by addition of hydrazoic acid to *N*-sulfonylcarbodiimides *(1)*[2–4]. Equimolar amounts of

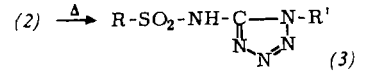
$$R\text{–}SO_2\text{–}N{=}C{=}N\text{–}R' \rightarrow R\text{–}SO_2\text{–}NH\text{–}C(N_3){=}N\text{–}R'$$
*(1)* *(2)*

the reactants are kept together for about 8 days in anhydrous benzene at room temperature with exclusion of moisture, and the solvent is then removed at not more than +5 °C. At higher temperatures there is a danger of the rearrangement *(2)* → *(3)*.

| | R | R' | M.p. (decomp.) [°C] | Yield [%] |
|---|---|---|---|---|
| *(2a)* | $C_6H_5$ | $(CH_3)_2CH$ | 69–71 | 69 |
| *(2b)* | $C_6H_5$ | $CH_3(CH_2)_3$ | 68–69 | 78 |
| *(2c)* | $C_6H_5$ | $CH_3(CH_2)_2$ | 70–71 | 75 |
| *(2d)* | $C_6H_5$ | $(CH_3)_2CH\text{–}CH_2$ | 65–66 | 79 |
| *(2e)* [*] | $C_6H_5$ | $C_6H_{11}$ | 110–111 | 54 |

[*] Compounds *(2f)* to *(2k)* (cf. the second table) were obtained only as oils. Distillation was not attempted because of the danger of explosion and rearrangement. The infrared spectra of the oils showed one intense azide band; the carbodiimide bands were absent.

*C*-Azido-*N*-sulfonylformamidines have infrared absorption bands between 2140 and 2160 $cm^{-1}$ characteristic of the $N_3$ group; bands due to the NH group occur between 3060 and 3200 and between 1590 and 1625 $cm^{-1}$.




*(3)*

When the formamidines *(2)* are heated in boiling anhydrous toluene for several hours they rearrange to substituted 5-(*N*-sulfonylamino)tetrazoles *(3)*. The structures of compounds *(3)* were proved by their infrared spectra. Thin-layer chromatography shows that they are single substances. The acidic hydrogen in compounds *(3)* can be titrated accurately with bases such as 0.1 N NaOH in ethanol.

| | R | R' | M.p. [°C] | Yield [%] |
|---|---|---|---|---|
| *(3a)* | $C_6H_5$ | $(CH_3)_2CH$ | 113–114 | 93 |
| *(3b)* | $C_6H_5$ | $CH_3(CH_2)_3$ | 96–97 | 90 |
| *(3c)* | $C_6H_5$ | $CH_3(CH_2)_2$ | 99–100 | 83 |
| *(3d)* | $C_6H_5$ | $(CH_3)_2CH\text{–}CH_2$ | 155–156 | 87 |
| *(3e)* | $C_6H_5$ | $C_6H_{11}$ | 197–198 | 88 |
| *(3f)* | $C_6H_5$ | $(CH_3)_3C$ | 165–166 | 64 |
| *(3g)* | $CH_3$ | $(CH_3)_2CH$ | 118–120 | 72 |
| *(3h)* | $CH_3$ | $CH_3(CH_2)_2$ | 72–73 | 68 |
| *(3i)* | $CH_3$ | $(CH_3)_2CH\text{–}CH_2$ | 74–76 | 60 |
| *(3k)* | $CH_3$ | $(CH_3)_3C$ | 132–133 | 75 |

Received: March 21st, 1966 [Z 190/25 IE]
German version: Angew. Chem. *78*, 548 (1966)

[1] For the very stable, water-insoluble *C*-chloro-*N*-sulfonylformamidines see *R. Neidlein* and *W. Haussmann*, Tetrahedron Letters, in press.

[2] *R. Neidlein* and *E. Heukelbach*, Tetrahedron Letters *1965*, 149.

[3] *R. Neidlein* and *E. Heukelbach*, Tetrahedron Letters *1965*, 2665.

[4] *B. Anders* and *E. Kühle*, Angew. Chem. *77*, 430 (1965), Angew. Chem. internat. Edit. *4*, 430 (1965).

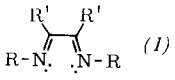
## 1,4-Diazabutadiene-Metal Carbonyls [1]

By Priv.-Doz. Dr. H. Bock and Dipl.-Chem. H. tom Dieck[2]

Institut für Anorganische Chemie
der Universität München (Germany)

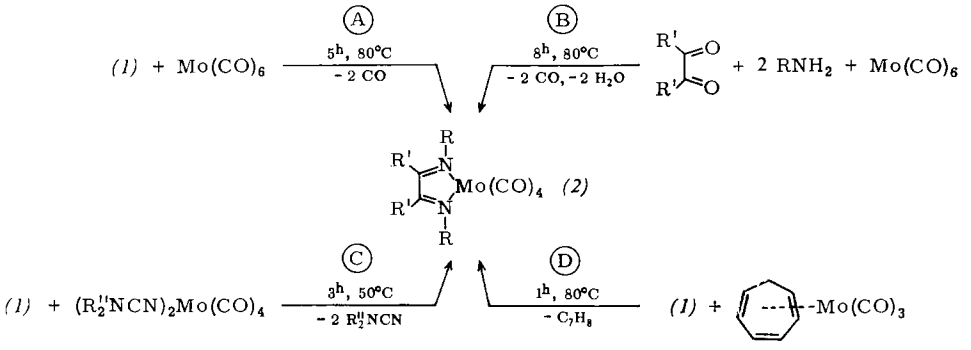
The n-orbitals of *cis-anti*-1,4-diaza-1,3-butadienes *(1)* are in positions that are geometrically favorable for formation of bidentate donor bonds. Since, moreover, the lowest unoccupied π*-level (symmetry $B_2$) of *(1)* has the symmetry

and energy required for π back-donation from metal d-functions, we expected [3] that these compounds would be suitable as metal(0) ligands.



*(1)*

Diazabutadienemolybdenum tetracarbonyls *(2)* are obtained as indicated in the scheme below, with benzene as solvent. The compounds have a metallic luster, are mostly stable to atmospheric oxygen, and give blue to orange-red solutions. The complexes are precipitated from the reaction solution either immediately or on concentration. They can be recrystallized from benzene when necessary.

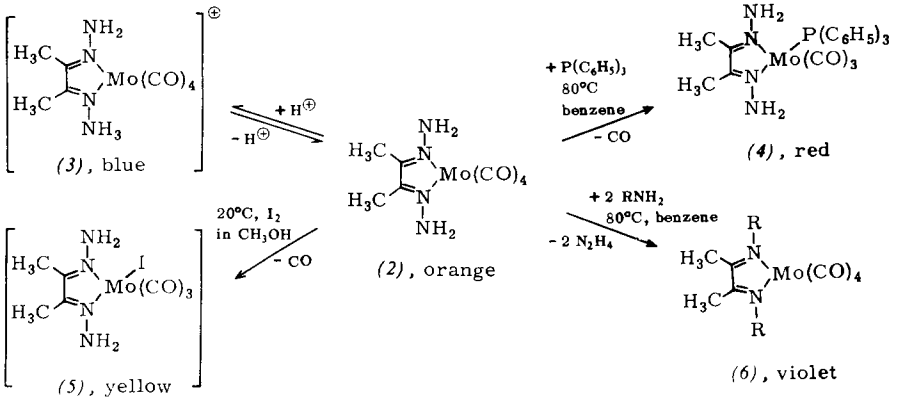


$R' = C_6H_5$; $R = OH$

$R' = CH_3$; $R = OH$, $OCH_3$, $NH_2$, $N(CH_3)_2$, Alkyl, Aryl

$R'' =$ Alkyl, Cyclopropyl, $C_6H_{11}$, Benzyl, $C_6H_5$, p-Cl-$C_6H_5$, etc.

Process A is generally applicable; process B, as a complex-induced synthesis, is the most elegant method for difficultly accessible ligands (*e.g.* R = alkyl [4]). Process C has proved advantageous for the preparation of thermally sensitive complexes *(2)* (*e.g.* R = OH or OH/$NH_2$) in a pure state.



*(3)*, blue

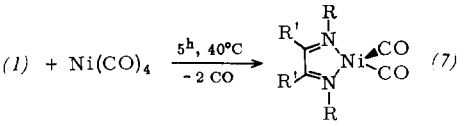
*(4)*, red

*(5)*, yellow

*(6)*, violet

All the complexes with R = $NH_2$ or $N(CH_3)_2$ are reversibly protonated by concentrated mineral acids, yielding *(3)*. The diazabutadiene ligand is not removed by triphenylphosphine, which, instead, replaces carbon monoxide, yielding the tricarbonyl derivative *(4)*. The complexes *(2)* are not oxidized by mercuric oxide or silver oxide; reaction with iodine in methanol gives presumably carbonyl iodides *(5)*. Remarkably, primary amines replace the hydrazone group by an imine group [see *(6)*].

Formation of diazabutadiene-metal carbonyls is not restricted to molybdenum. Analogous complexes are formed from chromium and tungsten hexacarbonyls by method A on additional ultraviolet irradiation. Nickel tetracarbonyl reacts with some ligands *(1)* even at room temperature, yielding diazabutadienenickel dicarbonyls *(7)* that are insensitive to air, have a metallic luster, and give wine-der solutions [5].



*(7)*

$C_{2v}$ symmetry and diamagnetism is demonstrated for the chromium, molybdenum, tungsten, and nickel compounds by their infrared and $^1$H-NMR spectra. An intense, long-wavelength absorption is characteristic of all the diazabutadiene-metal(0) complexes, largely independent of the nature of the central metal and the substituents R on the nitrogen; the maxima (in cyclohexane 18000–19000 $cm^{-1}$; in methanol 19000–21000 $cm^{-1}$) are more strongly influenced by solvatochromism ($\Delta\nu_m$ = 2000–3000 $cm^{-1}$) than by the substituents R on the nitrogen ($\Delta\nu_m$ = 1000–2000 $cm^{-1}$). The molar extinctions lie between 5000 and 12000 l $mole^{-1}$ $cm^{-1}$. These long-wavelength bands can be assigned to an allowed $A_2$–$B_2$ transition, which arises from an $A_2$ combination of metal d-orbitals into the lowest antibonding state of the system (interaction of the unoccupied ligand orbital $\Psi_3$ ($B_2$) with the $B_2$ combination of two d-orbitals).

Received: March 16th, 1966 [Z 193/28 IE]
German version: Angew. Chem. 78, 549 (1966)

[1] Part 4 of Metal(0) Compounds with Non-aromatic Nitrogen π-Systems. – Part 2: *H. Bock* and H. tom Dieck, Chem. Ber. *99*, 213 (1966).

[2] Part of the Dissertation of *H. tom Dieck*, Universität München, 1966.

[3] Part 3: *H. Bock* and *H. tom Dieck*, Z. anorg. allg. Chem., in press.

[4] Peralkylated diazabutadienes *(1)* (R = $CH_3$, R' = cyclopropyl, cyclohexyl, or benzyl) can be obtained in 10–35% yield by direct condensation of biacetyl and a primary amine in benzene at 980 °C.

[5] In view of the lower donor strength of compounds *(1)*, comparison of the CO stretching frequencies of 2,2'-bipyridylnickel dicarbonyl [6] and the diazabutadienenickel dicarbonyls *(7)* (*e.g.* R = $OCH_3$: $A_1$ = 2012, $B_2$ = 1946 $cm^{-1}$ in Nujol) leads to the expectation that bisdiazabutadienenickel(0) will exist (cf. also [7]).

[6] *R. S. Nyholm* and *L. N. Short*, J. chem. Soc. (London) *1953*, 2670.

[7] *H. Behrens* and *A. Müller*, Z. anorg. allg. Chem. *341*, 124 (1965).

## Germyl Compounds of Strontium, Barium, and Zinc

By Univ.-Doz. Dr. E. Amberger, Dipl.-Chem. W. Stoeger, and Dr. R. Hönigschmid-Grossich

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Whereas silyl, $M^{II}(SiR_3)_2$, and stannyl derivatives, $M^{II}(SnR_3)_2$, (R = $CH_3$, $C_6H_5$) of the elements of the second main group and sub-group have been extensively studied [1,2], analogous germyl compounds $M^{II}(GeR_3)_2$ have hitherto been unknown.

Hexaphenyldigermane reacts with strontium or barium in the molecular ratio 1:1 in liquid ammonia at −40°C, giving bis(triphenylgermyl)metal derivatives *(1)*.

$$(C_6H_5)_3Ge{-}Ge(C_6H_5)_3 + M^{II} \rightarrow M^{II}[Ge(C_6H_5)_3]_2$$
($M^{II}$ = Sr, Ba) *(1)*

After removal of the ammonia at −35 °C the products are extracted with tetrahydrofuran as yellow solutions, whence they are recovered by evaporation of the tetrahydrofuran and drying *in vacuo* (2 days at 40 °C) as THF adducts (1:1). They decompose with blackening without melting at 40 to 45 °C (Sr) and 60 to 70 °C (Ba). The adducts are sensitive to air and somewhat to light, reduce $AgNO_3$ to Ag, and are soluble in ammonia but insoluble in benzene and hydrocarbons; they are unstable in solution. Their compositions were proved by determination of the content of alkaline-earth metal and by C–H analysis. The THF-free compounds *(1)* could not be obtained.

Only small amounts of hydrogen are obtained on hydrolysis with moist methanol because of the stability of triphenylgermane against hydrolysis:

$$M^{II}[Ge(C_6H_5)_3]_2 + H_2O \xrightarrow{\text{Fast}} HGe(C_6H_5)_3 + M^{II}(OH)_2$$

$$(C_6H_5)_3GeH + H_2O \xrightarrow{\text{Slow}} (C_6H_5)_3GeOH + H_2$$

The triphenylgermane formed, and the tetrahydrofuran liberated from the THF adducts by heating *in vacuo*, were identified by infrared spectroscopy. Ammonolysis, as observed for the analogous silyl compounds [1], could not be established.

Preparation of bis(triphenylgermyl)zinc *(2)* was achieved by reaction of zinc chloride with triphenylgermyl-sodium or -potassium in liquid ammonia (molar ratio 1:2, −40 °C).

$$2\ M^{I}Ge(C_6H_5)_3 + ZnCl_2 \rightarrow Zn[Ge(C_6H_5)_3]_2 + 2\ M^{I}Cl$$
($M^{I}$ = K, Na) *(2)*

After removal of the ammonia *in vacuo* at −35 °C the product *(2)* was extracted into tetrahydrofuran (yellow solution). On evaporation of the solvent there remained a yellow adduct *(2)*·THF [reaction with $KGe(C_6H_5)_3$] or a pale yellow adduct $Zn[Ge(C_6H_5)_3]_2 \cdot 0.5THF \cdot 0.5NH_3$ [reaction with $NaGe(C_6H_5)_3$]. Both these adducts decomposed at 110 to 120 °C, resembled *(1)*·THF in properties, and were analogously identified.

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German version: Angew. Chem. *78*, 549 (1966)

[1] *E. Wiberg, O. Stecher, H. J. Andrascheck, L. Kreuzbichler*, and *E. Staude*, Angew. Chem. *75*, 516 (1963); Angew. Chem. internat. Edit. *2*, 507 (1963).

[2] *R. Egger*, Dissertation, Universität München, 1961.

## Correlation between Phosphorylation and Chlorophyll-b Dissociation in Photosynthesis

By Dr. B. Rumberg, Dipl.-Phys. P. Schmidt-Mende, Dipl.-Ing. U. Siggel, and Prof. Dr. H. T. Witt

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Technische Universität Berlin (Germany)

In the primary processes of photosynthesis, electrons are transferred from water to triphosphopyridine nucleotide. The rate of the electron transport is characterized by the rate of the oxygen production which takes place simultaneously; the intermediates can be identified by the wavelength of absorption changes on irradiation with flashes of light. The mechanism of the electron transport follows *inter alia* from the analysis of the kinetics of absorption changes [1]. A cyclic and a non-cyclic phosphorylation can be coupled with the electron transport [2].

The absorption changes at 478, 515, and 648 mμ are caused by a reaction of chlorophyll-b (Chl-b). This reaction, however, evidently does not participate directly in the electron transport [3]. Addition of ethanol eliminates the absorption changes of Chl-b without affecting those of Chl-$a_I$, Cyt-f, Cyt-b, and plastoquinone (PQ), or the oxygen production. We have now found that the reaction of Chl-b is related directly to phosphorylation coupled to electron transport: The electron transport is not affected when the phosphorylation is blocked by a specific poison, such as desaspidine [2,4]. Confirmation of these results is shown in Fig. 1.

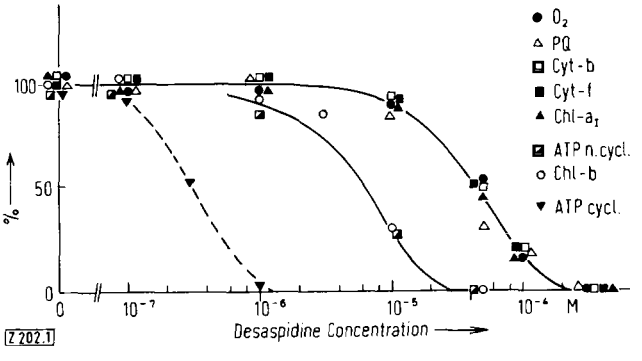


Fig. 1. Oxygen production, non-cyclic phosphorylation, cyclic phosphorylation, and absorption changes of plastoquinone (PQ) (at 254 mμ), cytochrome-b (Cyt-b) (at 405 mμ), cytochrome-f (Cyt-f) (at 405 mμ), chlorophyll-$a_I$ (Chl-$a_I$) (at 703 mμ), and chlorophyll-b (Chl-b) (at 515 mμ), as a function of the desaspidine concentration in illuminated spinach chloroplasts.

The 100% rates correspond to 38 μmole $O_2$/(h·mg Chl) for the $O_2$-production, to 116 μmole ATP/(h·mg Chl) for the non-cyclic, and to 240 μmole ATP/(h·mg Chl) for the cyclic phosphorylation. All measurements were performed 10 min after addition of desaspidine. Excitation time 5 min for $O_2$-production, 0.02 sec for absorption change; light intensity $3 \times 10^5$ ergs $cm^{-2}$ $sec^{-1}$. Temperature 20 °

Reaction volume 3 ml; chlorophyll content 0.1 mg. Additives (in μmole) for $O_2$-production: tris buffer 150 (≈ pH 7.2), $K_3Fe(CN)_6$ 10; for non-cyclic phosphorylation: tris buffer 80 (= pH 8), $MgCl_2$ 10, $K_2HPO_4$ 20, ADP 10, benzylviologen 0.1; for cyclic phosphorylation (anaerobic): tris buffer 80 (= pH 8), $MgCl_2$ 10, $K_2HPO_4$ 20, ADP 10, *N*-methylphenazonium methyl sulfate 0.1, *N*-(*p*-chlorophenyl)-*N'*,*N'*-dimethylurea 0.06; for absorption changes: as for $O_2$-production or non-cyclic phosphorylation. Oxygen determined manometrically, ATP with $^{32}P$ according to [6]. Separation of the absorption changes of cytochromes according to [7].

At desaspidine concentrations of $10^{-7}$ M the cyclic and the non-cyclic phosphorylation (measured by the formation of ATP) and the electron transport (measured by $O_2$-production) are unchanged. With $10^{-6}$ M desaspidine, cyclic phosphorylation is blocked, and only at $2\times10^{-5}$ M non-cyclic phosphorylation as well. The $O_2$-production, *i.e.* the electron transport, is not blocked at desaspidine concentrations below $2\times10^{-4}$ M. The absorption changes of the participants of electron transport such as Chl-aI, Cyt-f, Cyt-b, and PQ show the same dependence on the concentration of desaspidine as the $O_2$-production. However, the reaction of Chl-b parallels the behavior of the non-cyclic phosphorylation (Fig. 1). Addition of ethanol also blocks phosphorylation without interrupting the electron transport[5].

From the position of the absorption changes of chlorophyll-b it can be supposed that a dissociation of $H^+$-ions[8] from chlorophyll-b takes place. Obviously phosphorylation and this dissociation (pH-change) are related to each other.

Received: April 12th, 1966 [Z 202 IE]
German version: Angew. Chem. *78*, 550 (1966)

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[2] *Z. Gromet-Elhanan* and *D.I. Arnon*, Plant Physiol. *40*, 1060 (1965).
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[4] *H. Baltscheffsky* and *D.Y. de Kiewiet*, Acta chem. scand. *18*, 2406 (1964).
[5] *H. Baltscheffsky*, Acta chem. scand. *17*, 308 (1963).
[6] *M. Avron*, Biochim. biophysica Acta *40*, 257 (1960).
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[8] *A. Weller*, J. Amer. chem. Soc. *76*, 5819 (1954).

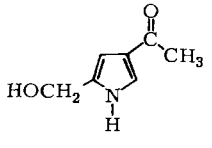
# CONFERENCE REPORTS

## Recent Results of Antibiotics Research

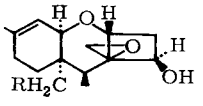
*Ch. Tamm*, Basel (Switzerland)

To date, 14 antibiotics termed verrucarines and roridines[1] have been isolated from *Myrothecium verrucaria* and *M. roridum*. The principal products are antifungal and, in particular, potent cytostatic agents; however, they are also very toxic

Verrucarine E, one of the minor N-containing metabolites, has been assigned the structure of the hitherto unknown 4-acetyl-2-hydroxymethylpyrrole *(1)*. On basic hydrolysis, verrucarines A, B, J, and H, and roridines A, D, and E, yield the same sesquiterpene alcohol, verrucarol ($C_{15}H_{22}O_4$), but they differ in the products of acidic hydrolysis. Verrucarine A ($C_{27}H_{34}O_9$) gives *cis,trans*-muconic acid and verrucarinolactone ($C_6H_{10}O_3$), verrucarine B ($C_{27}H_{32}O_9$) gives *cis,trans*-muconic acid and 2,3-epoxy-3-methyl-5-valerolactone ($C_6H_8O_2$); verrucarine J ($C_{27}H_{32}O_8$) gives *cis,trans*-muconic acid and the known 3-methyl-2-pentenolactone (anhydromevalolactone) ($C_6H_8O$); roridine A ($C_{29}H_{40}O_9$) gives roridinic acid ($C_{14}H_{22}O_7$), roridine D ($C_{29}H_{38}O_8$) gives anhydroepoxyroridinic acid ($C_{14}H_{20}O_7$); roridine E ($C_{29}H_{38}O_8$) gives anhydrororidinic acid ($C_{14}H_{20}O_6$); and verrucarine H ($C_{29}H_{36}O_8$) gives 3-methyl-2-pentenolactone and myrothecinic acid ($C_8H_{10}O_8$). The structures and stereochemistry of the new lactones and dicarboxylic acids have been elucidated. The constitutions of verrucarol *(2)* and roridine C (= trichodermol) *(3)* were derived by correlation with trichothecolone and trichodermine[2].



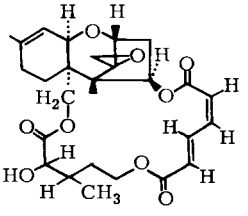
*(1)*



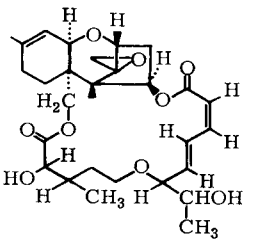
*(2)* R = OH; *(3)* R = H

Numerous rearrangements were observed with verrucarol and trichothecolone, some of which were discussed in detail. Oxidative degradations and partial hydrolyses showed that the above hydrolysis products are linked in the original antibiotics in the form of macrocyclic di- and tri-esters[3]. For instance, formulae *(4)* and *(5)* were derived for the two principal metabolites verrucarine A and roridine A, respectively. These many-membered cyclic esters present a new structural type.

Experiments on the biosynthesis of verrucarine A and roridine A with [2-$^{14}$C]mevalonate show that mevalonate is a biogenetic precursor of verrucarol and verrucarinic acid;



*(4)*



*(5)*

degradation experiments showed that the radioactivity of the verrucarinic acid was derived from C-2 of mevalonate.

[Lectures given at Freiburg, Göttingen, and Marburg (Germany), on December 3rd, 1965, and January 20th and 21st, 1966] [VB 983/290 IE]

German version: Angew. Chem. *78*, 496 (1966)

[1] *E. Härri et al.*, Helv. chim. Acta *45*, 839 (1962); *B. Böhner et al., ibid. 48*, 1079 (1965).
[2] *J. Gutzwiller et al.*, Helv. chim. Acta *47*, 2234 (1964); *J. Gutzwiller, Ch. Tamm*, and *H. P. Sigg*, Tetrahedron Letters *1965*, 4495.
[3] *J. Gutzwiller* and *Ch. Tamm*. Helv. chim. Acta *48*, 157, 177 (1965); *W. Zürcher, J. Gutzwiller*, and *Ch. Tamm, ibid. 48*, 840 (1965); *E. Fetz, B. Böhner*, and *Ch. Tamm, ibid. 48*, 1669 (1965).

## Synthesis and Decomposition of Organic Peroxides

*A. Rieche*, Berlin (Germany)

According to the "RH scheme"[1] of oxygen attack on organic compounds, the first products to be isolated are alkyl hydroperoxides, in accordance with reaction (a). The radicals initiating the chain reaction are formed, according to *Dulog*, by dehydrogenation [reaction (b)]. The hydroperoxides act autocatalytically by partial decomposition into radicals [reactions (c) and (d)].

$$RH + O_2 \rightarrow ROOH \quad (a)$$

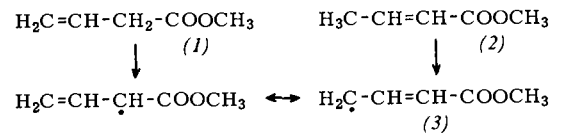
$$RH + O_2 \rightarrow R\cdot + \cdot OOH \quad (b)$$

$$ROOH \rightarrow RO\cdot + \cdot OH \quad (c)$$

$$2\,ROOH \rightarrow RO\cdot + ROO\cdot + H_2O \quad (d)$$

Decomposition of hydroperoxides and peroxidation are reactions of the same order: at very low concentrations they are usually of the first order, at higher concentrations of the second order (owing to dimerization). In ethers, hydroperoxides decompose at all concentrations by a reaction of the first order; here adducts ROOH·R′OR″ are present.

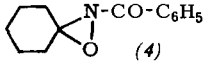
On peroxidation of unsaturated compounds, several isomeric alkyl hydroperoxides may arise, according to the number of double bonds. The cause of this is the mesomerism of allyl radicals formed by reaction (b), *e.g.* from methyl 3-butenoate *(1)* and crotonate *(2)*.



Although the butenoate *(1)* is more easily oxidized, the hydroperoxide derived from *(3)* is the main product obtained from the two esters. The formation of isomeric alkyl hydroperoxides makes it difficult to study the aerial oxidation of natural unsaturated oils and rubbers, so experiments to this end have been carried out with unsaturated model substances [2]. We were able to synthesize allyl hydroperoxide [3]; it proved to be surprisingly stable.

Ozonolysis of olefins in the presence of amines afforded geminal hydroperoxyamines $RHN-\overset{|}{\underset{|}{C}}-OOH$ (by way of the zwitterion $\rangle C^{+}-OO^{-}$), which are also obtained from Schiff bases and $H_2O_2$; they are precursors of 2-alkyloxaziridines. On treatment with ammonia and ozone, olefins give isooximes (3-substituted oxaziridines) ("ammozonization").

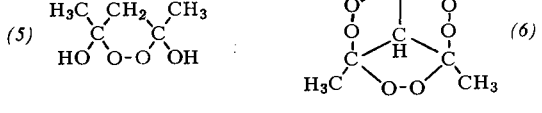
Cyclohexanone isooxime was isolated as its *N*-benzoyl derivative *(4)*, which is also formed on ozonization of bi-(cyclohexylidene) in the presence of benzamide.



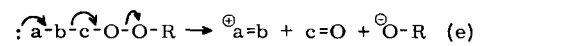
*(4)*

Peroxidation of nitrogen compounds occurs at the carbon atom next to the nitrogen atom. Tetrahydroisoquinoline and azepine give peroxides ROOR directly, by way of hydroperoxides ROOH. Hydrazones and hexanolactam give hydroperoxides; pyrrolidone gives $H_2O_2$ and succinimide.

Cyclic peroxides such as *(5)* and *(6)* are obtained from β-diketones and "triacetylmethane" by means of $H_2O_2$. Like acetals, compounds of type *(5)* readily undergo exchange of OH groups for OOH or OOR by way of cations stablized by mesomerism. The symmetrical peroxide *(6)* has a high melting point and is chemically unusually stable, although explosive.



Preparative use of peroxides has received new impulses by the discovery of "fragmentable" peroxides. Polar cleavage and synchronous electron shifts lead, by reaction (e), to only a few fragments, whereas radical decomposition of peroxides yields a large number of products.



This method leads, for instance, to quantitative cleavage of 2,3,4,6-acetylated t-butyl glucosyl peroxide into arabinose, formic acid, and t-butyl alcohol (a new method of sugar degradation).

The so-called halogen-induced oxidation, hitherto incorrectly interpreted, has been clarified. β-Bromo hydroperoxides are obtained from olefins, HBr, and oxygen [4].

[Lectures at Magdeburg and Berlin (Germany), January 6th and January 21st, 1966] [VB 987/293 IE]

German version: Angew. Chem. *78*, 496 (1966)


[1] *A. Rieche*, Angew.Chem.*50*, 520 (1937); *A. Rieche, E.Schmitz*, and *M. Schulz*, Z. Chem. *3*, 443 (1963).

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## Modern Methods for Electrical Indication of Titrations


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Of the modern procedures for electrical determination of endpoint those involving noble-metal electrodes polarized by a few μA of direct current were discussed. These electrodes differ from the potentiometric ones (which respond to chemical events occurring during the titration without drawing current) in that their potential is determined only by their state of polarization, although this in thurn is a fuction of chemical events during the titration. Against this loss in specificity is to be set the advantage that polarized indicator electrodes are universally applicable – for redox titrations as well as for argentometric, complexometric, and even acidimetric titrations.

Platinum foil electrodes 10 to 100 $mm^2$ in size and polarized with currents between about 0.3 and 3 μA or potentials up to several hundred mV have proved valuable. Au, Ag, and Au-amalgam electrodes can also be used successfully. If polarization is effected with a constant current, the indication is described as voltametric, if with constant polarization potential as amperometric (or as dead-stop technique if only small polarization potentials are applied).

Details were discussed for the less well-known voltametry. The following two forms of indication technique are differentiated: A) Both electrodes are polarized and function simultaneously for potential measurement. B) Only one of the two polarized electrodes is a measuring electrode; it operates in conjunction with an additional, unpolarized electrode, such as a calomel electrode, also placed in the solution to be analysed.

For electrochemically reversible titration reactions the technique A gives a titration curve (potential/volume curve) characterized by a sharp peak; for irreversible systems it gives a steeply rising curve that somewhat resembles a potentiometric curve in appearance. The maximum or point of inflection corresponds to the equivalence point.

Independently of the reversibility of the chemical process, technique B leads to a steeply rising potential-volume curve; the point of inflection does not correspond exactly to the equivalence point. The deviation may be positive or negative according to whether the indication process occurs at the anode or the cathode, and increases with increasing dilution of the solution being analysed. This technique is thus useful for studying electrode reactions rather than for determination of endpoints.

Independently of which technique is used, voltametric indication involves a connection between polarization current density at the electrodes and concentration of the solution being analysed. Conditions are optimum at a polarization current density of about 0.05–0.1 $\mu A/mm^2$ in titration with 0.1 N solutions, or about 0.02–0.05 $\mu A/mm^2$ or 0.005 to 0.02 $\mu A/mm^2$ for titration with 0.01 N or 0.001 N solutions, respectively.

Voltametric indication (technique A) is usually superior to potentiometric indication, giving readily interpretable curves for titration of Ce(IV) or V(V) with Fe(II) even in 0.0001 N solutions. Complexometric titration of *e.g.* Cu, Pb, Zn, or Ca, which cannot be followed directly by the potentiometric method, can be carried out so precisely that the resulting accuracy of analysis exceeds that of the usual color-indicator methods.

[Lecture at Clausthal-Zellerfeld (Germany), Feb. 4th, 1966]

[VB 985/285 IE]
German version: Angew. Chem. *78*, 551 (1966)

## Rearrangements of α-Substituted Aldehydes

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Attack of nucleophilic reagents on α-halogenated aldehydes takes place primarily at the carbonyl group. With the nucleophilic reagents $OH^-$, $OR^-$, $NH_2^-$, or $CN^-$, it can lead to the products of Favorski rearrangements or to stable epoxides, *e.g.* with alkoxides or, particularly, cyanides. The substituted aldehydes (substituent: SH, SR, SAr, or $NR_2$) that are first formed are often not very stable and rearrange to ketones, sometimes spontaneously, *e.g.* $RCH(NR_2)CHO \rightarrow R{-}CO{-}CH_2{-}NR_2$, or on acid (substituent: OH, OR, SR) or basic catalysis (substituent: OH, OAc), or on reaction with amines by way of enediamines in accordance with reaction (a):

$$C_6H_5{-}CH(NR_2){-}CHO \rightarrow C_6H_5{-}C(NR_2){=}CH{-}NR_2 \rightarrow C_6H_5{-}CO{-}CH_2{-}NH_2 \quad (a)$$

Correspondingly substituted epoxides are often very unstable and rearrange thermally to aldehydes (substituent: OAc, Cl), or catalytically[*] to ketones (substituent: OR, Cl) [see reaction (b)]. The catalytic rearrangement proceeds by way of enols.

$$R{-}CO{-}CH_2Cl \xleftarrow{\text{Catalysis}} R{-}CH\text{—}CH{-}Cl \xrightarrow{\Delta} R{-}CHCl{-}CHO \quad (b)$$

(O bridges the CH–CH)

The reaction with alkalis and amines is bimolecular only for branched chloro aldehydes. An intermediate formed from two molecules of aldehyde must be assumed in the case of unbranched α-halogeno aldehydes.

Use of epoxy nitriles permits the synthesis of *e.g.* α-fluoro aldehydes that are difficultly accessible by other routes [see reaction (c)].

$$R{-}CH\text{—}CH{-}CN + HF \rightarrow R{-}CHF{-}CH(OH){-}CN \rightarrow R{-}CHF{-}CHO \quad (c)$$

(O bridges the CH–CH)

[Lecture at Munich (Germany), February 15th, 1966]

[VB 990 / 292 IE]
German version: Angew. Chem. *78*, 552 (1966)

[*] Catalysts: Brønsted or Lewis acids.

## Heterogeneous Catalysis with Elemental Boron and with Nickel Borides

*H. J. Becher*, Münster (Germany)

In continuation of previous experiments[1], comparative measurements, at various streaming velocities, were made of catalytic dehydration of 2-propanol vapor on elemental boron (prepared by various methods[*]) and on technical $Al_2O_3$ catalysts. The most active catalyst was finely divided boron in the α-modification, with a surface area of 15 to 30 $m^2/g$; this was superior to the most active $Al_2O_3$ catalyst by a factor of two in respect of amount of catalyst and by a factor of 50 in respect of surface area.

Determination of the oxygen content and of the protons that are exchangeable with $D_2O$ indicates that an average of one OH group per boron atom is present in the surface of finely divided α-boron. On dehydration of $CD_3CH(OD)CD_3$ and $CH_3CD(OH)CH_3$ on α-boron hardly any of the hydrogen attached to secondary carbon is removed or exchanged, in contrast to the deuterium and hydrogen of $CD_3$ and $CH_3$ groups. Exchange experiments between $CH_3CH{=}CH_2$ and $D_2O$ at 300 °C also showed that the H atoms of $CH_2$ and $CH_3$ groups are exchanged preferentially in presence of the α-boron catalyst; in absence of α-boron there is no exchange under similar conditions. These observations accord with the representation for catalytic dehydration on metal oxides put forward by *Eucken* and *Wicke*[2]; according to this model, finely divided boron is a weakly acidic, oxidic dehydration catalyst by virtue of the BOH groups on the surface; the high activity of the BOH groups is to be emphasized. It seems to be intensified by the peculiar arrangement of boron atoms in the α-boron lattice[**] since boric acid itself does not dehydrate 2-propanol under these conditions but on the contrary converts it into an ester.

Nickel borides, $Ni_3B$, $Ni_2B$, and NiB, have a dehydrogenating action on alcohols. Their activities in heterogeneous gas catalysis are less than that of finely divided nickel (nickel carbonyl), but nickel boride electrodes have more favorable properties than nickel electrodes[3] for anodic oxidation of hydrogen and methanol in a fuel cell. Reaction of nickel borides with aluminum at 675 °C leads to nickel-aluminum phases and to nickel borides very rich in boron, one such ($NiB_{12}$) having been characterized. These alloys can be converted by NaOH solution into a mixture of Raney nickel and $NiB_{12}$, and electrodes prepared therefrom are superior to electrodes made from $NiB_{12}$-free Raney nickel for anodic oxidation of methanol in fuel cells.

[Lecture at Marl (Germany), March 9th, 1966]

[VB 989/291 IE]
German version: Angew. Chem. *78*, 552 (1966)

[*] Samples: finely powdered α-boron made by reduction of gaseous $BBr_3$ with $H_2$; amorphous boron supplied by Borax Consolidated Co., London, and Consortium für electrochemische Industrie, Munich.

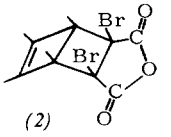
[**] Cf. *B. F. Decker* and *J. S. Kasper*, Acta crystallogr. *12*, 503 (1959).

[1] *H. J. Becher*, *L. Marosi*, and *H. Widmann*, Lecture at the Westdeutsche Chemiedozententagung, Freiburg 1964; cf. Angew. Chem. *76*, 574 (1964); Angew. Chem. internat. Edit. *3*, 644 (1964).

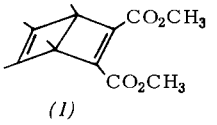
[2] *E. Wicke*, Angew. Chem. *59*, 34 (1947).

[3] From measurements in the physikalisch-chemische Laboratorien of Robert Bosch GmbH., Stuttgart (Germany). – Cf. *H. Jahnke*, Lecture at the Journées Internationales d'Etude des Piles à Combustile, Brussels 1965.

**Dimethyl 1,4,5,6 - tetramethylbicyclo[2.2.0]hexa - 2,5-diene-2,3-dicarboxylate** *(1)*, a derivative of "Dewar phthalic acid", was prepared by *R. Criegee* and *F. Zanker*. Reaction of 3,4-diiodotetramethylcyclobut-1-ene with dibromomaleic anhydride in the presence of mercury gives in 67% yield the anhydride *(2)*, which readily gives the dibromodimethyl ester *via* the dibromomonomethyl ester. Dehalogenation is achieved



*(2)*

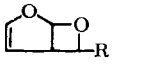


*(1)*

in 92% yield with copper-plated zinc in boiling ether. Compound *(1)*, m.p. 32–33 °C, shows no absorptions characteristic of aromatic systems. The bicyclohexadiene system in *(1)* is surprisingly stable. At 130 °C, dimethyl tetramethylphthalate is formed exothermically and quantitatively. / Chem. Ber. *98*, 3838 (1965) / –Ma. [Rd 453/662 IE]

**The bond lengths in non-aromatic hydrocarbons** depend only on the hybridization states of the C atoms involved and on the corresponding differences in electronegativity. They are not influenced by conjugation and hyperconjugation effects. As experimental evidence in support of this theory, *B. M. Mikhailov* showed that there is a linear relationship between the decrease in bond length ($\Delta d$) and the s-character of the C orbitals in ethylene, allene, and butatriene (length of the central C=C bond). Similarly, the lengths of the C≡C bonds in *e.g.* acetylene, propyne, 2-butynenitrile, and hexa-2,4-diyne are equal within the limits of experimental error. This theory also applies satisfactorily to O–H bond lengths, but the differences in electronegativity are more important in this case than in C–C bonds. It should be noted that, contrary to *Pauling*'s views, an increase in the electronegativity difference (and hence an increase in the ionic character) of a C–H bond should lead to a C–H bond longer than that expected from the sum of the covalent radii. However, this effect is outweighed by the decrease in the covalent radius of the carbon atom with increasing ionic character. / Tetrahedron *21*, 1277 (1965) / –Bu. [Rd 438/647 IE]

**Substituted dioxabicyclohexenes** *(1)* have been obtained by *S. Tobi*, *K. Shima*, and *H. Sakurai* in a photochemical reaction between aldehydes and furan. For example, exposure of furan and benzaldehyde to a 350 W high-pressure mercury vapor lamp for 6 h leads to the formation of 6-phenyl-2,7-dioxabicyclo[3.2.0]hept-3-ene *(1a)* (m.p. 49 to 50 °C) in 80% yield (based on the quantity of aldehyde consumed).



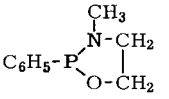
*(1a)* R = $C_6H_5$

*(1)*

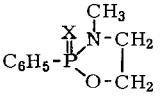
The structure of the product is confirmed by the infrared and NMR spectra. / Bull. chem. Soc. Japan *38*, 760 (1965) / –Bu. [Rd 439/648 IE]

**The partial fluorination of methane by an electrochemical method** is reported by *S. Nagase*, *K. Tanaka*, and *H. Baba*. These authors used a polyethylene gas inlet tube with a Teflon attachment, which produced very fine gas bubbles directly below the electrode. The electrolyte used was NaF in liquid hydrogen fluoride. As an example, a current density of 2.2 A/dm² (current yield 45 %) gave 45 % conversion, and the product consisted of 13 % $CF_4$, 26 % $CHF_3$, 15 % $CH_2F_2$, and 46 % $CH_3F$. Compounds such as $C_2F_6$ or $C_3F_8$, which are formed during the fluorination of $CH_4$ in the gas phase, could not be detected. / Bull. chem. Soc. Japan *38*, 834 (1965) / –Bu. [Rd 440/649 IE]

**A new method for the preparation of isocyanides** has been described by *T. Mukaiyama* and *Y. Yokota*. Isocyanates or isothiocyanates are allowed to react with 3-methyl-2-phenyl-1,3,2-oxazaphospholidine *(1)* under reflux in petroleum ether or ligroin.



*(1)*



*(2)*

For example, phenyl isothiocyanate reacts with *(1)* at 34 to 36 °C with loss of sulfur and formation of phenyl isocyanide (yield 93 %) and *(2)*, X = S. *(1)* is prepared from $C_6H_5PCl_2$ and *N*-methylaminoethanol in the presence of 2 moles of triethylamine (yield 41 %) or from phenylbisdiethylaminophosphine and *N*-methylaminoethanol at 120 °C (yield 83 %). / Bull. chem. Soc. Japan *38*, 858 (1956) / –Bu. [Rd 441/650 IE]

**Complex methylchromium compounds** have been prepared be *E. Kurras* and *J. Otto* in diethyl ether at –180 °C by thy reaction

$$CrCl_3 + 6\ LiCH_3 \rightarrow Li_3Cr(CH_3)_6\bullet + 3\ LiCl$$

$$\xrightarrow{C_4H_8O_2} Li_3Cr(CH_3)_6 \cdot 3\ C_4H_8O_2$$

*(1)*

The dioxane adduct *(1)* is formed in about 45 % yield as blood-red, rod-shaped crystals. Excess methyl-lithium and lithium chloride are precipitated as sparingly soluble adducts with dioxane. *(1)* is soluble in diethyl ether and dioxane, but insoluble in hexane; decomposition occurs in benzene at room temperature. The complex is extremely sensitive to oxidation and hydrolysis, and burns in air. Cryoscopic studies show that it is present in dioxane as the monomer. The magnetic moment of $\mu_{eff}$ = 3.75 B.M. indicates a spin-free complex with a $d^3$ configuration.

If the reaction mixture is heated to boiling, fractional precipitation with dioxane yields a finely crystalline yellow precipitate, which recrystallizes from tetrahydrofuran as the dimeric dilithium tetramethyl chromate(II)-tetrahydrofuran adduct *(2)*. Water and other protonic solvents hydrolyse this complex instantaneously.:

$$[Li_2Cr(CH_3)_4(THF)_2]_2 + 8\ H^+$$

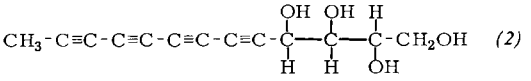
*(2)*

$$\rightarrow 4\ Li^+ + 2\ Cr^{2+} + 8\ CH_4 + 4\ THF$$

Molecular weight determinations in benzene showed that *(2)* is present as the dimer; the compound gives no ESR signals. / J. organomet. Chemistry *4*, 114 (1965) / –Sch. [Rd 430/639 IE]

**A naturally occurring tetrayne and tetrayne-tetraol** have been found for the first time by *E. R. H. Jones*, *G. Lowe*, and *P. V. R. Shannon* in ether extracts of fermented solutions of *Fistulina hepatica* (Huds.) The compounds are trideca-2,4,6,8-tetrayne *(1)*, translucent needles of m.p. 25–26 °C, and 2D; 3L;4L-trideca-5,7,9,11-tetrayne-1,2,3,4-tetraol *(2)*, silvery plates of m.p. 155 °C (decomp.), $[\alpha]_D^{24} = +1.8°$.

$$CH_3\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}(CH_2)_3\text{-}CH_3 \quad (1)$$



*(2)*

**Hexahalogenotitanates(III)** were prepared by *B. T. Russ* and *G. W. A. Fowles*. They obtained the orange-red tripyridinium salt $(C_5H_6N)_3[TiCl_6]$ from $TiCl_3$ and an excess of anhydrous pyridinium chloride. The latter was removed by extraction with chloroform at room temperature. The same product is obtained from pyridinium chloride and $(CH_3CN)_3TiCl_3$ in $CHCl_3/CH_3CN$. Tetraethylammonium chloride or bromide and $(CH_3CN)_3TiCl_3$ give $[(C_2H_5)_4N][TiCl_4(CH_3CN)_2]$ or the tribromochloro salt, respectively. The tetrabromo salt is obtained from $(CH_3CN)_3TiBr_3$ and $[(C_2H_5)_4N]Br$. Reaction of $(C_2H_5N)_3TiBr_3$ with anhydrous liquid HCl gives $(C_5H_6N)_3[TiCl_4Br_2]$. – Tripyridinium hexachlorotitanate(III) is orthorhombic with lattice parameters a = 16.0, b = 16.8, c = 20.8 Å. The compound is oxidized even by nitrobenzene. It gives a green solution in acetonitrile, from which it is recovered unchanged on evaporation of the solvent. Its diffuse reflection spectrum is almost identical to that of $[(C_2H_5)_4N][TiCl_4(CH_3CN_2)]$.

Evidently a reversible dissociation occurs:

$$(C_6H_5N)_3[TiCl_6] + 2\ CH_3CN \rightleftharpoons (C_6H_5N)\ [TiCl_4(CH_3CN)_2] + 2\ C_5H_6NCl$$

Chem. Commun. *1966*, 20 / –Kr. [Rd 458/667 IE]

**The primary process in the thiamine pyrophosphate catalysis of the decarboxylation of pyruvate is not enzyme-catalysed.** According to *J. Ullrich* and *A. Mannschreck*, the ionization at C-2 of the thiazole ring, which must precede the addition of the carbonyl group, has a half-life of 3 min at pH 5 and 38 °C. The half-life is shorter at higher pH. At pH 5, no catalysis by pyruvate decarboxylase from yeast could be detected by measurement of the H–D exchange, although the enzyme is capable of functioning at this pH (pH-optimum *ca.* pH 6). For the kinetic studies the change in intensity of the $^1H$–NMR signal at $\tau = 0.32$ of the thiazole proton (relative to the practically constant signal at $\tau = 2.06$ of the pyrimidine proton in $D_2O$) was measured. / Biochim. biophysica Acta *115*, 46 (1966) / –Hö. [Rd 460/669 IE]

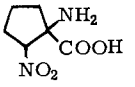
**The redox properties of ferredoxin** from *Clostridium pasteurianum* were studied by *E. Sobel* and *W. Lovenberg*. Contrary to previous views, two electrons are required for the reduction of oxidized ferredoxin. One mole of NADPH is required per mole of ferredoxin in the ferredoxin reductase-catalysed reduction of the latter. Conversely one mole of ferredoxin (after reduction with light and chloroplasts) reduces one mole of NADP. In the reaction with hydrogenase, one mole of $H_2$ per mole of oxidized ferredoxin is taken up. During the reduction two $Fe^{3+}$ ions are converted into $Fe^{2+}$. Neither in the reduced nor in the oxidized state do free thiol groups appear. The redox potential between pH 6 (–360 mV) and pH 9 (–496 mV) is a linear function of pH. / Biochemistry *5*, 6 (1966) / –Hö. [Rd 461/670 IE]

**Alkyl-substituted indenes** were synthesized independently in good yields from 1,1-dihalocyclopropanes by *J. Buddrus* and *F. Nerdel* and by *L. Skatteböl* and *B. Boulette*. The starting materials, easily accessible from olefins and trihalomethane, are treated with aromatic hydrocarbons under conditions of the Friedel-Crafts reaction. Examples: 1,1-dibromotetramethylcyclopropane *(1)* and benzene give 1,1,2,3-tetramethylindene (80% yield); *(1)* and toluene give a mixture of 1,1,2,3,5-pentamethylindene and 1,1,2,3,6-pentamethylindene (overall yield 81%). / Tetrahedron Letters *1965*, 3197; J. org. Chemistry *31*, 81 (1966) / –Bu. [Rd 463/672 IE]

**Solutions of toluenesulfonyl perchlorate** were prepared from *p*-toluenesulfonyl bromide and silver perchlorate by *F. Klages* and *F. Malecki*. The substance is preferably prepared, stored, and handled in nitromethane, in which it is stable up to –25 °C. Conductivity measurements in liquid $SO_2$ showed that *p*-sulfonyl perchlorate is ionized to a large extent. It has an extraordinary sulfonylating capacity, which makes accessible for the first time *N,N,N*-trialkylsulfonamidium salts from tertiary amines. These salts, *e.g.*

$[(C_2H_5)_3N{-}SO_2C_6H_4{-}CH_3]^+ClO_4^-$, can only be detected in solution. / Liebigs Ann. chem. *691*, 15 (1966) / –Bu. [Rd 464/673 IE]

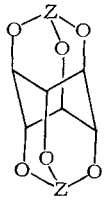
**1-Amino-2-nitrocyclopentanecarboxylic acid, a naturally occurring nitro compound,** has been isolated from culture filtrates of *Aspergillus wentii*. *B. F. Burrows* and *W. B. Turner* have elucidated the structure of the acid *(1)* (needles, decomp. above 150 °C) by degradation and by spectroscopy, and have synthesized it *via* 1-iodo-2-nitrocyclopentanecarboxylic acid.



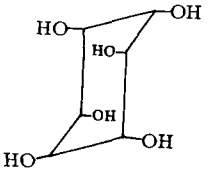
*(1)*

Only few nitro compounds are known in nature. Compound *(1)* has unusual growth-regulating and inhibiting properties and acts as L-leucine antagonist. / J. chem. Soc. (London) org. *C 1966*, 255 / –De. [Rd 457/666 IE]

**Hexaoxadiamantane** *(1)* **and hexaoxadiphosphadiamantane** *(2)*, heteroanalogues of diamantane (congressane), were synthesized by *O. Vogl* and *B. C. Anderson*. Compounds *(1)*, m.p. 303–305 °C, is obtained in 15% yield by heating scyllite



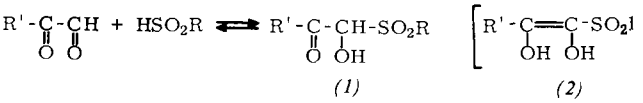
*(1)*, Z = CH
*(2)*, Z = P



*(3)*

*(3)* with an excess of triethyl orthoformate in dimethyl sulfoxide at 200 °C. Analogously *(2)*, m.p. 276–280 °C, is obtained from scyllite and trimethyl phosphite. / Tetrahedron Letters *1966*, 415 / –Ma. [Rd 448/657 IE]

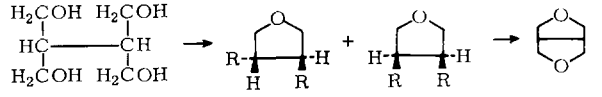
**α-Hydroxy-β-oxosulfones** *(1)* have been synthesized in good yields by *K. Schank* by the reaction of aliphatic or aromatic glyoxals with aliphatic or aromatic sulfinic acids. The colorless, crystalline compounds *(1)* tend to dissociate into the



*(1)* *(2)*

components on being heated or in solution, particularly in basic solvents. The free ene-diol form *(2)* probably does not exist. Examples: $R = R' = C_6H_5$, m.p. 104 °C, yield 82%; $R = p\text{-}CH_3{-}C_6H_4$, $R' = C(CH_3)_3$, m.p. 91–93 °C, yield 68%. Chem. Ber. *99*, 48 (1966) / –Ma. [Rd 449/658 IE]

**3,7-Dioxabicyclo[3.3.0]octane** *(1)*, of which pinoresinol, sesamin, and syringaresinol are naturally occurring derivatives, has been synthesized by *K. Weinges* and *R. Spänig*. Dehydration of the tetraol *(2)* gives *(1)*, b.p. 173 °C, yield 42%, probably *via* equimolar amounts of *cis*- and *trans*-3,4-bis(hydroxymethyl)tetrahydrofuran *(3a, 3b)*. Only *(3a)* can lead to *(1)*. / Chem. Commun. *1966*, 9 / –Ma.



*(2)* *trans (3b)* *cis (3a)* *(1)*

R = $CH_2OH$

[Rd 450/659 IE]

**Houben-Weyl: Methoden der organischen Chemie** (Houben-Weyl: Methods of Organic Chemistry). Vol. 10, Part 3 "Stickstoffverbindungen I/3" ("Nitrogen Compounds I/3"). Georg Thieme Verlag, Stuttgart 1965. 4th Edit., edited by *Eugen Müller*. XLiii + 971 pp., 69 tables, subscription price before publication of the last volume DM 229.50 (about $57.–). Single volumes DM 255.– about $63.–).

The new edition of Houben-Weyl, having treated amines and quaternary ammonium compounds in volume 11/1–3, allots three volumes to the remaining nitrogen compounds, the third of these now being the first to appear. In this the well-tried method of presentation is used for the preparation and reactions of compounds containing multiply bonded nitrogen attached to at least one aromatic residue. The individual sections, except for the two chapters on azides and nitrile oxides (see below), are written by industrial chemists (Farbenfabriken Bayer) whose experience guarantees reliable reporting. It should, however, be emphasized that general scientific importance attaches to the azo compounds treated, as is particularly clear in the content and style of chapters 1, 4, and 5. In all sections the literature of the past 80 (!) years (modern authors please note) is carefully evaluated and it is good to see that this continues up to 1964.

1. Aromatic Diazonium Salts (200 pp., 35 tables, *R. Pütter*). This chapter conveys a lively impression of the numerous reactions available for the preparation of diazonium salts and of the influence of conditions and substituents. It includes heterocyclic diazonium salts. Direct introduction of the diazonium group, oxidation of arylhydrazines, and use of amine derivatives are described as well as methods of diazotization. Reactions involving loss of nitrogen are also described extensively. The article is enriched by inclusion of the most important theoretical results and of numerous tables.

2. Diaryl Azo Compounds (244 pp., 2 tables, *K. H. Schundehütte*). This unusually extensive field is made clear by means of skillfully chosen examples. First the tautomerism of hydroxy- and amino-azo compounds is described, and then the various coupling reactions of diazonium salts with hydrocarbons, derivatives of aromatic amines and phenols, reactions affording polyazo compounds, and the preparation of macromolecular azo compounds. Here one also finds reactions that are seldom considered, such as the $Cu^{\oplus}$-catalysed conversion $2\ ArN_2^{\oplus} \rightarrow Ar{-}N{=}N{-}Ar + N_2$ (*Vorländer*), as well as the preparation of azo compounds from reactive methylene compounds or phenols and active azides, and oxidative coupling. The section on alkylation and acylation of amino-azo compounds includes the preparation of reactive dyestuffs. The numerous methods for preparation of metal complexes of azo dyes occupy 22 pages. This chapter will appeal particularly to the technologically oriented chemist, not least because the patent literature is extensively evaluated.

3. Aromatic-Aliphatic Azo and Azoxy Compounds from Arylhydrazones by Coupling (73 pp., 6 tables, *E. Enders*). This scientifically interesting chapter describes the oxidative conversion of hydrazones into azo compounds, also their coupling with reactive methylene compounds (Japp-Klingemann reaction). Other relevant methods are also considered.

4. Other Arylazo Compounds (72 pp., 8 tables, *R. Pütter*). Under this heading are collected arene-diazotates, -diazo ethers, -diazosulfonates, -diazosulfones, -diazocarboxylates, *etc.* The original literature about this many-sided group of compounds, that is so troublesome to read, is here explained by means of characteristic examples.

5. Formazans (33 pp., 2 tables, *R. Pütter*). This class of compounds has long been known, but it has recently gained importance owing to the reversible conversion into tetrazolium salts and stable radicals. Views on the mechanism of the syntheses are critically examined.

6. Aromatic Triazenes and Higher Azo Homologues (44 pp., 8 tables, *C. Süling*). Aromatic-aliphatic as well as purely aromatic triazenes can be singled out on account of their technical importance as "protected" diazonium salts, and on account of the acid-catalysed fission. Surprisingly, triazatrimethinecyanines also occur in this section. Tetrazenes and pentazadienes are also treated.

7. Aromatic Azoxy Compounds (26 pp., 1 table, *K. H. Schündehütte*). This section describes the constitutional problem and then the synthesis from aromatic nitroso and hydroxyamino compounds, by reduction of nitro compounds, and by oxidation of azo compounds. Particular interest attaches to the Wallach rearrangement of azoxy compounds which takes different courses in light and in sulfuric acid.

The last two chapters depart from the form of the previous ones. *C. Grundmann* gives an excellent exposition of the importance of two functional groups in the whole field of organic chemistry:

8. Organic Azides (54 pp., 4 tables). First the preparation of hydrazoic acid and its salts is described and then introduction of the azido group into organic compounds by addition and substitution as well as by reactions of other nitrogen-containing groups. The reactions of azido compounds are of general importance: addition to multiple bonds, the Schmidt and the Curtius degradation, and the mode of reaction (described in detail) of the nitrenes that occur as intermediates.

9. Nitrile Oxides (29 pp., 3 tables). The very instructive description of this class of compounds, to which little attention is usually paid, includes not merely their preparation (with a review in tabular form) but also particularly their very numerous addition reactions to multiple bonds that lead, *e.g.*, to furoxans and isoxazole derivatives. This and the preceding chapter end with methods of detection of the two groups.

This short indication of content must suffice to show that this volume maintains the high standard of the complete work. In accordance with its aims the methodological aspect is in the foreground, and the experimental detail is intended as a help for analogous experiments.

The volume ends with an exhaustive author (42 pp.) and subject index (38 pp.), to which is added a special index of diazonium salts and the azo compounds treated (arranged according to their methods of preparation). A patent index would in this case have been useful.

A proposal for future volumes: preparative yields should be restricted to whole units percent. The extensive list of journals (37 pp.) would be better placed at the end, with the table of abbreviations on "fold-out" pages.

*S. Hünig* [NB 479 333 IE]

**Klassische und molekulare Genetik** (Classical and Molecular Genetics). By *C. Bresch*. Springer-Verlag, Berlin-Göttingen-Heidelberg 1964. 1st Edit., viii + 319 pp., numerous figs., 14 tables, cardboard DM 32.– (*ca.* $ 8.–).

Publication of this book is most welcome. The central position of genetics in biology, already recognized by far-sighted investigators at the turn of the century, is nowadays clearly acknowledged.

*C. Bresch*, the author of the present book is a representative of the modern "molecular" biologists; he came to biology through physics. He has reviewed the total content of mole-

cular genetics – up to date almost to the last minute – in a clear, readily intelligible, and "learnable" form, and, moreover, he has had the courage to place it in the framework of a brief presentation of the classical theory of heredity. In view of this grandly conceived attempt and the tremendous effort behind it, the reviewer hardly feels himself in a position to criticize. If criticism is at all justified, it applies almost entirely to the "classical" chapters of the book. Many topics have been dealt with in a rather aphoristic way, and it is to be hoped that the author finds the time to present them in a more thorough fashion in the next edition.

More serious, in the reviewer's opinion, is a general deficiency of the classical section: the chromosome theory forms the very kernel of classical genetics. It is true that to day only historical interest attaches to the stepwise logical derivation of this relation from experiments that have since become famous, yet it cannot be simply omitted – pushed out of sight – from a textbook of genetics, if only for didactic reasons. The reviewer would gladly receive a clear exposition of these relations in exchange for reductions in other parts of the book that have been included probably for the sake of completeness (*e.g.* tetraploid heredity, "Heredity and Culture"). The description of life cycles could also be shortened: information on these matters may be essential for the non-biologist, but it could equally well be given in a biological-technical appendix. Whether, in fact, the principles of Mendelism are better derived from haploid genetics than from *Mendel*'s experiment is in the reviewer's opinion, an open question. One should proceed from the known to the unknown: who, other than a botanist, knows what *Sphaerocarpus* is? And if haplonts, then why not unicellular organisms, such as *Chlamydomonas*?

As in many parts of its content, the book is unorthodox in arrangement and production. Short summaries and references at the end of each chapter, clear diagrams and schemes, and occasional naively drastic comparisons are reminiscent of American textbook make-up. All this admittedly is refreshing and in no way lessens the value of the book as a source of information. Nevertheless, the German reader would welcome a stylistic revision; in the long run it becomes annoying to stumble upon phrases such as "Sexuality can take place between any individuals of the species" (p. 86), and "Crosses between different species are seldom succesful and even then almost always lead to sterile bastards owing to the difficulty of meiosis" (p. 80 – incidentally, in this lapidary brevity the statement is untrue!).

All in all: a good and complete introduction into modern molecular genetics, *i.e.* into the principles of molecular transmission of information in viruses and bacteria, and their experimental derivation; further, a first introduction into the complexity of the phenomena of heredity in higher organisms that invites further quests. The low price of the book permits wide distribution, and this is certainly to be hoped for.

*W. Beermann* [NB 430/337 IE]

**Fortschritte der Chemie organischer Naturstoffe** (Progress in the Chemistry of Organic Natural Products). Vol. 22. Edited by *L. Zechmeister*. Springer-Verlag, Vienna-New York 1964. 1st edit., vii + 340 pp., 15 figs., linen DM 88.– (ca. $22.–).

Volume 22 of this progress series, which has been appearing for 27 years, contains the following contributions:

1. *K. Schaffner* (Zurich): Photochemical Transformations of Selected Natural Products (94 pp., 413 refs.). This treats fragmentation of carbonyl compounds (terpenes, usnic acid, and griseofulvin), skeletal rearrangement of alicyclic ketones (steroids, santonin, and related substances), and ring contraction of cyclic diazo-ketones (terpenoids); there are also examples of intramolecular substitution with hydrogen shift, transformation of double-bond systems (including suprasterin$_2$-II, homoannular dienes, tropolones, *etc.*), and the photochemical behavior of pyrimidines, riboflavine, and amino acids. Particular attention is paid to results obtained in the last 5 years.

2. *G. Billek* (Vienna): Stilbenes in the Plant Kingdom (29 pp., 129 refs.). Individual stilbene derivatives (including the glucosides) and 3,4-dihydroisocoumarins are recorded, as well as isolation, determination of constitution, syntheses, and biosyntheses of stilbenes; also data on their taxonomic importance and biological action.

3. *T. G. Halsall* and *R. T. Aplin* (Oxford): A Pattern of Development in the Chemistry of Pentacyclic Triterpenes (37 pp., 239 refs.). The article supplements earlier reports in this series (vols. 7 and 13). Results obtained in this field since 1949 are reported, the various systems and numerous physical data for 177 individual compounds are collected in tables, and facts concerning pentacyclic triterpenoids of unknown structure are included.

4. *J. F. Grove* (London): Griseofulvin and Some Analogues (55 pp., 121 refs.). This section treats the isolationsof grisans, their structure and stereochemistry, reactions of the various functional groups, optical properties, methods of detection and determination syntheses, biosyntheses, and behavior in metabolism of animals and plants.

5. *P. J. Scheuer* (Honolulu): The Chemistry of Toxins Isolated from Some Marine Organisms (84 pp., 53 refs.). This deals with an important field that has as yet been little worked on. Discoveries concerning the toxins of teleosteres (tetrodopahu-, and cigua-toxin), echinoderms (holothurins, starfish saponins), molluscs and protozoa (saxitoxin), annelids and coelenterates (nereis- and paly-toxin) are reported.

6. *W. Keller-Schierlein, V. Prelog*, and *H. Zähner* (Zurich): Siderochromes (37 pp., 123 refs.). After a description of the detection, isolation, and action, the authors present in detail the chemical and biological relations between the iron(III) trihydroxamato complexes (sideramines, sideromycins), isolated from microorganisms, and their chelating agents. The stability of the complexes and the uses of desferrioxamin B in human medicine are also described.

In sum, the present volume, whose use is made easier by an author- and a good subject index, deserves warm recommendation both as introduction and for further information of organic chemists, biochemists, and biologists.

*H.-J. Bielig* and *G. Rohns* [NB 436/343 IE]

**Synthetic Methods of Chemistry,** Vol. 19. By *W. Theilheimer*. Verlag S. Karger AG, Basel-New York 1965. 1st Edit., Vol. 19 xvi + 498 pp., numerous illustr., sFr/DM 170.– (about $ 43.–).

This book reaches the same high level of achievement as previous members of the well-known series. 996 Examples, chosen with skill mostly from the literature of 1962–1964, illustrate the newest advances in the synthetic field. In accord with their importance, hetero-organic compounds, particularly those of phosphorus, silicon, and boron, come increasingly into the foreground, either as intermediates (*e.g.* in the Wittig reaction) or as end products. Much weight is laid on the synthesis of the most varied heterocycles. A particular advantage of this book is that many of the reaction steps described can be used as patterns for other syntheses. The method of arrangement, which is not praticularly simple but is used consistently, is reinforced by a comprehensive index (43 pp.). Nevertheless the reviewer would ask again whether the treasures gathered here would not be made more useful by addition of an index on the peephole principle.

*S. Hünig* [NB 456/309 IE]

**Interaction of Metals and Gases.** Vol. 1 of the series „Thermodynamics and Phase Relations". By *J. D. Fast*. Philips' Technical Library, Eindhoven 1965. 1st Edit., 310 pp., numerous figs., Dutch fl. 36.– (about $10.–).

In this volume, the author discusses heterogeneous gas equilibria and the thermodynamics of solution of gases in

metals (a second volume "Kinetics and Mechanisms" has been announced).

A didactically elegant and very readable theoretical introduction is followed by chapters on reactions between carbon and oxygen in steel and on solutions of gases in metals and in alloys.

The author's particular interest lies in the technological aspect of the subjects treated; much space is thus devoted to the metallurgy of iron, while other systems are treated more cursorily. The wealth of empirical material is carefully related to a theoretical background, and numerical examples, presented in detail, help the student to find his way into this important field. In sum, this is a book that can be very warmly recommended to a wide circle of metallurgists and students of metallurgy.

*H. Brodowsky* [NB 477/331 IE]

**Advances in Inorganic Chemistry and Radiochemistry.** Vol. 6. Edited by *H. J. Emeléus* and *A. G. Sharpe*. Academic Press, New York 1964. 1st edit., 530 pp., numerous figs. and tables, bound, $ 16.–.

The latest volume of these "Advances" really needs no commendation since earlier issues of the series have long been accepted as required reading for all concerned with research or teaching. Once again the editors have obtained authors who are recognized masters of their material, some of them by virtue of their own contributions. The subjects of chapters 1, 2, 5, 7, and 8 are by no means at the end of their development, so that supplements will soon be necessary, yet the reader can rely on completeness of the presentation to date and on the critical judgement of the authors, which is a great advantage at a time rich in scattered publications. The individual subjects treated are:

1. *G. Booth*: Complexes of the Transition Metals with Phosphines, Arsines, and Stibines; 2. *C. C. Addison* and *N. Logan*: Anhydrous Metal Nitrates; 3. *A. S Kana'an* and *J. L. Margrave*: Chemical Reactions in Electric Discharges; 4. *A. H. W. Aten*: The Chemistry of Astatine; 5. *U. Wannagat*: The Chemistry of Silicon-Nitrogen Compounds; 6. *J. A. Connor* and *E. A. V. Ebsworth*: Peroxy Compounds of Transition Metals; 7. *J. J. Zuckerman*: The Direct Synthesis of Organosilicon Compounds; 8. *E. Fluck*: The Mössbauer Effect and its Application in Chemistry.

Chapters 5 and 7, in particular, treat areas where a review was urgently required. Unfortunately, because of the space that would otherwise have been required, the treatment in chapter 5 is in part only that of a summary, and detailed results are not given (*e.g.* for the use of catalysts). Chapter 3 shows most impressively the possibilities of reactions under extreme conditions – a field with a large future; and in chapter 8 a still very young type of spectroscopy comes into focus which, while certainly not expected to attain the importance of NMR and ESR spectroscopy, nevertheless is a most valuable extension of those methods. The particular value of this book lies in its stimulation to further work.

*W. Sundermeyer* [NB 431/338 IE]

**Bridged Aromatic Compounds.** By *B. H. Smith*. Vol. 2 of the Series: Organic Chemistry. A Series of Monographs. Edited by *A. T. Blomquist*. Academic Press, New York-London 1964. 1st edit., xi + 553 pp., numerous tables, bound, $ 14.–.

There has hitherto been no modern complete review of the field of macrocycles, although it has been intensively studied particularly in recent years. It is, therefore, extremely welcome that the author has undertaken the laborious task of reporting on the special topic of bridged aromatic compounds, including furans, thiophens, and ferrocenes. The various sections are concerned with methods for the preparation of these compounds, the chemistry of the aromatic nucleus and the bridge, and atropisomerism, as well as ultraviolet, infrared, and NMR spectroscopy, electron resonance, and *X*-ray structure investigations.

The older work, in which structures are often falsely interpreted, is generally discussed in detail and critically, great stress being laid on a historically accurate presentation of the developments. A new proposal is made for a consistent nomenclature of this class of compounds on the basis of the cyclophane nomenclature introduced by *Cram* and *Steinberg*.

Since the author is an expert in the field of compounds with multi-membered rings, his numerous critical remarks have particular importance. Only in his evaluation of the methods of ring-closure will one occasionally not agree entirely with him. For instance, very recently it has been shown that the Thorpe-Ziegler dinitrile ring closure is superior to the acyloin ring-closure procedure in its range of application.

Numerous hitherto unpublished results and notes of eminent authors make the work particularly valuable. All the relevant substances prepared up to 1963 are collected in a final table. This excellent book is essential for every chemist who works with macrocycles, for it provides rapid information concerning the work so far carried out.

*G. Schill* [NB 432/339 IE]

**Organometallic Synthesis.** Vol. I: Transition-Metal Compounds. Edited by *J. J. Eisch* and *R. B. King*. Academic Press, New York 1965. 1st Edit., viii + 186 pp., $ 6.50.

In view of the increasing importance that attaches to organometallic compounds in all branches of modern chemical research, there has been a general wish for a collection of recipes for the synthesis of these sometimes difficultly accessible substances. In this volume the authors, who are true experts, treat the laboratory preparation of complexes of transition metals with carbon monoxide, aromatic compounds, and olefins, and some of their halogen, nitrosyl, and substituted derivatives. The general methods and techniques for their isolation, identification, and handling are clearly set out in an introductory chapter. The specialized section contains recipes, carefully chosen and worked out down to the smallest detail, of synthesis of more than 60 key compounds, together with their most important properties and their spectroscopic characterization. Other methods of preparation, and syntheses of analogous complexe are outlined and provided with references to the original literature, which is taken into account up to 1964.

The book can be placed alongside the well-known and popular volumes of the series "Inorganic Syntheses" and "Organic Syntheses" and is most warmly recommended to all who are interested in this field.

*Th. Kruck* [NB 457/310 IE]

**Advances in Heterocyclic Chemistry,** Vol. 3. Edited by *A. R. Katritzky*, *A. J. Boulton*, and *J. M. Lagowski*. Academic Press, New York-London 1964. 1st Edit., xiii + 434 pp., numerous tables and figs., $ 15.–.

Like the two previous volumes [1], volume 3 contains reviews of current heterocyclic chemistry, in particular of some types of substance and reaction that have been closely studied only in recent years, and of new methods.

In the chapters about substances there are sections on carbolines (*R. A. Abramovitch* and *I. D. Spenser*), thiatriazoles (*K. A. Jensen* and *C. Pedersen*), and pentazoles (*I. Ugi*). These classes have not yet received up-to-date treatment in the systematic series of heterocyclic chemistry (*R. C. Elderfield*; *A. Weissberger*).

The carboline chapter summarizes about 500 original papers (up to the end of 1962) in 130 pages, with a wealth of easily

[1] Angew. Chem. *77*, 466 (1965); Angew. Chem. internat. Edit. *4*, 451 (1965).

legible formulae. In its succinct but clear style this chapter reminds the reviewer of *H.-G. Boit*'s book on alkaloids. Nevertheless, it is not only the β-carbolines important for the alkaloid chemist that are handled; the other isomers that have become readily accessible in recent years are also included. There is a welcome and not too short discussion of the anhydro-bases and of spectra; however, the data about biosynthesis of naturally occurring carbolines are in part already out of date. The chapter on thiatriazoles includes the iodine-azide reaction that was discovered by *Raschig* and was recognized by *Feigl* as suitable for analytical purposes. The chapter on pentazoles deals with their chemical and particularly their physicochemical properties.

The remaining chapters of volume 3 are concerned with characteristic reactions, for instance, quaternization of nitrogen bases (*G. F. Duffin*), and with selected reactions that have only recently been studied for heterocycles, such as nucleophilic substitution, and uses of the Hammett equation.

*G. Illuminati*'s discussion of nucleophilic substitution – the original papers are rarely more than 10 years old – clarifies the differences as well as the analogies in chemical behavior of nitro-activated aromatic hydrocarbons and nitrogen heterocycles. There are detailed discussions of catalytic and autocatalytic effects, and of the limits of "normal" nucleophilic substitution (reactions by way of aryne intermediates). Particular attention is paid to reaction mechanism and intermediate states. The author favors a two-stage mechanism with a true intermediate. The initial impression of a dearth of pertinent compounds is later weake by the detailed table at the end of the chapter.

There is unavoidable, but not disturbing overlap between the preceding chapter and one also by expert hands (*H. H. Jaffé* and *H. L. Jones*) on applications of the Hammett equation (in its simpler forms . Here the organic chemist working in preparative chemistry will also find much of value once he has become accustomed to the particularly wide interpretation given to "side chain". It was not originally self-evident that the Hammett equation would be applicable at all to heterocycles, although this might have been suspected from the similarity of benzene to thiophene. Actually it is just in the field of five-membered heterocycles that results are sparse, because the necessary compounds are not known. The experiments have therefore been carried out mainly in the pyridine and quinoline series, and there even dissociation constants disclose an influence of substituents. One section each is devoted to development of such effects throughout heterocyclic systems, and another to the position of tautomeric equilibria. Equilibria of this sort can often be quantitatively estimated by means of the Hammett equation, even in extreme cases.

Finally, the present volume contains a chapter on the reactions of heterocycles with carbenes (*C. W. Rees* and *C. E. Smithen*), dihalogeno and α-keto carbenes playing a main part; subsequent rearrangements are considered.

This volume, in which only one printer's error was found (p. 39, formula 99), is not merely a progress report; it can also be recommended as a textbook for the advanced student. When further volumes have been published a subject index will be valuable, *e.g.* as for "Zechmeister". One can only congratulate the editors and authors on a successful volume.

*H.-J. Teuber* [NB 464/317 IE]

**Friedel-Crafts and Related Reactions.** Edited by *G. Olah*. Vol. III. Acylation and Related Reactions. Parts 1 and 2. Interscience Publishers, a Division of John Wiley & Sons, New York-London-Sydney 1964. 1st edit., Parts 1 and 2 together 1606 pp., numerous tables, bound, £ 22.10.0

As in the previous volume II, which was concerned with alkylation, so in the present volume III on "Acylation and Related Reactions" the editor's intention is to bring systematizing principles into the field, now almost too wide for review, of reactions occurring under the influence of Lewis or Brønsted acids.

In Part 1 are successively discussed the synthesis of aromatic ketones (chapter XXXI, *P. H. Gore*), Houben-Hoesch syntheses and related reactions (chapter XXXII, *W. Ruske*), the Fries reaction (chapter XXXIII, *A. Gerecs*), and acylation by di- and poly-carboxylic acids and their derivatives (chapter XXXIV, *A. G. Peto*). Part 2 contains cyclizing acylations (chapter XXXV, *S. Sethna*), a summary on acylation mechanisms (chapter XXXVI, *F. R. Jensen* and *G. Goldman*), acylation of aliphatic compounds (chapter XXXVII, *C. D. Nenitzescu* and *A. T. Balaban*), aldehyde syntheses by formylation (chapter XXXVIII, *G. Olah* and *S. J. Kuhn*), acid syntheses by carboxylation (chapter XXXIX, *G. A. Olah* and *J. A. Olah*), sulfonylation (chapter XL, *F. R. Jensen* and *G. Goldman*), and a short section on the Fries reaction of aryl arenesulfonates (chapter XLI, *F. R. Jensen* and *G. Goldman*); then follow sulfonation (chapter XLII, *K. L. Nelson*), nitration (chapter XLIII, *G. A. Olah* and *S. J. Kuhn*), amination (chapter XLIV, *P. Kovacic*), perchlorylation (chapter XLV, *C. E. Inman, R. E. Oesterling*, and *F. L. Scott*), and, finally, halogenation (chapter XLVI, *H. P. Braendlin* and *E. T. McBee*).

Although treatment of the general problems pertaining to reactions of organic compounds in the presence of Lewis acids as catalysts is reserved for volume I of the complete work, the individual chapters contain shorter theoretical considerations that are well worth reading Nevertheless, the value of the book to the practical chemist is retained, particularly by the very numerous tables that account for about a third of the number of pages in both Parts. It would, however, have helped the reader to find his information still more easily if the individual reactions listen in the tables had been, so far as possible, provided not only with a reference to the original literature but also with the number of the page where the reaction is discussed in the text.

The book is a happy combination of monograph and handbook. It provides the reader with a complete presentation of the field with which at present no other work compares in clarity, modernity, and balance of content; moreover, subjective exaggeration of this or that aspect, that so often goes with the treatment outlined above, has been carefully avoided. Thus purchase of the two Parts – even without the complete work – can be recommended with conviction.

*J. Gosselck* [NB 433/340 IE]

**Progress in Inorganic Chemistry,** Vol. 6. Edited by *F. A. Cotton*. Interscience Publishers, a Division of John Wiley & Sons, Inc., New York-London-Sydney 1964. 1st Edit., 360 pp., numerous figs. and tables. £5/–/– (*ca.* $15.00).

The following subjects are treated in the present volume:

1. Reactions of metal halides with ammonia and aliphatic amines (*G. W. A. Fowles*).

2. Magnetic properties of transition-metal complexes (*B. N. Figgis* and *J. Lewis*).

3. Reactions of noble gases (*John H. Holloway*).

4. The coordination model for the behavior of non-aqueous solvents (*R. S. Drago* and *K. F. Purcel*).

1. This article describes reactions with liquid and gaseous $NH_3$ that lead to addition or ammonolysis products, and reactions with aliphatic amines. The phenomena observed are interpreted according to modern points of view (*e.g.* formation of anionic complexes on ammonolysis of $TiI_4$). The presentation is very clear.

2. The magnetic properties of complexes of the transition metals are discussed on the basis of ligand-field theory. It becomes clear how much superior this method of presentation is to the vector model of the atom used previously. A knowledge of group theory, representation theory, and quantum theory is assumed in the reader; but the reviewer believes that the symbols in the mathematical equations are not always sufficiently explained. The article provides a very good and complete review of present knowledge in the field (670 references).

3. The chemistry of xenon has developed at a remarkable speed since the discovery of $XePtF_6$ and the fluorides $XeF_4$ and $XeF_2$, so that a comprehensive presentation of the results is very welcome. This article provides an excellent review, including the use of molecular-orbital theory to explain the nature of the bond betweenXe and other elements.

4. The object of the fourth article is to show that interaction between a solute and a solvent can be interpreted much more comprehensively on the basis of coordination chemistry than by other theories, the former being also in better agreement with the experimental results. This is clear, for instance, for a solution of $FeCl_3$ in $OPCl_3$, where the primary product is $[Cl_3POFeCl_3]$ which dissociates with formation of the cation $[(Cl_3PO)_nFeCl_2]^+$; this is contrasted with the earlier theory whereby self-dissociation of the medium ($OPCl_3 \rightleftarrows OPCl_2^+ + Cl^-$) is placed in the foreground (formation of the ions $POCl_2^+$ and $[FCl_4]^-$).

All in all, the articles in the present volume can be regarded as highly successful and a useful addition to the literature of the field.

*O. Schmitz-Du Mont* [NB 478/332 IE]

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# Functional Groups on the Surfaces of Solids

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*Atoms or groups foreign to the structure of a solid are often bonded to its surface. On diamond, graphite, and even silicon dioxide, the foreign atoms are bonded covalently, whereas the bonding of the structural groups to titanium oxide and alumina is predominantly ionic. Oxides are normally covered with a monomolecular hydroxide layer. Changes in the valence of the metal atoms lead to changes in the acidity of the surface; for example, reduction of surface $Ti^{4+}$ ions gives the surface of $TiO_2$ an acidic nature.*

## 1. Introduction

The three-dimensional periodic arrangement of atoms in a crystalline solid is interrupted at the surface. The surface may therefore be regarded as an extreme lattice defect. Surfaces of molecular lattices contain entire molecules; the only forces acting at the surface are those that hold the molecules together in the crystal. These van der Waals forces can form only relatively loose bonds with molecules or atoms foreign to the crystal, *i.e.* only physical adsorption can occur on such surfaces.

In ionic lattices and lattices consisting of covalently bonded three-dimensional networks, on the other hand, the surface ions or atoms are coordinatively unsaturated, *i.e.* they possess "free valences". Thus foreign atoms, groups, or ions can be relatively firmly bound (chemisorption).

In most compounds the bonding is intermediate between ionic and covalent. Accurate measurement of the electron-density distribution [1] has shown that even in LiF, there are indications of the presence of "bonds", *i.e.* increased electron density, between the cations and anions.

The situation in amorphous solids is similar to that in crystals, since the former also contain small regions of quasi-crystalline short-range order due to the geometrical arrangement of the valence directions. For example, in amorphous silica, such as silica gel, the $sp^3$ hybridization of silicon gives rise to $SiO_4$ tetrahedra.

[1] *J. Krug, B. Wagner, H. Witte,* and *E. Wölfel,* Naturwissenschaften *40*, 599 (1953).

The strength of the bonds formed with the chemisorbed atoms can vary widely. A surface compound is formed when the bond corresponds in nature and strength to the bonds in the body of the solid or in ordinary chemical compounds.

Really "clean" surfaces are rare, since reactive substances, particularly oxygen and water, are present in the atmosphere. Under normal conditions, therefore, many substances are covered with surface oxides or hydroxides. This covering has a decisive influence on the character of the surface.

It is important for many technical applications to know how these surface coverings behave. Surface compounds play an important part, not only in heterogeneous catalysis, but also in friction and lubrication processes, in the reinforcement of rubber with fillers or of synthetic resins with glass fibers, in the behavior of pigments in lacquers and inks, in textile processing agents, in the adhesion of phosphors to television screens, and in many other processes. Nevertheless, very little work has been done with a unified approach to this field. This may be partly because only in substances with large specific surface areas does the number of foreign atoms bonded to the surface become analytically important. The usual chemical methods of analysis can only be used for substances with specific surface areas of several hundred square meters per gram. For smaller specific surface areas, down to values of the order of 1 $m^2/g$, specially adapted micromethods are required, while for still smaller specific surface areas, such as are found in coarse-grained material, the foreign atoms bound to the surface can be determined only by physical methods, if at all.

The structures and reactions of some typical surface compounds are described below. Chemisorption on metals, which is important in many catalytical processes, cannot be treated here.

## 2. Surface Compounds on Diamond-Like Structures

Diamond is a particularly suitable substance for the study of surface compounds. In the diamond lattice, which is also the lattice structure of silicon and germanium, the atoms are linked tetrahedrally because of their $sp^3$ hybridization. Diamond is the prime example of a crystal with purely covalent bonds. The most frequent cleavage plane is (111), *i.e.* the octahedral face, in which one bond is broken per C atom. It was observed as early as 1918 that diamond powder, which is normally hydrophobic, becomes hydrophilic on treatment with oxidizing agents [2]. Natural diamonds from volcanic pipes (*e.g.* at Kimberley) are hydrophobic; on the other hand diamonds from secondary deposits (placers) are hydrophilic.

This behavior is due to the formation of surface oxides [3]. Diamond powder with surface oxides has a higher heat of wetting in water than diamond powder without surface oxides. When diamond powders with surface oxides are treated with water, carboxyl groups are formed (Fig. 1a). Determination of the active hydrogen by the method of *Zerevitinoff* or by deuterium exchange shows that nearly all the hydrogen atoms present are in the form of carboxyl groups [4]. However, most of the oxygen is not bound in the carboxyl groups, but in a form that is not yet definitely known. No confirmation has been found for the conjecture that tertiary hydroxyl groups are bonded to the octahedral face (Fig. 1c). Other groups containing oxygen that could conceivably be attached to the surface of diamond are indicated in Figures 1b, 1d, and 1e.

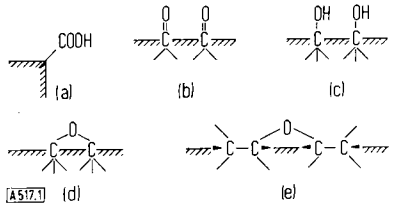



Fig. 1. Functional groups on the surface of diamond.
(a) Carboxyl groups on an edge (detected);
(b) Carbonyl groups on a (100) face (presumed);
(c) Tertiary hydroxyl groups on a (111) face (not detectable);
(d) Ether grouping on a (111) face (presumed);
(e) Ether grouping on a (110) face (presumed).

A surface oxide structure with unpaired electrons on the oxygen has also been ruled out. Electron-spin resonance measurements on a sample with an oxygen content of 320 μg-atom/g of diamond indicated only 7 μequiv of unpaired electrons/g of diamond [5]. Similar results were obtained when diamond powder was heated to remove surface oxides, and then treated with fluorine, chlorine, or hydrogen at elevated temperatures, whereby 200 μequiv of halogen per gram and 230 μequiv of hydrogen per gram were bound to the surface [3]. The infrared spectra of the substances contained corresponding absorption bands. Though the ESR signal showed only a small decrease in intensity during these reactions, its shape and width changed appreciably. It follows that the unpaired electrons are situated close to the surface.

Even diamond that had been freed from surface oxides in a high vacuum ($10^{-5}$ to $10^{-6}$ mm Hg) at 800 °C did not exhibit a much greater ESR absorption (11 μequiv of free radicals/g of diamond). A possible explanation is the rapid contamination of the surface by impurities such as vapor from the vacuum grease. Even at this low pressure, however, surface oxides are probably reformed on cooling. The coefficient of friction of diamond increases markedly when the surface oxides are removed in an ultrahigh vacuum ($5 \times 10^{-10}$ mm Hg). If the surface of this diamond is exposed to the residual gas pressure of $5 \times 10^{-10}$ mm Hg, the frictional coefficient decreases within 20 min to the value normally found in air [6]. However, chemical analysis revealed practically no bound oxygen on diamond that had been heated at 950 °C in a high vacuum and allowed to cool therein [4]. Confirmation of the formation of surface oxides under these conditions has been obtained in diffraction studies with low-energy electrons [7].

Low-energy electron diffraction [8] is particularly suitable for the investigation of the structures of surface compounds, as well as of the "bare" surface. The surface of a crystal with a diameter of a few millimeters is irradiated with an electron beam, the energy of which is varied between 20 and 200 eV. The corresponding wavelength (0.6 Å at 20 eV) is of the same order as the interatomic distances in the lattice. Since the penetration depth is small, amounting to only a few layers of atoms, the diffraction pattern represents the structure of the surface. Owing to the low energy of the electrons, the measurements must be carried out at $10^{-4}$ to $10^{-10}$ mm Hg, *i.e.* under conditions in which some surface compounds are not stable.

A pure, fault-free surface gives the diffraction pattern of the basic structure. If the foreign atoms or the surface atoms of the crystal have a periodic arrangement with unit cells larger than those of the crystal lattice, the reflections due to the latter are accompanied by others having fractional indices with respect to the "normal" reflections. A structure analysis of the surface layer is thus possible, but the difficulties involved are considerably greater than in normal X-ray analysis.

The principal results obtained by diffraction of slow electrons can be summarized as follows. Whereas "atomically pure" metal surfaces, *e.g.* the (100) face of nickel [9] or chromium [10], have the ideal face-centered and body-centered cubic lattices, respectively, "clean" silicon or germanium surfaces (diamond lattice) give reflections with fractional indices [11–13]. In a fresh (111)

[2] *K. A. Hofmann*: Anorganische Chemie. Verlag Vieweg, Braunschweig 1918, p. 287.

[3] *H.-P. Boehm, E. Diehl, W. Heck*, and *R. Sappok*, Angew. Chem. *76*, 742 (1964); Angew. Chem. internat. Edit. *3*, 669 (1964).

[4] *R. Sappok* and *H.-P. Boehm*, unpublished work.

[5] We thank Prof. *U. Hausser* for these measurements.

[6] *F. P. Bowden* and *A. E. Hanwell*, Nature (London) *201*, 1279 (1964).

[7] *J. B. Marsh* and *H. E. Farnsworth*, Surface Sci. *1*, 3 (1964).

[8] The results obtained by this method are reviewed by *J. J. Lander*, Surface Sci. *1*, 125 (1964).

[9] *A. U. MacRae*, Surface Sci. *1*, 319 (1964).

[10] *C. A. Haque* and *H. E. Farnsworth*, Surface Sci. *1*, 378 (1964).

[11] *R. E. Schlier* and *H. E. Farnsowrth*, J. chem. Physics *30*, 917 (1959).

[12] *J. J. Lander* and *J. Morrison*, J. chem. Physics *37*, 729 (1962).

[13] *J. J. Lander* and *J. Morrison*, J. appl. Physics *34*, 1403 (1963).

cleavage surface, the Si tetrahedra are distorted to such an extent that the distance between pairs of surface Si atoms is only 2.6 Å compared to 3.84 Å within the crystal. Naturally, the Si atoms in the next two layers are also displaced from their normal positions. This structure is still unstable. When the crystal is annealed at 700 °C (300 °C for Ge), about 25% of the surface Si atoms diffuse to other positions. The result is a surface structure containing puckered six-membered rings [12]. Calculation of the Si–Si distance in the rings from the atomic coordinates gives a value of 2.2 Å, whereas the normal bond length is 2.35 Å. This indicates some double-bond character; *Lander* [8, 13] refers to the rings as "warped benzene rings". A structure consisting of Si chains with conjugated double bonds of length 2.2 Å has also been suggested [14].

In both of these structures, there is a regular pattern of vacancies in the topmost layer. However, it has been observed that surface structures with ideal periodicity are formed when oxygen [11] or iodine [13] is chemisorbed on these surfaces at low temperatures [15]. Moreover, compounds of silicon or germanium containing double bonds are unknown.

The free valences in the surface exhibit a marked tendency to saturate one another, and the energy liberated in this way is sufficient to cause severe distortion of the lattice. These results explain the observation that diamond does not exhibit strong electron spin resonance. It is apparently impossible to obtain a clean diamond surface with two-dimensional order. Diffraction patterns are observed only after treatments that lead to the formation of surface compounds, *e.g.* after treatment with aqua regia or hydrogen (at 700 °C) [7]. The normally very effective process in which clean surfaces are obtained by bombardment with $Ar^+$ ions leads to an "amorphous surface" with no periodic order [*].

After treatment of diamond powder with $H_2$ at 700 °C, the diffraction pattern of the surface contains strong reflections with integral number indices, and only weak reflections of half-integral order. Presumably this treatment generates C–H groups, as is also indicated by the low heat of wetting in water [3].

Significant effects were also observed on treatment of the diamond surface with oxygen at $2 \times 10^{-6}$ mm Hg [7]. The diffraction pattern changes only slowly at room temperature, and more rapidly at higher temperatures. Whereas chemisorption of oxygen on silicon leads to extinction of the reflections of half-integral order [11], these reflections occur frequently in surface oxides of diamond [7]. No structure analysis has been carried out, but it may be assumed that the free valences of the C atoms are saturated by oxygen bridges, again with distortion of the diamond lattice (Fig. 1d and 1e).

One atom of iodine or bromine per atom of Si (or Ge) is chemisorbed on the (111) face of silicon (or germanium). Contrary to expectations, the halogen atoms are not situated directly above the surface Si atoms, but above the centroid of a triangle formed by three Si atoms [12]. The bonding presumably involves the d-orbitals of the halogens.

Further peculiar surface structures are formed when phosphorus [12] or aluminum [16] is chemisorbed on the (111) surface of silicon.

The bonding of chlorine on diamond is different from that of oxygen or hydrogen. The infrared spectrum of diamond treated with hydrogen contains an absorption band at 2850 $cm^{-1}$ [4] (C–H bond). In diamond treated with chlorine, on the other hand, a weak absorption occurs at 1410 $cm^{-1}$, and not between 600 and 800 $cm^{-1}$ as expected. Diamond treated with oxygen absorbs at 1760 $cm^{-1}$, indicating the presence of carbonyl groups. These could easily be formed on the (100) surface of diamond (Fig. 1); on the (111) surface, however, their formation requires the cleavage of another C–C bond. Carbonyl groups on the (100) surface form part of a warped, rigid $C_6$ ring if the C atoms in the second and third layers are also considered. This would agree with the relatively high frequency of the absorption. A very broad absorption at 1000–1300 $cm^{-1}$ could be due to ether bridges on the (111) and (110) surfaces (Fig. 1d and 1e).

Microgravimetric and gas-analytical studies of the oxidation showed that diamond powder is not continuously oxidized below 360 °C [3]. The weight increases to a terminal value. Nevertheless $CO_2$ is formed, presumably by oxidation of exposed C atoms. The surface oxides are almost completely decomposed in a vacuum at 950 °C, with further formation of $CO_2$ in addition to CO. If it is assumed that one O atom is bonded to each surface C atom, isolated C atoms must remain on the surface after decomposition; when the surface is oxidized again, these atoms are removed as $CO_2$ before a new oxide layer is formed.

### 3. Surface Compounds on Black Carbon

Elementary carbon occurs as diamond, graphite, and graphite-like microcrystalline carbon. Whereas aliphatic carbon compounds are derived from the diamond lattice, the graphite layer lattice forms the basis of aromatic compounds. Each atom in these layers is linked by σ-bonds to three neighbors ($sp^2$ hybridization). The fourth valence electron is bound as a π-electron, which can easily migrate from one atom to another within the layer. The layers are relatively loosely held together by van der Waals forces (distance 3.35 Å). Microcrystalline carbon consists of packets of layers, in which some 3 to 30 aromatic layers about 10 to 1000 Å in diameter are stacked in an unordered manner (turbostratic order) [17]. The surface compounds correspond to the end groups

[14] *R. Seiwatz*, Surface Sci. *2*, 473 (1964).

[15] Cf. *N. R. Hansen* and *D. Haneman*, Surface Sci. *2*, 566 (1964).

[*] Note added in proof: *J. J. Lander* and *J. Morrison*, Surface Sci. *4*, 241 (1966), report a structure with puckered $C_6$ rings for a clean (111) face of diamond, similar to that of Si. After treatment with $H_2$ at 900–1000 °C, the ideal periodicity was observed, whereas $O_2$ did not produce an ordered surface structure.

[16] *J. J. Lander* and *J. Morrison*, Surface Sci. *2*, 553 (1964).

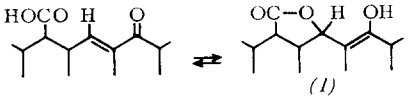
[17] *U. Hofmann* and *D. Wilm*, Z. Elektrochem. angew. physik. Chem. *42*, 504 (1936).

of polymers. It follows from the highly-condensed aromatic layer structure that surface compounds on graphite or microcrystalline carbon can be expected only at the layer edges (prism faces of graphite). Foreign atoms or molecules can be only weakly adsorbed on the basal faces by means of the π-electrons, except where they are bound at lattice defects.

When microcrystalline carbon is treated with oxygen just below its ignition temperature, surface oxides with acidic properties are formed. If, on the other hand, the carbon is heated to remove surface compounds, and cooled to room temperature in vacuum or in an inert gas, it can bind acids with simultaneous uptake of oxygen and formation of basic surface oxides. Thus depending on its pretreatment, the same sample may carry predominantly acidic groups or only basic groups [18]. The quantity of the basic surface oxides formed is always smaller than the quantity of acidic surface oxides; however, all charcoals with acidic surface oxides also carry basic surface oxides. Typical neutralization values are about 80–250 mequiv of NaOH/100 g and 10–15 mequiv of HCl/100 g.

The first attempts to elucidate the constitution of the acidic surface oxides by the methods of chemical analysis were made by *Villars* [19] and by *Hofmann* and *Ohlerich* [20].

The acidic surface oxides formed by the action of oxygen on microcrystalline carbon at about 400 °C contain four types of acidic groups. Carboxyl, phenolic hydroxyl, and carbonyl groups have been detected. One carboxyl and one carbonyl group probably combine to form a lactone *(1)* [21] or *(2)*.

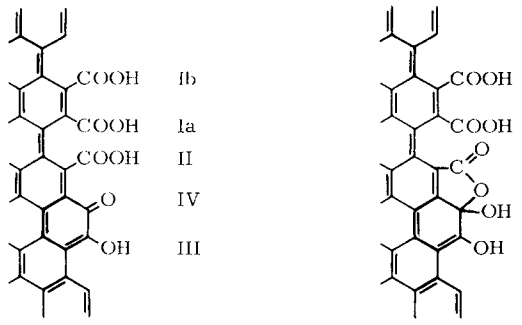


*(1)*

*(2)*

In fully oxidized samples, the four groups are present in equivalent amounts. When the carbon is treated with aqueous solutions of strong oxidizing agents (*e.g.* ammonium persulfate) at room temperature, two carboxyl groups are found for every one of the other groups, one of the two carboxyl groups decomposing at about 200 °C with liberation of $CO_2$. Fig. 2 shows a model containing all the functional groups that have been detected.

The acidic surface groups are most easily detected by neutralization with bases. Free carboxyl groups react with hydrogen carbonate ions, the lactone rings are opened by sodium carbonate, and the phenolic groups require sodium hydroxide for neutralization. The carbonyl group adds sodium ethoxide to form a salt of a hemiacetal, $C(OC_2H_5)O^-$




Open form Lactone form

Fig. 2. Model containing all the functional groups detected in acidic surface oxides of carbon. The arrangement of the groups in a closely spaced row has not been proved. Two carboxyl groups or two carbonyl groups often appear to be close together. The carboxyl groups can then form anhydrides [3].

Ia. Carboxyl group which is removed at about 200 °C (occurs only in products that have been oxidized at 20–150 °C);
Ib. Carboxyl group, removable only above 325 °C;
II. Carboxyl group that occurs as a lactone;
III. Phenolic hydroxyl groups;
IV. Carbonyl group that reacts with the carboxyl group II to form the lactone (or lactol).

$Na^+$ [22]. Moreover, unpaired electrons have also been detected in oxidized carbon [23].

The acidic surface groups are usually determined by neutralization with dilute sodium hydroxide solution. The samples are shaken with standard NaOH, and aliquots of the solution are back-titrated. It is important that shaking is continued to complete neutralization [3, 22, 24]. The time required for complete neutralization is 96 hours with 0.01N NaOH, or 12 hours with 0.05N NaOH [24a]. When concentrated sodium hydroxide solutions are used, more base is consumed, corresponding to the sodium ethoxide value; this value is reached after 96 hours with 0.25 N NaOH, and after 36 hours with 1 N NaOH. The use of barium hydroxide [24] has two disadvantages: 1. Porous charcoals nearly always contain adsorbed $CO_2$, which forms insoluble $BaCO_3$ ($Na_2CO_3$, on the other hand, is included in a back-titration, and so does not affect the result); 2. exchange of acidic hydrogen for bivalent cations may occur either between equivalent quantities or between equimolar quantities (Fig. 3). Equivalent ion exchange occurs when the charged surface groups are situated close together, *e.g.* in synthetic ion exchange resins. In equimolar ion exchange, a bivalent (or multivalent) cation, together with additional anions to preserve electrical neutrality, is bound instead of a monovalent cation; this occurs when the charges are relatively far apart. The possibility of equimolar ion exchange with multivalent ions must be borne in mind in all reactions used for the determination of surface groups. Charge compensation is better in this case than in

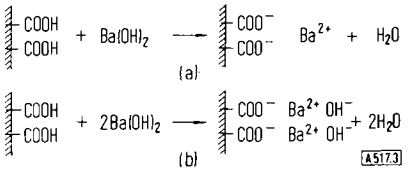



Fig. 3. Reaction schemes for equivalent (a) and equimolar (b) ion exchange. Example: neutralization of surface carboxyl groups.

[18] *H. R. Kruyt* and *G. S. de Kadt*, Kolloid-Z. *47*, 44 (1929).

[19] *D. S. Villars*, J. Amer. chem. Soc. *69*, 214 (1947); *70*, 3655 (1948).

[20] *U. Hofmann* and *G. Ohlerich*, Angew. Chem. *62*, 16 (1950).

[21] *V. A. Garten, D. E. Weiss*, and *J. B. Willis*, Austral. J. Chem. *10*, 295 (1957).

[22] *H.-P. Boehm, E. Diehl*, and *W. Heck*, Ind. Carbon and Graphite, in press.

[23] *J. B. Donnet* and *G. Henrich*, Bull. Soc. chim. France *1960*, 1609; *J.B. Donnet, G. Henrich*, and *G. Riess*, Rev.gén. Caoutchouc Plastiques *38*, 1803 (1961).

[24] *B. R. Puri* and *R. C. Bansal*, Carbon *1*, 457 (1964).

[24a] *H. P. Boehm* and *H. J. Kuhn*, unpublished work.

equivalent exchange. *Pauling*[25] has pointed out that the positive ions in a crystal lattice occupy the positions at which the negative potential is greatest, and *vice versa*. The same is true on the surface[26]. The state adopted is that with the minimum potential and the smallest possible distance between opposite charges. The phenomenon of equimolar ion exchange was first observed in kaolinite by *Weiss*[26], and was subsequently also observed on the surface of $SiO_2$[27]. However, the more strongly acidic groups of the surface oxides of carbon appear to lie sufficiently close together to ensure equivalent exchange[3,24].

It has been shown[28] that oxygen is almost entirely chemisorbed on the prism faces of graphite crystals. Single crystals 2 mm in diameter and about 0.1 mm high were treated with $O_2$ at 700 °C. The oxides of carbon given off in vacuum at 900 °C were determined by mass spectrometry. The experiment was then repeated, but the crystals were first cleaved five times parallel to the layer planes, so that while the area of the prism faces remained the same, the area of the basal faces was increased by a factor of six. The quantity of gas given off was not affected by this treatment.

Carbon blacks that have been graphitized at 2400 to 3000 °C have a very homogeneous surface[29]. The surface of the isometric particles consists almost entirely of the basal surfaces of pyramidal graphite crystals, the apices of which are situated in the center of the particle[30]. Consequently, graphitized carbon blacks form practically no acidic surface oxides[31].

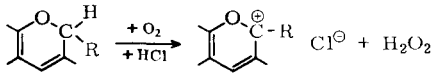
The functional groups on the carbon surface undergo the usual reactions of organic chemistry. The carboxyl groups react with diazomethane[3,20,22,31–33], alcohols[3], acetyl chloride[3], or $SOCl_2$[3,22,31]. Friedel-Crafts reactions and Curtius rearrangements can be carried out[3,22]. The phenols react with *p*-nitrobenzoyl chloride or with 2,4-dinitrofluorobenzene[3,22]. The carbonyl groups add ethoxide, and react with hydroxylamine to form oximes[22].

Although the basic surface oxides have been known longer[34] than the acidic ones, nothing definite is known as yet about the constitution of the former. Carbon binds mineral acids only in the presence of oxygen[35]. The extent of adsorption depends on the partial pressure of oxygen, at least below 20 mm Hg[36, 37]. Part of the bound acid is undoubtedly physically adsorbed, particularly at higher concentrations, since it can be displaced by solvents such as toluene[38,39]. This result indicates that a relatively weak interaction occurs with the π-electrons of the layers; perhaps proton complexes of the aromatic layers are formed[38,40].

According to *Burstein* and *Frumkin*[41], the reaction of basic surface oxides with acids yields $H_2O_2$:

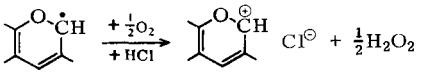
$$C_xO_2 + 2\,H^+ + 2\,X^- \rightarrow C_x^{2+}(X^-)_2 + H_2O_2$$

However, this product has never been detected in the expected quantities, possibly because of carbon-catalysed decomposition. A substance that oxidizes KI has been repeatedly observed[42]. More recent studies[43] have shown that the acid is adsorbed relatively slowly, and that the concentration of $H_2O_2$ in the surrounding solution passes through a maximum. The salts of the basic surface oxides decompose in vacuum above 60 °C[43]. *Garten* and *Weiss*[39] believe that the oxygen is present in chromene-like structures *(3)*, in which the positive charge is delocalized after the addition of acid as in benzopyrylium salts.




*(3)*

Free radicals such as *(4)* could also be responsible for the reaction[39].




*(4)*

On the other hand, carbonium and oxonium bases are normally very weak, and washing would be expected to lead to complete hydrolysis; the charcoals, however, cannot be completely freed from bound acids by washing with water [44, 45].

The anion must be ionically bound, since it is exchangeable[38,45]. Cationic sites have been detected in carbon blacks by hydride-transfer reactions[45]; thus isopropanol in 50% $H_2SO_4$ has been oxidized to acetone:

$$R^+X^- + CH_3\,CH(OH)\,CH_3 \rightarrow R{-}H + HX + CH_3COCH_3$$

The original carbon black, after oxidation with triphenylmethyl perchlorate, can also oxidize isopropanol:

$$R{-}H + (C_6H_5)_3C^+ClO_4^- \rightarrow R^+ClO_4^- + (C_6H_5)_3CH$$

The corresponding formate decomposes with evolution of $CO_2$[45]:

$$R^+HCOO^- \rightarrow R{-}H + CO_2$$

Since acids are bound only in the presence of oxygen, which can be detected in the reaction product[43], it is justifiable to speak of basic surface oxides. These prob-


[25] *L. Pauling*, J. Amer. chem. Soc. *51*, 1010 (1929).

[26] *A. Weiss*, Kolloid-Z. *158*, 22 (1958); Z. anorg. allg. Chem. *299*, 92 (1959).

[27] *H.-P. Boehm* and *M. Schneider*, Z. anorg. allg. Chem. *301*, 326 (1959).

[28] *G. R. Hennig* in: Proc. 5th Conf. on Carbon, 1961. Pergamon Press, London-New York 1962, Vol. I, p. 143.

[29] *R. A. Beebe* and *D. M. Young*, J. physic. Chem. *58*, 93 (1954).

[30] *E. A. Kmetko* in: Proc. 1st and 2nd Conf. on Carbon, University of Buffalo, N.Y. (1956), p. 21; *H.-P. Boehm*, Z. anorg. allg. Chem. *297*, 315 (1958).

[31] *H.-P. Boehm*, *E. Diehl*, and *W. Heck*, Rev. gén. Caoutchouc Plastiques *41*, 461 (1964).

[32] *M. L. Studebaker*, *E. W. D. Huffman*, *A. C. Wolfe*, and *L. G. Nabors*, Ind. Engng. Chem. *48*, 162 (1956).

[33] *H.-P. Boehm* and *E. Diehl*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *66*, 642 (1962).

[34] *F. E. Bartell* and *E. J. Miller*, J. Amer. chem. Soc. *44*, 1866 (1922); *45*, 1106 (1923); *E. J. Miller*, *ibid. 46*, 1150 (1924); *47*, 1270 (1925).

[35] *R. Burstein* and *A. Frumkin*, Z. physik. Chem. *A 141*, 219 (1929).

[36] *N. Schilow*, *G. Schatunowskaja*, and *K. Tschmutow*, Z. physik. Chem. *A 149*, 211 (1930).

[37] *O. Bretschneider*, Z. physik. Chem. *A 159*, 436 (1932).

[38] *B. Steenberg*, Dissertation, University of Uppsala 1944.

[39] *V. A. Garten* and *D. E. Weiss*, Austral. J. Chem. *10*, 309 (1957).

[40] See, *e.g.*, *H. H. Perkampus* and *E. Baumgarten*, Angew. Chem. *76*, 965 (1964); Angew. Chem. internat. Edit. *3*, 776 (1964).

[41] *R. Burstein* and *A. Frumkin*, Doklady Akad. Nauk SSSR *32*, 327 (1941).

[42] *A. B. Lamb* and *L. W. Elder*, J. Amer. chem. Soc. *53*, 137 (1931); *J. M. Kolthoff*, *ibid. 54*, 4473 (1932); *A. King*, J. chem. Soc. (London) *1934*, 22.

[43] *H.-P. Boehm* and *M. Voll*, unpublished work.

[44] *E. J. Miller*, J. physic. Chem. *36*, 2967 (1932).

[45] *D. Rivin*: Proc. 5th Conf. on Carbon, 1961. Pergamon Press, London-New York 1963, Vol. II, p. 199.

ably play an important part in the transfer of oxygen by carbon in fuel cells using atmospheric oxygen or in the use of carbon as a depolarizer in other cells.

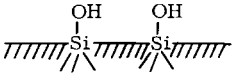
Hydrogen and halogens, as well as other elements, are bound on the surface of graphite and of microcrystalline carbon. In carbons (*e.g.* carbon black) obtained from hydrocarbons or other organic materials, most of the free valences at the edges of the carbon layers are saturated by hydrogen.

## 4. Surface Compounds on Silica

Silica occurs in many crystalline forms and in an amorphous form. Apart from stishovite, which has the rutile structure, and the very unstable fibrous silica, which has the $SiS_2$ structure [46], all the modifications have the well-known three-dimensional network of $SiO_4$ tetrahedra with common corners. The Si–O bond is partially ionic [47,48]. The bond angle at the oxygen atom in the siloxane bond Si–O–Si is close to 140° [49]. This value suggests that the electron pairs of oxygen that are not used in the $\sigma$-bonds are also involved in the bonding ($d_\pi$-$p_\pi$ bond).

The surface chemistry of silica appears at first sight to be much simpler than that of carbon. Under normal conditions, only two types of "end groups" are conceivable on the surface, namely siloxane groups *(5)* and silanol groups *(6)*.

*(5)*




*(6)*

By far the most investigations have been carried out with amorphous silica with a large specific surface area, mainly because this material has many industrial uses. Porous silica gel, for example, is used as an adsorbent and drying agent, while other types with spherical particles are used as fillers in rubbers and plastics. $SiO_2$ is also used as a powder base, as a toothpaste additive, and in the textile industry.

The very pure and non-porous "Aerosil" [*] and Cabosil [*], which are produced by flame hydrolysis of $SiCl_4$, have proved to be particularly suitable for many measurements.

*U. Hofmann et al.* [50] were the first to recognize that the free valences at the edges of the silicate layers in the clay minerals must be saturated by silanol groups. *Carman* [51] came to the same conclusion for colloidal amorphous $SiO_2$.

The number of surface silanol groups was at first determined from the loss on ignition at 1000–1100 °C. However, this method raises certain difficulties. Many products obtained by condensation of low molecular-weight silicic acids also contain silanol groups in the interior of the particles, since some of the silanol groups fail to find partners during the condensation. These groups are mostly, but not entirely, decomposed at 1000 °C. Small amounts of OH groups have even been detected in vitreous silica [52,53] and in rock crystal [54] by their infrared absorption. Water molecules may also be very strongly adsorbed, and they may fail to escape on drying at 150 to 200 °C [55]. This adsorbed water can be titrated by the Karl Fischer method. If a suitable correction is made to the loss on ignition, the resulting silanol contents agree satisfactorily [56] with the values obtained *e.g.* by reaction with thionyl chloride [27].

Calculation from the loss on ignition often gives a very high value for the packing density of the silanol groups on the surface. The maximum possible packing density can be estimated from the structure of the crystalline modifications of $SiO_2$. In this way *de Boer* [57] obtained a value of 4.55–4.85 OH/100 Å$^2$ for cristobalite and tridymite. The calculated values [58] for various crystal faces are listed in Table 1. If the lower density of amorphous $SiO_2$ is taken into account, averaging over all the crystal faces gives a packing density of about 5 OH/100 Å$^2$ for amorphous $SiO_2$. However, the values found by measurement are nearly always lower [59].

Table 1. Packing density of silanol groups on various crystal faces of silicon dioxide.

| Modification | Face | Packing density (OH/100 Å$^2$) | |
|---|---|---|---|
| | | [a] | [b] |
| Quartz | (001) | 9.6 | 8.5 |
| (d = 2.655) | (101) | 6.0 | 5.2 |
| Cristobalite | (100) | 7.9 | 7.6 |
| (d = 2.32) | (101) | 5.6 | 5.3 |
| | (111) | 4.5 | 4.4 |
| Tridymite | (001) | 4.5 | 4.5 |
| (d = 2.26) | (100) | 4.8 | 4.7 |

[a] for crystalline $SiO_2$.
[b] calculated value for amorphous $SiO_2$, based on density d = 2.20.

Hydroxyl groups on the $SiO_2$ surface have also been detected by infrared spectroscopy. Aerosil that had been degassed at 30 °C showed absorptions at 3750 cm$^{-1}$ (isolated silanol groups), 3660 cm$^{-1}$ (hydroxyl groups with weak hydrogen bonds), and 3520 cm$^{-1}$ (strong hydrogen bonds) [60]. When the sample was heated, the absorption at 3520 cm$^{-1}$ receded first; outgassing at 940 °C led to the disappearance of the peak at 3660 cm$^{-1}$, and the intensity of the absorption at 3750 cm$^{-1}$ increased at the same time. It can be concluded, therefore, that more than two hydroxyl groups must be present in the complexes that absorb at 3660 cm$^{-1}$, since no OH groups would otherwise remain after the removal of


[46] *A. Weiss* and *A. Weiss*, Z. anorg. allg. Chem. *276*, 95 (1954).

[47] *W. Noll*, Angew. Chem. *75*, 123 (1963); Angew. Chem. internat. Edit. *2*, 73 (1963).

[48] *H. Schmidbaur*, Angew. Chem. *77*, 206 (1965); Angew. Chem. internat. Edit. *4*, 201 (1965).

[49] *F. Liebau*, Z. Naturforsch. *15b*, 468 (1960); Acta crystallogr. *14*, 1103 (1961).

[*] Aerosil is manufactured by Degussa, Hanau (Germany), and Cabosil by Cabot Corp., Cambridge, Mass. (U.S.A.).

[50] *U. Hofmann, K. Endell*, and *D. Wilm*, Angew. Chem. *47*, 539 (1934).

[51] *P. C. Carman*, Trans. Faraday Soc. *36*, 964 (1940).

[52] *A. J. Moulson* and *J. P. Roberts*, Nature (London) *182*, 200 (1958).

[53] *H. Schäfer* and *K. Etzel*, Z. anorg. allg. Chem. *301*, 137 (1959).

[54] *G. O. Brunner, H. Wondratschek*, and *F. Laves*, Z. Elektrochem. angew. physik. Chem. *65*, 735 (1961).

[55] *W. Stöber*, Kolloid-Z., *145*, 17 (1956).

[56] *W. Noll, K. Damm*, and *R. Fauss*, Kolloid-Z. *169*, 18 (1960).

[57] *J. H. de Boer* and *J. M. Vleeskens*, Proc. Kon. nederl. Akad. Wetensch., Ser. B *61*, 2 (1958).

[58] *M. Schneider*, Dissertation, Universität Heidelberg 1962.

[59] *H.-P. Boehm* and *M. Schneider*, Kolloid-Z. *187*, 128 (1963).

[60] *R. S. McDonald*, J. physic. Chem. *62*, 1168 (1958).

water. The observation that the OH groups with the stronger hydrogen bonds are the first to be split off has been repeatedly confirmed [61,62]. Different reaction rates were also observed in the OH/OD exchange on the silanol groups [62]. The combination and overtone vibrations in the region between 1 and 3 μ [63–65] are particularly suitable for differentiation between silanol groups and water.

A silica particle may be regarded as very highly polymeric polysilicic acid. The silanol groups on the $SiO_2$ surface enter into many chemical reactions. They are weakly acidic, and can be titrated in concentrated NaCl solution with NaOH [66]. In our experience, all the silanol groups are neutralized at pH 9.0; further addition of NaOH leads to cleavage of siloxane bonds. On neutralization with $Ca(OH)_2$ an equimolar reaction occurs [27].

The reaction with thionyl chloride

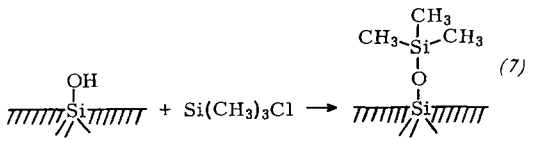
$$\equiv Si{-}OH + SOCl_2 \rightarrow \equiv Si{-}Cl + SO_2 + HCl$$

can also be used for the determination of silanol groups if the substance does not contain narrow pores [27,67,68]. The reagent and the reaction products are held so firmly in narrow pores that they cannot be completely removed by degassing at 200 °C.

However, the content of active hydrogen found by Zerevitinoff determinations was higher than that corresponding to the chloride uptake from $SOCl_2$ [69], but this may be due to very strongly adsorbed water (see below). The OH absorption in the infrared spectrum of porous Vycor glass (which is 96% $SiO_2$) disappeared when the glass was treated with $SOCl_2$, and after subsequent treatment of the glass with $NH_3$, the spectrum indicated the presence of $Si{-}NH_2$ groups [70].

Esterification with alcohols can be used for the analytical determination of silanol groups *via* the methoxy or carbon content. The silica is heated with the alcohol in an autoclave or, for higher alcohols, in a vessel fitted with a rectifying column, the water formed being distilled off as an azeotrope [71–73]. The silanol groups can also be methylated with diazomethane [27,74]. Esterification makes the surface hydrophobic, and leads to a finely divided silica which can be readily incorporated into oils or waxes [71].

Of the many other reactions of these surface hydroxides, we shall mention only those with $Si(CH_3)_3Cl$ [75,76], $BCl_3$ or $AlCl_3$ [67], with trialkylaluminum [77], and with $B_2H_6$ [78,79], in which the hydrogen of the silanol groups reacts to form HCl, alkane, and $H_2$ respectively. Coating as in *(7)* with trimethylsilyl groups leads to a marked decrease in the rate of dissolution of finely divided



(7)

silica in water [75]. Although some of the silanol groups remain unchanged, the surface is protected by the trimethylsilyl "umbrellas". Coating with a monoatomic layer of $Al^{3+}$ practically prevents the removal of $Si(OH)_4$ from the surface of Aerosil [67,77]. These ions are adsorbed hydrolytically on the $SiO_2$ surface from basic aluminum chloride solutions containing 1 to 2 hydroxide ions per $Al^{3+}$ ion [80]; one $Al^{3+}$ ion is firmly bound per silanol group [81]. During hydrolytic adsorption, the polynuclear complexes $[Al_x(OH)_y(H_2O)_z]^{(3x-y)+}$ in the basic aluminum chloride solution give up aluminum hydroxide to the $SiO_2$ surface.

The solubility of orthosilicic acid in water is about 1.67 mmole/l. In a solution of $NaCl/NaHCO_3$ buffered to pH 8.2, 123 μg of $SiO_2$ dissolves per ml of solution at 20 °C. When the solution is shaken with Aerosil (specific surface area about 150 $m^2/g$), this value is reached in about 24 hours. If the solvent is agitated under the same conditions with Aerosil coated with $Al^{3+}$ ions, only 6 μg/ml dissolves in three weeks [67]. The aluminum layer can be readily removed with mineral acids.

Many other ions are hydrolytically adsorbed on the silanol groups of the $SiO_2$ surface [82,83]. This behavior can be used for the analytical separation of ions on silica gel columns [84,85].

Table 2 summarizes results of many reactions on Aerosil. The packing density of the surface silanol groups can be calculated from the specific surface area and the conversion. Table 2 shows remarkable agreement between the results obtained by various methods, particularly in the experiments carried out with the same Aerosil sample of specific surface area 145 $m^2/g$.


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Table 2. Amount and packing density of silanol groups on the surface of Aerosil.

| Reaction | Specific surface area ($m^2/g$) | Silanol groups: amount (meq/100 g) | Silanol groups: packing density (OH/100 Å$^2$) | Ref. |
|---|---|---|---|---|
| Weight loss at 1000 °C — free $H_2O$ (K. Fischer titration) | 180 | 103 | 3.45 | [56] |
| Reaction with $SOCl_2$ | 178 | 62 | 2.10 | [69] |
| Zerevitinoff method with $CH_3MgI$ or $CH_3Li$ | 178 | 122 | 4.12 | [69] |
| Reaction with $SOCl_2$ | 165 | 87 | 3.17 | [27] |
| Reaction with $SOCl_2$ | 145 | 55 | 2.30 | [59] |
| Titration with NaOH [66] | 145 | 57 | 2.38 | [86] |
| Reaction with $BCl_3$ | 145 | 56 | 2.34 | [67] |
| Sorption of $Al^{3+}$ from $Al(OH)_2Cl$ solution | 145 | 60 | 2.50 | [81] |
| Sorption of $UO_2^{2+}$ from $UO_2(CH_3COO)_2$ at pH 5.4 [82] | 145 | 52 | 2.17 | [87] |
| Methylation with $CH_3OH$ at 200–250 °C | 145 | 55 | 2.29 | [88] |
| $D_2O$ exchange after outgassing at 200 °C | 145 | 113 | 4.69 | [89] |
| Zerevitinoff method with $CH_3MgI$ after outgassing at 120–200 °C | 145 | 109 | 4.52 | [89] |
| Infrared spectra | 145 | 115 | 4.77 | [64] |

Values much smaller than 5 OH groups per 100 Å$^2$ were found by all methods except the Zerevitinoff active hydrogen determination and the $D_2O$ exchange method. The value found by the active hydrogen determinations was exactly twice as high. *Stöber* [55] attributed this result to the fact that for every two silanol groups, one molecule of water is adsorbed so strongly that it is not released even in a high vacuum at 100–200 °C. This argument is supported by the results of the reaction with $BCl_3$ or $AlCl_3$ [67]. However, the results of the Zerevitinoff determinations do not fit this explanation, since only one H atom of water reacts with $CH_3MgI$. The infrared spectrum of Aerosil treated with $SOCl_2$ still contains OH absorptions [89]. Aerosil deuterated with $D_2O$ was treated with $SOCl_2$; it then contained half as much exchangeable deuterium as before. Thus the OH groups that are stable towards $SOCl_2$ are situated at the surface.

It is difficult to see why only half of the silanol groups react with the other reagents, since it is very unlikely that the surface contains only silanediol groups $=Si(OH)_2$. These conflicting results require further experimental study. The packing density of silanol groups is influenced by the particle size of the $SiO_2$, and appears to decrease with increasingly fine division [90].

The existence of siloxane groups on the surface of silica has been inferred only from the observation that the number of silanol groups detected is not sufficient to cover the surface completely. Silica that has been heated to a high temperature contains practically no residual silanol groups. The dehydration is reversible if carried out below 450 °C. If, however, $SiO_2$ is heated to 800 to 1000 °C, no rehydroxylation occurs at room temperature on exposure to water vapor below saturation pressure [61,91,92], and the silanol groups are regenerated slowly over a period of several months in aqueous suspension [93,94]. This difference in behavior is ascribed to the stability and inertness of the siloxane grouping. Siloxane bridges formed at low temperatures are still strongly "strained". The strain can lead to distortion of the bond angles or bond lengths and to strongly polar bonds. Only above 450 °C is the thermal energy sufficient for rearrangement of the tetrahedra to such an extent as to remove the strain.

The inertness of the siloxane linkage is due to the $d_\pi$-$p_\pi$ component; it is the only reason for the resistance of silica vessels to many reagents at relatively low temperatures. The Lewis basicity of oxygen is greatly reduced in the siloxane group, and there is practically no tendency for the oxygen to form hydrogen bonds [95]. Consequently, the surface of silica that has been heated to high temperatures becomes hydrophobic. Water-vapor adsorption isotherms are of type III [61] in *Brunauer*'s classification [96], or type V for narrow-pored substances [91,92,97] (Fig. 4).

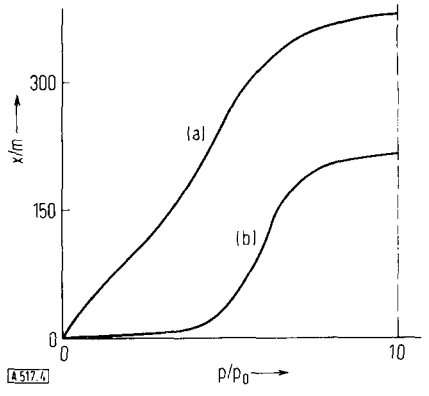


Fig. 4. Adsorption isotherms of water vapor on silica gel at 18 °C, after vacuum treatment at (a) 100 °C, (b) 1000 °C. The desorption branches are not shown (after [97]).

$p/p_0$ = equilibrium pressure/saturation pressure at 18 °C; x/m = quantity of water adsorbed in mm$^3$/g of silica gel.

Siloxane linkages are cleaved by nucleophilic attack on the silicon. The best-known example is the dissolution of $SiO_2$ in alkalis. Similarly, Aerosil is attacked by organolithium compounds [98]. The reaction with phenyl-lithium gives tetraphenylsilane, triphenylsilanol, diphenylsilanediol, and polymeric siloxanes. The $SiO_2$ surface contains phenyl groups bound to Si.


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Silanol groups have been detected on the surface of crystalline quartz [55]. Chemical detection is difficult in this case owing to the small specific surface area. The $Na^+$ uptake from sodium hydroxide solution labelled with $^{22}Na$ gives a value of 4.25 OH/100 Å$^2$ for the packing density of the silanol groups [99]. OH groups have also been detected in the high-pressure modifications coesite and stishovite [100]. Stishovite, in which the silicon atoms have the coordination number 6, dissolves more rapidly in water than the other modifications of $SiO_2$, but is completely insoluble in hydrofluoric acid [100]. Its surface chemistry should resemble that of its structural analogue, rutile, *i.e.* it should point to the presence of strongly polar Si–O bonds.

## 5. Surface Compounds on Titanium Dioxide

Titanium dioxide has three naturally occurring modifications, rutile, anatase, and brookite, the first two of which are produced industrially as important white pigments. In all three crystal lattices, the $Ti^{4+}$ ions are surrounded by slightly distorted octahedra of six $O^{2-}$ ions, and the coordination number of the oxygen with respect to titanium is 3. The bonding may be regarded as essentially ionic. This leads to differences in behavior between the surfaces of titanium dioxide and of silica.

Hydroxyl groups have been detected on the surface of titanium dioxide by their infrared absorption [101, 102]. Whereas anatase still contained water molecules (bending vibration at 1605 cm$^{-1}$) after vacuum drying at 150 °C, two types of hydroxyl groups, which absorb at 3715 and 3675 cm$^{-1}$, remain at 350 °C. Under the same conditions, rutile gives only one band at 3680 cm$^{-1}$.

Water vapor adsorption and the heats of adsorption [103, 104], and the heat of wetting in water [105] also indicate that OH groups are still present on the surface of $TiO_2$ after evacuation at high temperatures. NMR measurements showed the presence of very firmly bound water in rutile after outgassing at 350 °C [106].

How can the presence of hydroxyl groups be explained? Figure 5 shows a section through an anatase crystal in the (100) plane. If the crystal is imagined to be cleaved along the (001) plane (broken line), it has the surface structure shown in Figure 5a: each $Ti^{4+}$ ion lacks one $O^{2-}$ ion in its coordination sphere, and each $O^{2-}$ ion has only two $Ti^{4+}$ neighbors. It may be assumed that in the

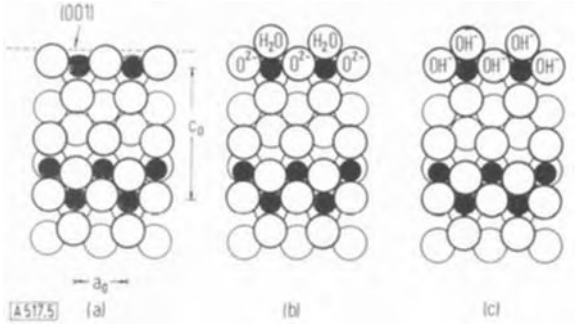


Fig. 5. Addition of water and formation of hydroxide ions on a fresh cleavage plane of anatase ( ●: Ti; O:O).

(a) Fresh cleavage plane along (001); (b) completion of coordination of the $Ti^{4+}$ ions by addition of water; (c) formation of hydroxide ions by proton transfer to the $O^{2-}$ ions on the surface.

presence of water vapor, the coordination gaps on the $Ti^{4+}$ ions are immediately filled by $H_2O$ molecules (Fig. 5b). The equilibrium vapor pressure of the water adsorbed in this way can be expected to be very low. However, even this state is not stable. Proton transfer from $H_2O$ to $O^{2-}$ (Fig. 5c) gives a surface covered with hydroxide ions, in which the charge distribution is much more favorable.

According to *Pauling*'s electrostatic valence rule [107], the negative charge on any anion in a stable ionic lattice is equal or nearly equal to the sum of the "strengths" of the electrostatic bonds joining the anion to the surrounding cations (and *vice versa*). The strength of a bond is defined as the quotient of the charge, z, and the coordination number, ν, of the cation. Thus the charge on the anion, ζ, is given by

$$\zeta = \sum_i z_i/\nu_i$$

Thus in anatase, the charge on the anion situated above the $Ti^{4+}$ ion should be −2/3, while the charge on the oxygen ion bound to two cations should be −4/3. This requirement is better satisfied by the charge −1 on the hydroxide ion than by the arrangement of Fig. 5b, in which the charge on the water is zero and that on the oxygen is −2. In other words, the stable state is that with the lowest potential, *i.e.* with the lowest free energy, and with the lowest possible charges and the minimum separation of opposite charges. Since the bonding forces on the surface OH groups act in only one direction, the distance from these groups to the $Ti^{4+}$ ions should be slightly shorter. A very similar situation is found on the other cleavage planes of anatase[(111) is the most common] and on those of rutile. This is also true of many other metal oxides.

In experiments with titanium dioxide, its sensitivity to reduction is important. When finely divided titanium dioxide is heated in vacuum, it turns gray to blue-gray, whereas it remains white when heated in air. This color change can be attributed to adsorbed organic impurities which are nearly always present [104, 108]. On decomposition these form carbon, which reduces $Ti^{4+}$ to $Ti^{3+}$.

Organic contamination of the surface is a very common phenomenon, and the contaminants can be determined analytically in substances with sufficiently large specific surface areas. Finely divided anatase ($TiO_2$ P 25 [*], specific surface area 56 m$^2$/g) was found to have a carbon content of 0.11%, and Aerosil ($SiO_2$, specific surface area 145 m$^2$/g) also to contain 0.11% of carbon [109]. The organic impurities are presumably derived from volatile constituents (*e.g.* antioxidants) of

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[*] $TiO_2$ P 25 is a very pure, finely divided anatase, produced by Degussa, Hanau (Germany), by flame hydrolysis of $TiCl_4$.

[109] *M. Herrmann*, Dissertation, Universität Heidelberg 1965.

the plastic containers, from solvents in the laboratory atmosphere, from vacuum greases, and from respiration products of plants [110]. The carbon content of titanium dioxide could be reduced to 0.06% by extraction with petroleum ether followed by vacuum outgassing or by treatment with ozone at 100 °C [109]. The carbon remaining after this treatment was traced to $CO_2$, which is adsorbed on anatase even at low partial pressures. At 25 °C and a $CO_2$ pressure of 7 mm Hg (corresponding to a relative pressure $p/p_o = 1.4 \times 10^{-4}$), the product $TiO_2$ P 25 adsorbs 2 mg of $CO_2$ per g of $TiO_2$. The adsorbed $CO_2$ can be detected in the infrared spectrum [101].

The oxidizing power of $TiO_2$ is greatly increased by ultraviolet light [111]. Under these conditions, triphenylmethane derivatives can be oxidized to the leuco bases of the corresponding dyes [112]. Owing to this oxidizing power on irradiation, paints containing untreated $TiO_2$ rapidly deteriorate in light. To avoid this "chalking", the pigment particles are coated with thin layers of other oxides, such as alumina or silica.

The hydroxide ions on the surface of $TiO_2$ can be detected by their reactions, *e.g.* by esterification with alcohols [77, 113, 114]. Reactions with trimethylsilyl chloride and with triisopropylaluminum have also been described [77, 114] (see also Table 3).

Table 3. Reactions of OH groups on the surface of anatase ($TiO_2$ P 25), specific surface area 56.1 $m^2/g$ [109].

| Reaction | Conversion (mmole/100 g of $TiO_2$) |
|---|---|
| Deuterium exchange with $D_2O$ after outgassing at 100 °C | 38 |
| Sorption of $F^-$ from unbuffered NaF solution | 22 |
| Sorption of $F^-$ from NaF solution at pH 4.65 | 44 |
| $F^-$ content after washing with $H_2O$ | 16 |
| Sorption of $Na^+$ from NaOH | 36 |
| Sorption of $Ba^{2+}$ from $Ba(OH)_2$ | 42 |
| Sorption of $Al^{3+}$ from basic $AlCl_3$ solutions | 43 |
| Sorption of $H_2PO_4^-$ from $Na_2HPO_4$ solution | 40 |
| Chlorination with $SOCl_2$ vapor, outgassing at 250 °C | 43 |
| Sorption of $NH_3$ at 20 °C, $NH_3$ determined after outgassing at 20 °C | 23 |
| Sorption of $NO_2$ at 20 °C, N determined after outgassing at 20 °C | 21 |
| Sorption of $SO_3$ from solution in $C_2H_2Cl_2$, $SO_3$ determined after outgassing at 200 °C | 40 |
| Methylation with diazomethane, $OCH_3$ determined | 18 |
| Benzylation with phenyldiazomethane, C determined | 17 |
| Reaction with the $(CH_3)_2C^{\bullet}-CN$ radical, N determined | 43 |
| Same as above, N determined after extraction with ethanol | 20 |
| Reaction with the $(C_6H_5)\dot{N}$ radical, N determined | 18 |
| Reaction with the 2,4-dichlorophenyl radical Cl determined | 23 |

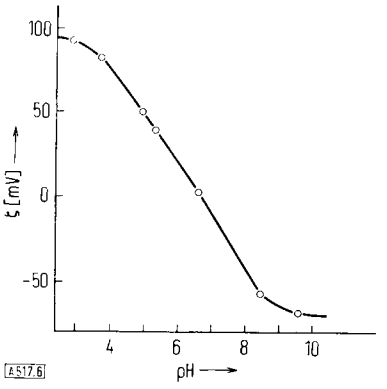


Fig. 6. Electrokinetic potential $\zeta$ of anatase ($TiO_2$ P 25) as a function of the pH, calculated from the electrophoretic mobility. Isoelectric point: pH 6.6.

The hydroxylated surfaces of anatase and of rutile are amphoteric [109, 115]. Figure 6 shows the relationship between the electrokinetic potential and pH for $TiO_2$ P 25. The isoelectric point is at pH 6.6. Consequently, $TiO_2$ can exchange hydrogen ions for cations in alkaline solutions, and the OH groups can be neutralized with alkali hydroxides [109]. Anions, and particularly fluoride, sulfate, and phosphate ions, are bound in acidic media. Industrial $TiO_2$ nearly always contains phosphate, most of which can be washed off with NaOH, and which must therefore be attached to the surface. The exchange of fluoride proceeds to completion even at low equilibrium concentrations (cf. Fig. 7). Unbuffered solutions are weakly alkaline.

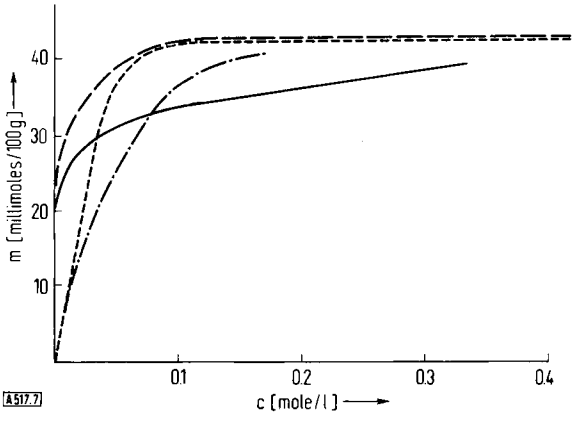


Fig. 7. Adsorption isotherms on anatase ($TiO_2$ P 25) at 23 °C.
———— $Na^+$ and $Ba^{2+}$ from NaOH and $Ba(OH)_2$, respectively.
— — — $F^-$ from NaF at pH 4.65.
—·—·— $PO_4^{3-}$ from $Na_2HPO_4$.
--------- $Al^{3+}$ from $Al(OH)_2Cl$.
Ordinate: m = millimoles of bound ions/100 g of anatase.
Abscissa: c = equilibrium concentration (mole/l).

An interesting observation was made in the adsorption of $F^-$ ions from NaF [109]: whereas finely divided $TiO_2$ (anatase) forms very stable suspensions in aqueous media, which separate only slowly even in a high-speed centrifuge, rapid flocculation occurs when fluoride is added. This is explained by the replacement of $OH^-$ ions on the surface by $F^-$ ions, so that dissociation to form $H^+$ is no longer possible. The surface charge of the $TiO_2$ particles in neutral or weakly alkaline media is then insufficient to stabilize the suspension.

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[115] *P. G. Johansen* and *A. S. Buchanan*, Austral. J. Chem. *10*, 392 (1957).

The results of a number of reactions on an anatase sample are summarized in Table 3. Either 16–20 or about 40 milliequivalents of OH groups react per 100 g of $TiO_2$, in agreement with the presence of two infrared absorptions (3715 and 3675 $cm^{-1}$) [101]. 40 mequiv/100 g corresponds to a packing density of 4.3 OH/100 Å$^2$. The average packing density estimated from the structure of the various crystal surfaces is 14 OH/100 Å$^2$, and 7 OH/100 Å$^2$ in the outermost layer. As in $SiO_2$, fewer OH groups are found than expected. From the water loss on ignition of anatase, a value of 12 μmole of $H_2O/m^2$, corresponding to 14.4 OH/100 Å$^2$, was obtained [103]. When the sample was heated to high temperatures and rehydroxylated, the content of chemisorbed water decreased to 4.1 μmole/m$^2$, corresponding to 4.9 OH/100 Å$^2$.

Fig. 7 shows a number of adsorption isotherms for the same sample. In the presence of the alkalis, half of the hydroxyl groups are neutralized even at very low equilibrium concentrations (0.002 M). Further sorption involves less energy, as shown by the small slope of the isotherm, perhaps because half of the OH groups are much less acidic, or because additional $OH^-$ ions are adsorbed on the surface. In the reaction with $F^-$ ions, 20 mmole of $OH^-$ ions/100 g again react at very low equilibrium concentrations. The isotherms rise much more slowly in the sorption of phosphate ions ($Na^+$ ions are adsorbed at the same time) and in the hydrolytic adsorption of $Al^{3+}$.

The dye dimethylaminoazobenzene (butter yellow) is not adsorbed from benzene solutions on anatase, whereas methyl red is adsorbed as the red cation. Butter yellow ($pK_a = 3.3$) changes color at a lower pH than methyl red ($pK_a = 4.9$). When anatase is exposed to sunlight or ultraviolet radiation, however, butter yellow is also adsorbed to give a red color (18 mmole of butter yellow/100 g of anatase P 25). Evidently the surface becomes more strongly acidic on reduction, as is also shown by the increase in catalytic activity in the elimination of water from tert.-butyl alcohol [109]. Partially reduced $TiO_2$ also catalyses the Fischer-Tropsch synthesis [116]. Magnetic susceptibility and electrical conductivity measurements [116] show that the $Ti^{3+}$ ions formed on reduction are situated at the surface. It may therefore be assumed that protons are added to equalize the charge, and that these protons are responsible for the more strongly acidic reaction. The acidity of the reduced surfaces probably also contributes to the breakdown of paint binders, particularly in the case of esters such as alkyd resins.

## 6. Surface Compounds on Alumina and on Silica-Alumina

The surface of aluminum oxide is fundamentally similar to that of $TiO_2$. The number of crystalline modifications of $Al_2O_3$ is large. Apart from α-$Al_2O_3$ (corundum), there are at least eight other oxides, which are generally grouped together under the name γ-$Al_2O_3$ [117]. Some of these forms are probably non-stoichiometric oxide-hydroxides. Hydroxyl groups are present even in samples that have been heated to high temperatures, and can be detected by infrared spectroscopy [118, 119] and by proton magnetic resonance measurements [120]. The presence of hydroxyl groups on the surface was demonstrated by deuterium exchange [121] and by esterification with alcohols [114, 122]. The surface esters are very readily hydrolysed.

Interest in the surface chemistry of alumina and of the amorphous mixed oxides of silicon and aluminum is concentrated mainly on the strongly acidic groups formed when the samples are heated to 500–600 °C. Owing to these acidic properties, the oxides are used on a large scale as catalysts in petroleum chemistry. The question of whether the acidity is due to readily dissociable protons (Brønsted acids) or to electron acceptors in the surface (Lewis acids) is a subject of lively discussions.

A description of the many experimental arguments for and against the wo views would lead beyond the scope of the present paper. A dehydrated alumina catalyst is readily poisoned by water, whereas the catalytic activity of $SiO_2$–$Al_2O_3$ mixed oxides is impaired, but not inhibited completely. The spectrum of pyridine adsorbed on γ-$Al_2O_3$ dehydrated at 450 °C indicates that only Lewis acids are present [123]. On the other hand, both Lewis acids and Brønsted acids have been detected in $SiO_2$–$Al_2O_3$ mixed oxides [123, 124]. Accurate measurement of the wavelength of the X-ray fluorescence of the aluminum shows that up to relatively high $Al_2O_3$ contents, all the $Al^{3+}$ ions are tetrahedrally coordinated, *i.e.* they presumably replace $Si^{4+}$ in the three-dimensional $SiO_2$ lattice [125]. Electroneutrality is probably achieved by protons incorporated in the network. Chemical reactions have so far revealed only silanol groups, and no Al–OH groups [87].

Aromatic hydrocarbons such as perylene are oxidized to radical cations on adsorption on the surface of such a catalyst, as is shown by absorption spectra and electron spin resonance measurements [126–129]. This oxidation occurs even in the absence of oxygen [127]. Triphenylamine [130] and iodide anions [131] are also oxidized. The number of oxidation equivalents of a mixed-oxide catalyst of this type is much lower than the number of Lewis or Brønsted acid equivalents. For this reason, suggestions that these acidic centers are connected with

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[117] See, *e.g.*, *S. H. Ginsberg, W. Hüttig*, and *G. Strunk-Lichtenberg*, Z. anorg. allg. Chem. *293*, 33, 204 (1957).

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[122] *M. M. Egorov, L. A. Ignatjeva, V. F. Kiselev, K. G. Krasilnikov*, and *K. V. Topchieva*, Zh. fiz. Khim. *36*, 1882 (1962).

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[129] *R. L. Hodgson* and *J. H. Raley*, J. Catalysis *4*, 6 (1965).

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[131] *S. D. Mellor, J. J. Rooney*, and *P. B. Wells*, J. Catalysis *4*, 632 (1965).

the oxidizing power [128-129] appear unlikely. The oxidizing power and the catalytic activity may be due to defects in the structure, *i.e.* in the coordination of the metal ions in the oxides [132]. Different types of reactions are evidently catalysed by different active sites; thus the addition of alkali, which suppresses the catalysis of one reaction, often has relatively little influence on another [87, 133]. Cracking processes may proceed *via* carbonium ions formed on acidic centers, as well as *via* free radicals formed at oxidizing centers [134]. The nature of the products depends on which of these routes is followed.

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# The Structure of Glasses

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*A melt can readily solidify to a glass with a three-dimensional or two-dimensional network, or a chain structure, provided that an irregular bonding system can be formed by virtue of free rotation about the bonds between a central atom and the ligands which function as bridging atoms. Such an irregular structure can arise when the system contains a sufficient amount of bridging atoms such as O, F, and S, or bridging groups such as $CH_2$, with bond angles less than 180°. When the network is formed predominantly by trivalent and tetravalent elements, such as As and Ge, the glasses – though they cannot be prepared by cooling of melts – can be obtained by other processes, e.g. by condensing the vaporized substances onto a surface (glasses in the wider sense of the word). As a result of extensive network formation, the bonding system and, therefore, the short-range order of the atomic arrangement in the melt differ from those in the glass or the crystal. A liquid mixture of substances having unlike molecular size and shape also can form a glass on solidification. Moreover, glasses can be formed even when the system contains only one component opposing regular packing into a crystal lattice.*

## I. Introduction [1a–1c]

In 1945, the American Society for Testing Materials (ASTM) defined glass as "an inorganic product of fusion which has cooled to a rigid condition without crystallizing". This definition is unsatisfactory, since it excludes transparent plastics and glasses prepared by a process other than fusion. Thus, vitreous selenium can also be obtained by the condensation of selenium vapor on a slightly warm surface. Furthermore, β- or γ-arsenic exhibiting a conchoidal fracture typical of glasses, and amorphous to X-rays like vitreous selenium, can be prepared only by condensation of arsenic vapor on a surface heated to about 100 °C [2], since it crystallizes at 270 °C (far below the softening point). Using the term in the wider sense, we can, therefore, define glass as a solid substance characterized by dense packing of the atoms and a lack of long-range order in the network. According to this definition, amorphous $Al(OH)_3$ and $Cr(OH)_3$, for example, are not regarded as glasses; they are loose powders containing empty spaces ranging in size down to atomic dimensions.

*Tammann* [3] was the first to carry out systematic investigations concerning the vitreous state by means of modern scientific techniques. *Goldschmidt* [4] correlated structural parameters with glass formation, and his pupil, *Zachariasen* [5], developed these concepts further and expressed them in the simple form which has since become well known.

## II. Causes of Glass Formation

### 1. Glasses Having a Three-Dimensional Network

*Zachariasen* has attributed glass formation to the possibility of the formation of a three-dimensional network differing from a crystalline lattice by the lack

[1] *J. D. Mackenzie*: Modern Aspects of the Vitrous State. Butterworth, London. a) Vol. I, 1960; b) Vol. II, 1962; c) Vol. III, 1964.

[2] *H. Stöhr*, Z. anorg. allg. Chem. *242*, 138 (1939).

[3] *G. Tammann*: Aggregatzustände. Voss, Leipzig 1923 (transl. by *R. F. Mehl*: The States of Aggregation. Van Nostrand, New York 1925); Der Glaszustand. Voss, Leipzig 1933.

[4] *V. M. Goldschmidt* Geochemische Verteilungsgesetze der Elemente, VIII. Vid. Akad. Ser. Oslo, No. 8, 137 (1926).

[5] *W. H. Zachariasen*, J. Amer. chem. Soc. *54*, 3841 (1932).

of the regular, periodic repetition of the structural unit. However, the ordered and the defect networks have the same basic structure, and their energy contents are, therefore, similar. In a two-dimensional representation, Fig. 1 shows the difference in the way the $SiO_4$-tetrahedra are joined to one another in vitreous and crystalline silica. In the former, ordered domains are interspersed with disordered ones [6]. According to *Zachariasen*, a pure oxide can form a glass if

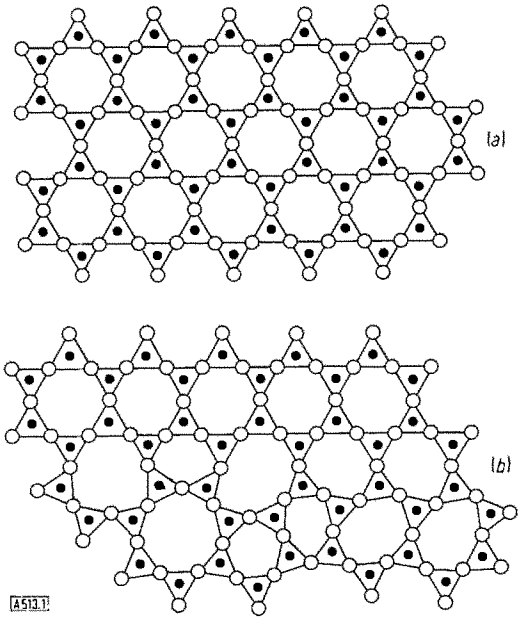



Fig. 1. Two-dimensional schematic representation of a crystalline (a) and a vitreous (b) $SiO_2$ network.
● network former (Si); ○ oxygen.

a) each oxygen atom is linked to not more than two central atoms (M);

b) the coordination number x of the $[MO_x]$ polyhedra is small;

c) these polyhedra share only corners, but not edges or faces;

d) in the case of a three-dimensional network, each polyhedron is joined to its neighbors by at least three corners.

Since glasses of the type of $M_2O$ and MO were unknown at that time, *Zachariasen* believed that only the oxides of elements having a coordination number (C.N.) of 3 or 4 can form glasses. Glass-forming oxides satisfying the above four conditions include $B_2O_3$, whose structural unit is the planar triangle $[MO_3]$; $As_2O_3$, whose structural unit is the trigonal pyramid $[MO_3]$; and $SiO_2$, $GeO_2$, $P_2O_5$, and $As_2O_5$ based on the $[MO_4]$ tetrahedra. Using the X-ray diffraction method, *Warren* [7] showed in 1933, within the accuracy then possible, that vitreous $SiO_2$ and $B_2O_3$ are in fact built of $SiO_4$ tetrahedra and $BO_3$ planar triangles, respectively.

[6] *A. E. Lebedev*: Stroenie stekla. Moskow-Leningrad, 1955. Cf. discussions in: The Structure of Glass. Proceedings of the Third All-Union-Conference on the Glassy State, Leningrad. Consultants Bureau, New York, Vol. I, 1958; Vol. II, 1960.

[7] *B. E. Warren*, Z. Kristallogr., Mineralog. Petrogr. *A 86*, 349 (1933).

In order to seek an explanation, the following reasons for irregular coupling of the coordination polyhedra, *i.e.* for glass formation, may be discussed:

a) Each M–O bond is capable of free rotation, though it is only when the oxygen has a coordination number of 2 that this free rotation effectively leads to the irregular linking of atoms. When oxygen has a coordination number of 3 or 4, fixing the position of two coordinated atoms automatically entails a complete or partial fixing of the direction of the third and fourth bonds. In such a case, therefore, disordered arrangement of the atoms is strongly opposed. We now understand not only the first, but also the second and the third of *Zachariasen*'s conditions, since a low coordination number of oxygen implies a low coordination number of the metal, owing to the fact that the ratio of the coordination numbers is inversely proportional to the stoichiometric ratio of the metal and oxygen atoms. Furthermore, if the coordination polyhedra share edges or faces, their mobility is again strongly restricted [8].

Oxygen also has a coordination number of 2 in the $ReO_3$ structure and in the perovskites ($CaTiO_3$ structure), which likewise are characterized by frequent lattice distortions, particularly well known in ferroelectrics with perovskite structure. It is thus understandable that for the preparation of optical glasses the oxides of Ca, Sr, Ba, and La, which readily occupy the calcium positions in the perovskite structure, are used in combination with the oxides of Al, Zr, Ta, and W [9], which are able to take up the titanium positions. However, glass formation is not very common for these structures, since the bond angle of the oxygen atom does not differ sufficiently from 180°. The perovskite structure of these glasses has not yet been confirmed experimentally.

b) Free rotation alone could hardly guarantee the saturation of valences and the formation of the typical $[MO_x]$ coordination polyhedra of all the atoms contained within a relatively large domain of an irregular network. In order to obtain irregular coupling, it must be possible to vary easily the valence angle of oxygen. Theoretically, this angle can lie between 90° (in a pure p-bond) and 180° (in a pure $sp^1$-hybrid bond); its value in crystalline silicates is between 130 and 180° [10].

c) In silicates, each oxygen atom invariably connects two $[SiO_4]$ tetrahedra, and only corners, but no edges and faces, are shared. There is only one unstable modification of silica in which the $[SiO_4]$ tetrahedra share edges and form chains [11] (Fig. 2). However, just as anomalous linkages arise on defect sites in crystal

Fig. 2. Structure of fibrous silica.
● silicon; ○ oxygen [11].

[8] *A. Dietzel*, Glastechn. Ber. *22*, 41 (1948).

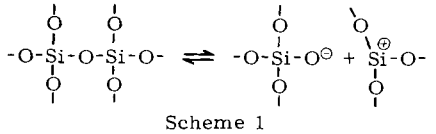
[9] *P. L. Baynton, H. Rawson*, and *J. E. Stanworth*, Trav. IV, Congrès international de verre, Paris 1956, p. 52, 62.

[10] *F. Liebau*, Acta crystallogr. *14*, 1103 (1961); *D. W. J. Cruickshank, H. Lynton*, and *G. A. Barclay*, *ibid. 15*, 49 (1962).

[11] *Alarich Weiss* and *Armin Weiss*, Z. anorg. allg. Chem. *276*, 95 (1954).

lattices, the [$SiO_4$] tetrahedra in silica glass will occasionally share edges whenever the requirements to neutralize all valences and to occupy the coordination sites cannot otherwise be fulfilled on steric grounds. Similarly, an oxygen atom is sometimes linked to three [$SiO_4$] tetrahedra [12]. At the same time either an equivalent number of oxygen atoms gives up its bridging function and remains linked to only one silicon atom, or the coordination number of Si must increase, *e.g.* to 6, as is the case in a modification of silica with rutile structure, formed at 1300 °C under pressures exceeding 160000 atm [13].

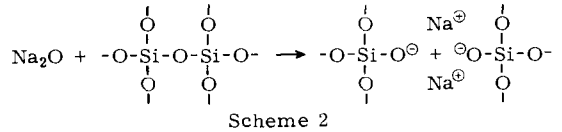
All the states mentioned in Section c), which are not normal for silicates, permit the continuation of the network in silicate glasses even when the disorder inhibits normal linking of the [$SiO_4$] tetrahedra. Such atom arrangments arise particularly in the softening of glasses, since local change of configuration results in a certain mobility of the atoms. The energy requirement involved is probably smaller than for the thermal dissociation shown in Scheme 1.



Scheme 1

The pronounced tendency of $GeO_2$ towards glass formation is connected with the fact that [$GeO_6$] octahedra of the rutile modification can easily arise, in addition to [$GeO_4$] tetrahedra of the quartz modification. *Kordes et al.* [14] have shown that in $BeP_2O_6$, $ZnP_2O_6$, and $MgP_2O_6$ glasses the central atom also has a tetrahedral configuration. When additional quantities of BeO, ZnO, and MgO are introduced, the extra Zn and Mg atoms become surrounded by six oxygens, but Be retains its coordination number of 4, which it can do only if a corresponding number of oxygen atoms becomes linked to three central atoms (P or Be).

The technically important silicate glasses contain, besides $SiO_2$, large amounts of basic oxides such as $Na_2O$, $K_2O$, MgO, CaO, and BaO, as well as more nearly neutral oxides such as $Al_2O_3$. In the melt the basic oxides contribute their oxygens to the network as shown in Scheme 2.



Scheme 2

The network is partially broken and becomes more mobile. Consequently, the softening point falls from about 1500 °C (pure $SiO_2$ glass) to 400–800 °C for technical grade silicate glasses.

Fig. 3 is a two-dimensional representation of a partially disrupted network. The central atoms M (*e.g.* Si) at the centers of the oxygen polyhedra are known as network formers, while the basic metal oxides (or in some cases

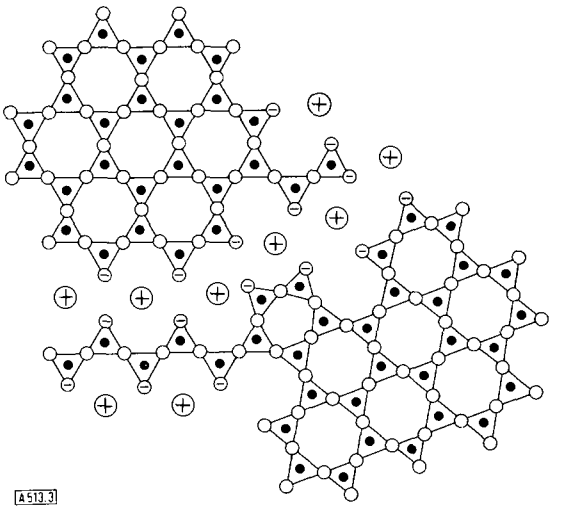


Fig. 3. Two-dimensional schematic representation of an $SiO_2$ glass containing network modifiers.

● network former (Si); ⊕ network modifier (cation); ○ bridging oxygen; ⊖ oxygen linked to network former and network modifier atoms.

the metals themselves) disrupting the network are called network modifiers. Fig. 3 shows that some of the oxygen atoms still act as bridges, while others are now linked to the network former atom only by one bond, the other valence being saturated ionically. Strongly basic metal oxides, such as $Cs_2O$, have a very pronounced tendency to contribute oxygen ions to the $SiO_2$ network, and are miscible in all proportions with $SiO_2$ in the silica-rich region. The depression caused in the melting point of silica (cristobalite) obeys Raoult's law [15] (see Fig. 4). When the melt is subjected to

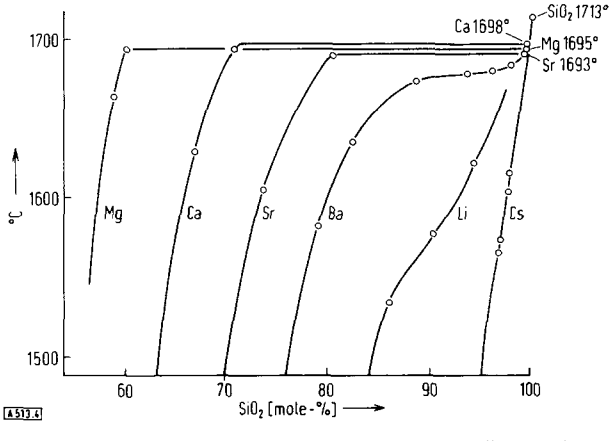



Fig. 4. Phase diagrams of the systems formed by cristobalite and the oxides of various alkali and alkaline earth metals [15].

moderately slow cooling, a glass is obtained. Substitution by a less basic oxide, such as $Li_2O$ or BaO, results in a deviation from the ideal behavior. With weakly basic oxides (*e.g.* MgO, CaO, and SrO), two melts are formed, each of which can solidify to a glass. One melt contains about 99 mole-% of $SiO_2$ and about 1 mole-% of MgO (or CaO or SrO), and the other about 60, 70, or 80 mole-% of $SiO_2$ and about 40, or 30, or 20 mole-% of the metal oxide. Cristobalite is in equilibrium with the melts at 1695, 1698, and 1693 °C.

[12] *E. D. Lacy*, Physics Chem. Glasses *4*, 234 (1963).

[13] *S. M. Stishow* and *S. V. Popova*, Geokhimiya *10*, 837 (1961); *A. Preisinger*, Naturwissenschaften *49*, 345 (1962).

[14] *E. Kordes, W. Vogel*, and *R. Feterowsky*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *57*, 282 (1953).

[15] *F. C. Kracek*, J. Amer. chem. Soc. *52*, 1436 (1930).

The reason for the formation of two melts is that less basic oxides, such as MgO, have a greater tendency towards formation of suitable oxygen polyhedra than strongly basic oxides[15a]. One can, therefore, assume that, just as in crystalline magnesium-oxygen compounds, each magnesium atom in the melt and the glass is surrounded octahedrally by six oxygen atoms. Apparently, the network of $SiO_2$ melts contains only few octahedral holes (about 1 %) of suitable size to accept the magnesium atoms. In order that a larger number of $[MgO_6]$ octahedra may be formed, the linkage of the $[SiO_4]$ tetrahedra must be altered completely. It is relevant in this connection to compare, for example, the tridymite-like structure of ice with the network of water molecules in the gas hydrates[16].

As in the series of crystalline silicates, there will be an abundance of short-range order in the glasses. However, it has not yet been possible to ascertain the ways in which the coordination polyhedra are connected. X-ray investigations, ESR-s and NMR-spectroscopic methods, and optical measurements normally give information only about the nearest neighbors, and only occasionally the next nearest. As a result, only the coordination polyhedra can be described, and not the manner in which they are interconnected.

For example, the absorption spectrum of a glass containing 16 wt-% of $Na_2O$, 10 wt-% of CaO, 74 wt-% of $SiO_2$, and traces of $Cr_2O_3$ corresponds fully to that of a solution of Cr(III) in 80 % sulfuric acid[17]. X-ray determination of short-range order in glasses containing $Cs_2O$ or BaO has revealed that, whatever their concentration, the distances between Cs or Ba atoms are only about 4 Å, indicating that the metal atoms they are connected by oxygen atoms into units containing at least two Cs or Ba atoms[18].

More recently, it became obvious that *Zachariasen*'s rules are only of limited validity. For example, the requirement that the coordination number of the network formers must not exceed 4 is not valid. Thus $TeO_2$, whose crystalline form (brookite lattice)[19] consists of $[TeO_6]$ octahedra interconnected in a complicated manner, forms a glass when a few mole-% of a metal oxide (*e.g.* 9 mole-% of $Li_2O$) is added. According to an X-ray determination of the atomic distribution curve[20], the glass, too, is composed of $[TeO_6]$ octahedra, these being also evidenced by infrared absorption measurements[21]. It should be borne in mind, however, that Te(IV) [like Se(IV)] tends to form distorted trigonal bipyramidal coordination polyhedra in which one apex is occupied by an electron pair. In this case, the coordination number is 4 for tellurium and 2 for oxygen. Tellurium can, therefore, easily change its configuration on sites where no $[TeO_6]$ octahedra can be formed. Being isoelectronic with trivalent bismuth, Te(IV) can possibly also form the same kind of coordination polyhedra as bismuth, with C.N. = 4 or 3. In oxide glasses containing $GeO_2$ and $Ga_2O_3$ and an alkali oxide, a maximum in density and refractive index is observed in the neighborhood of 10 mole-% of alkali oxide[20a]. The $O^{2-}$ ions introduced with the alkali oxide make it possible for the Ge and Ga atoms to increase their coordination number to 6 in some instances, without the bridging oxygen atoms having to increase their coordination number to 3.

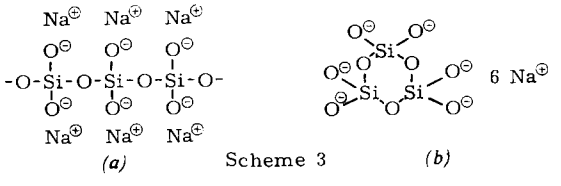
$$[GeO_{4/2}] + Na_2O \rightarrow Na_2^{+}[GeO_{6/2}]^{2-}$$

There are, furthermore, many glasses which do not have a three-dimensional network; the addition of a sufficient amount of network modifier oxides can break so many Si–O–Si bridges that a three-dimensional network can no longer exist.

### 2. Glasses Having a Chain Structure

In a glass having the composition $Na_2O{\cdot}2SiO_2$, each Si atom is linked to one negatively charged and three bridging oxygens. This gives rise to the possibility of formation of a two-dimensional lattice as in clay minerals, though it is not known yet whether such planar networks occur in silicate glasses.

It seems probable that at the composition of a metasilicate $Na_2O{\cdot}SiO_2$ the glass contains chains such as those in the pyroxenes (*e.g.* $MgCa(SiO_3)_2$; Scheme 3a), or rings such as those in benitoite ($BaTiSi_3O_9$; Scheme 3b). Glass formation can then be ascribed to the fact that these chains in the melt are no longer extended, but more or less coiled. Ordering to the long straight chains of a crystal is possible only with great difficulty.




*(a)* Scheme 3 *(b)*

Glasses with a chain structure include many organic high polymers such as polystyrene. The role of the bridging components of coordination number two (oxygen or methylene groups), frequently mentioned in the literature[22], is evident here.

### 3. Glasses Formed by Mixtures of Differently Shaped Molecules

A silica melt still solidifies into a glass when the $Na_2O$ content is increased beyond the equimolecular ratio, *e.g.* to 58 $Na_2O{\cdot}42\ SiO_2$, the long metasilicate chains being now shortened. Ignoring the rings, we find as a first approximation, on the basis of the chemical composition, that the mean chain length is 2.6 $[SiO_4]$ tetrahedra ($Na_{7.2}Si_{2.6}O_{8.8}$). The glass is probably formed from a mixture containing fairly short chains and small rings. In this case, glass formation depends not on

[15a] *A. Dietzel*, Z. Elektrochem. angew. physik. Chem. *48*, 9 (1942).

[16] *M. von Stackelberg* and *H. R. Müller*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *58*, 25 (1954).

[17] *T. Bates* in [1b], p. 234.

[18] *C. Brosset*, Physics Chem. Glasses *4*, 99 (1963).

[19] *T. Ito* and *H. Sawada*, Z. Kristallogr., Mineralog. Petrogr. *A 102*, 13 (1939).

[20] *G. W. Brady*, J. chem. Physics *27*, 300 (1957).

[20a] *M. K. Murthy et al.*, J. Amer. ceram. Soc. *47*, 328, 444 (1964); Nature (London) *201*, 285 (1964).

[21] *R. W. Douglas* in *V. P. Fréchette*: Non-Crystalline Solids. Wiley, New York, 1960, p. 382.

[22] *E.g. A. Smekal* in: Zur Struktur und Materie der Festkörper. Springer, Berlin-Göttingen-Heidelberg 1952, p. 223; cf. *G. Hägg*, J. chem. Physics *3*, 42 (1935).

network formation, but on the inability of a mixture of differently formed anions to crystallize on solidifying [23].

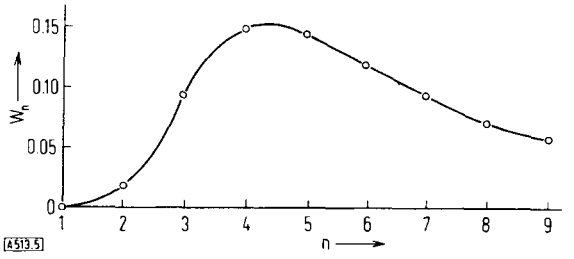



Fig. 5. Proportion $W_n$ of phosphorus present in chains of length n in a phosphate glass having the composition $Na_8P_6O_{20}$ [26] (cf. also [25] and [27]).

The structure of these silicate glasses cannot be elucidated by direct means, since, on being dissolved, these glasses react with the solvent. However, polyphosphate glasses may serve as models in an attempt to elucidate the structure of silicate glasses. Thus, *Thilo* and his school [23–26] have shown that alkali polyphosphates can be dissolved in water at room temperature without any change in their structure during the time required for chromatographic analysis (see Fig. 5).

### 4. Glasses from Single Compounds with Hindered Crystal Lattice Formation

Although the boiling point of toluene is higher (111 °C) than that of benzene (80 °C), which is to be expected on the basis of its higher molecular weight, the melting point of toluene (−95 °C) is surprisingly low in comparison with that of benzene (6 °C), indicating a hindered packing into a crystal lattice. When toluene is rapidly cooled, *e.g.* with liquid air, the time available is insufficient for the molecules to form an ordered arrangement, and therefore a glass is obtained. Similarly, it is easy to cool branched hydrocarbons to yield glasses, since thermal motion constantly changes the molecular configuration, and there is only one configuration which leads to the formation of a crystal lattice. As in the case of toluene, the asymmetry of these molecules opposes crystallization.

This group also includes nitrate mixtures whose melts readily solidify into glasses. Such a system is $KNO_3/Ca(NO_3)_2$ containing 53 to 70 mole-% of $KNO_3$ [28,29]. *Thilo* [30] has drawn attention to the fact that the transfer of the short-range order of cations from the melt to the crystal lattice of $KNO_3$ and $Ca(NO_3)_2$ is hindered in this system. Calcium nitrate crystallizes in a lattice related to that of fluorite [30a], while potassium nitrate can form a calcite lattice or an aragonite lattice; this dimorphism also facilitates glass formation.

### III. Microstructure of Glasses

In a number of cases the melting of glasses is accompanied by the appearance of opalescence due to the formation of small drop-shaped regions of a separate phase. This phenomenon depends on the composition and on the impurities (*e.g.* $SO_4^{2-}$) present in the glasses. It has been revealed by investigations based on small-angle X-ray diffraction [31,32] and electron microscopy [33,34] that many glasses which are clear to the naked eye actually contain such regions of inhomogeneity which may range in size down to the lower limit of detection (about 20 Å). Investigating the $Li_2O/SiO_2$ system, *Vogel* [35] has shown that these drop-shaped regions do not occur in pure $SiO_2$ glass and in the disilicate glass of composition $Li_2Si_2O_5$, but they do occur in the composition range between these two points, as well as in glasses containing a greater amount of $Li_2O$. The size of the droplets increases the more the composition deviates from pure $SiO_2$ and $Li_2Si_2O_5$. It has also been shown by chemical analysis that the composition of the droplets and the matrix in which they are embedded corresponds approximately to the limiting compositions $SiO_2$, $Li_2Si_2O_5$, and $Li_2SiO_3$.

Glasses are generally homogeneous, *i.e.* free from droplets, only within a narrow range of composition. As in the case of crystals (though not so critically) the short-range order in the glass lattice is apparently connected with certain fixed stoichiometric ratios. In a homogeneous glass, more ordered and less ordered regions alternate with one another (see Fig. 1), while in an inhomogeneous glass the phases are juxtaposed as in Fig. 3. This situation recalls the crystallite theory, developed in particular by Soviet authors [6].

The great variability in composition of a silicate glass appears, therefore, to rest not so much on the irregularity in atomic order, but rather on the mixing ratios of two finely divided phases. *Dietzel* [36] tried many years ago to trace some peculiarities of the variation in physical characteristics of glasses with composition to a heterogeneity in small regions. Furthermore, *Biltz et al.* [37] have shown that for many glasses the molar volume can be expressed as the sum of the molar volumes of suitably chosen components.

[23] *E. Thilo*, Silikattechnik *6*, 1 (1955); Forsch- u. Fortschr. *29*, 161 (1955).

[24] *E. Thilo*, J. Polymer Sci. *48*, 69 (1960).

[25] *H. Grunze*, Silikattechnik *7*, 134 (1956).

[26] *K. H. Jost* and *F. Wodke*, Makromolekulare Chem. *53*, 1 (1962).

[27] *A. E. R. Westman* and *J. Growther*, J. Amer. ceram. Soc. *37*, 420 (1954).

[28] *A. P. Rostkowskij*, Zh. russ. kkim. Obshchestva *62*, 2055 (1930).

[29] *A. Dietzel* and *H. J. Poegel*, Atti 3. Congr. internat. Vetro, Venice 1953, p. 219.

[30] *E. Thilo, Ch. Wieker*, and *W. Wieker*, Silikattechnik *15*, 109 (1964).

[30a] cf. *R. W. G. Wyckoff*, Crystal Structures. Interscience, New York 1964, Vol. 2, p. 480.

[31] *L. C. Hoffmann* and *W. A. Statton*, Nature (London) *176*, 561 (1955).

[32] *E. A. Poray-Koshits* and *N. S. Andrejew*, J. Soc. Glass Technol. *43*, 235 (1959).

[33] *G. Slayter*, Amer. ceram. Soc. Bull. *31*, 276 (1952).

[34] *A. E. Prebus* and *J. W. Michener*, Ind. Engng. Chem. *16*, 147 (1954).

[35] *W. Vogel*, Angew. Chem. *77*, 109 (1965); Angew. Chem. internat. Edit. *4*, 112 (1965); Struktur und Kristallisation der Gläser. Deutscher Verlag für Grundstoffindustrie, Leipzig 1965.

[36] *A. Dietzel*, Glastechn. Ber. *22*, 212 (1949).

[37] *W. Biltz* and *F. Weibke*, Z. anorg. allg. Chem. *203*, 845 (1932); Glastechn. Ber. *10*, 577 (1932).

A two-phase glass may contain one component in the crystalline, and the other in the vitreous state. Thus, the glass with a composition of 58 $MgO \cdot 42\ P_2O_5$ clearly includes a crystalline phase, probably having the composition $Mg(PO_3)_2$ [38]. In a silicate glass containing a large amount of PbO, a PbO-rich phase melts first, and the silicarich phase floats in it in the form of an extremely finely divided glass.

The two-phase character of the microdomains of glasses greatly depends on the temperature [35, 39], the droplets being larger at low temperatures. In silicate glasses containing $B_2O_3$ and an alkali oxide (*e.g.* 70 % of $SiO_2$, 25 % of $B_2O_3$, and 5 % of $Na_2O$), the cooling after molding can be directed in such a way that a coherent and water-soluble phase rich in $B_2O_3$ and the alkali oxide separates, which can be dissolved out of the glass with acids [40,41], leaving behind a porous structure containing about 95 % of $SiO_2$. The latter can be sintered into a dense mass at about 1200 °C. This "Vycor" glass closely resembles a pure $SiO_2$ glass in many of its properties.

The two-phase nature of the microdomains of many glasses also accounts for the observation that the distance between heavy atoms, in the cases so far investigated, is independent of their concentration: when the composition of a glass is varied, the composition of the phase that contains most of the heavy atoms essentially remains unchanged, and only its amount changes.

Thus, the Cs-Cs distance in the glass with composition $xCs_2O \cdot (1\text{-}x)SiO_2$ remains 4.1 Å when x is varied between 0.029 and 0.107 [42,43]. Cesium oxide crystallizes in an anti-$CdI_2$ lattice characterized by a Cs-Cs distance of 4.26Å. In the above glass, therefore, the cesium atoms appear to be interconnected *via* oxygen atoms. In a glass having the composition $xBaO \cdot yNa_2O \cdot (1\text{-}x\text{-}y)SiO_2$, the Ba–Ba distance is 4.0 Å in the composition range of x = 0.39 to 0.273 and y = 0 to 0.069 (in NaO with an NaCl lattice, $d_{Ba\text{-}Ba}$ = 3.9 Å) [42,43]. The corresponding value is appreciably larger (6.6–6.9 Å) in borate glasses of the type $NaO \cdot xB_2O_3$ in the range x = 1.7 to 4 [44]. These data indicate that the barium atoms are connected by an O–B–O group forming part of a $[BO_3]$ triangle or a $[BO_4]$ tetrahedron.

## IV. Special Glasses

### 1. Halide Glasses

According to some authors [22,45], the formation of a glass results from the fact that the atoms of the network are linked by a mixture of covalent, ionic, and metallic bonds as well as van der Waals forces. In our opinion, this condition is not essential. It is the steric circumstances – in case of the network glasses through the presence of bridging atoms – which has to allow for a disorder. Thus, $BeF_2$, like $SiO_2$, is an excellent glass-former. Its crystalline form is characterized by a cristobalite lattice, while its vitreous form is completely analogous to the $SiO_2$ glass [4]. Just as silica forms glasses with alkaline earth metal oxides, beryllium fluoride forms glasses with alkali metal fluorides. The relationship is so close that the following glass analogues have practically the same composition ranges of phase homogeneity: $LiF–BeF_2$ and $MgO–SiO_2$; $NaF–BeF_2$ and $CaO–SiO_2$; $KF–BeF_2$ and $SrO–SiO_2$; and $RbF–BeF_2$ and $BaO–SiO_2$ [46]. This is because beryllium, like silicon, invariably has a coordination number of 4 with tetrahedral arrangement of the ligands. Furthermore, fluorine has here a coordination number of 2 and has the same bridging function as oxygen in the silicate glasses. The differences in the nature of the bonds are of no importance.

Zinc chloride forms a viscous melt which, like $BeF_2$, sets to a glass. This glass is rapidly hydrolysed in air [47]. The fluoride glasses developed by *Sun* and *Huggins* [48] seem to belong to the glasses whose short-range order is probably the same as that of the $ReO_3$ lattice or the perovskite lattice.

### 2. Borate Glasses

Boric oxide readily forms glasses by itself or with numerous other oxides. An important point in this connection is whether the structure is based on $[BO_3]$ triangles or on $[BO_4]$ tetrahedra. Only recent investigations based on infrared absorption [49] and NMR spectroscopy [50] have revealed that in $B_2O_3$-glass each boron atom is surrounded by three oxygen atoms forming an equilateral triangle, and that each oxygen atom connects two boron atoms. When an alkali oxide (up to 30 mole-%) is added, each $O^{2-}$ ion introduced is utilized to increase the coordination number of boron to 4. On further addition of alkali oxide

$$M_2O + B_2O_3 \rightarrow 2\ M[BO_2]$$

(up to 50 mole-%), the proportion of tetrahedra first remains practically unchanged, and then rapidly decreases. When the glass contains 70 mole-% of $M_2O$, *i.e.* somewhat more than corresponds to the formula $M_4[B_2O_5]$, all the boron atoms again have a coordination number of 3. However, this phenomenon cannot yet be explained. Furthermore, the line-width of the NMR spectra indicates that the environment of the $[BO_3]$-triangles is not always the same in these glasses containing alkali oxides.

### 3. Lead Glasses

As has already been mentioned, polyvalent cations such as $Mg^{2+}$, $Cr^{3+}$, $Be^{2+}$, $Zn^{2+}$, $Pb^{2+}$, $Bi^{3+}$, $Al^{3+}$, $Ti^{4+}$, and $Zr^{4+}$ in glasses develop coordination polyhedra cor-


[38] *W. Vogel*, Silikattechnik *10*, 241 (1959).

[39] *J. F. Argyle* and *F. A. Hummel*, Physics Chem. Glasses *4*, 103 (1963).

[40] *M. E. Nordberg*, J. Amer. ceram. Soc. *27*, 299 (1944).

[41] Cf. *W. A. Weyl*, Angew. Chem. *63*, 85 (1951).

[42] *C. Brosset*, Trans. 8th internat. Ceramic Congress, Copenhagen, 1962, p. 15.

[43] *C. Brosset*, Physics Chem. Glasses *4*, 99 (1963).

[44] Results of *J. Krogh-Moe*, communicated in [42].

[45] *W. A. Weyl* and *E. Ch. Marboe*: The Constitution of Glasses. Interscience, New York 1962.

[46] *W. Vogel*, Glastechn. Ber. *32 K*, VII 12 (1959).

[47] *J. D. Mackenzie* and *W. K. Murphy*, J. chem. Physics *33*, 366 (1960).

[48] *K. H. Sun* and *M. L. Huggins*, US.-Pat. 2511224 (Dec. 15th, 1944), Eastman Kodak, Chem. Zbl. *1950* II, 1862.

[49] *J. Krogh-Moe*, Physics Chem. Glasses *3*, 1 (1962).

[50] *P. J. Bray* and *J. G. O'Keefe*, Physics Chem. Glasses *4*, 37 (1963).

responding to their own requirements. The greater their tendency towards formation of their own coordination sphere with oxygen atoms, the more closely do these network modifiers approximate to the role of network formers.

Glasses containing $Pb^{2+}$ and $Bi^{3+}$ deserve special mention. The amount of PbO in binary glasses can be very high, *e.g.* up to 67 mole-% in $SiO_2$, up to 77 mole-% in $B_2O_3$, and up to 62 mole-% in $P_2O_5$ [51]. This indicates that, despite the inability of pure PbO to form a glass, the lead atom in the above glasses must be able to form a network with oxygen. The ionization energy of the bivalent $Pb^{2+}$ ion (517 kcal/mole) is much higher than that of strontium (348 kcal/mole), which has the same atomic dimensions, indicating that the Pb–O bond is relatively strong. However, it is difficult to elucidate the exact nature of this bond, since bivalent lead forms a great variety of coordination polyhedra with oxygen, the coordination numbers of $Pb^{2+}$ being as follows: 12 in the perovskite-type lattice, 6 in magnetoplumbite; 4 in red tetragonal PbO; 3 in $Pb_3O_4$; and 2 in yellow rhombic PbO. It is, therefore, not surprising that lead can assume various functions in glasses.

Thus, recent NMR data indicate [52] that, similarly to alkali metal oxides, PbO acts at first as a network modifier in $PbO/B_2O_3$. The $Pb^{2+}$ ion here has a high coordination number and the oxygen is utilized for converting the $[BO_3]$ triangles into $[BO_4]$ tetrahedra, forming a network with the former. When the amount of PbO exceeds 15 mole-%, not all the oxygen atoms are used to form $[BO_4]$ tetrahedra. More specifically, in a glass containing 50 mole-% of PbO, *i.e.* having a composition of $Pb(BO_2)_2$, the proportion of the $[BO_4]$ tetrahedra is not 100 %, but only 50 %. This, in fact, is the highest attainable concentration of the $[BO_4]$ tetrahedra, since further addition of PbO is accompanied by a decrease in this concentration.

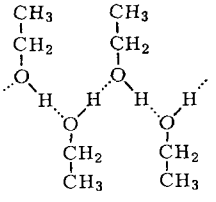
The NMR spectra show that when lead has a lower coordination number with respect to oxygen, it is linked only to $[BO_3]$ triangles and not to $[BO_4]$ tetrahedra [53]. This can be easily explained on the basis of *Pauling*'s electrostatic bond force [54], defined as the ratio of the oxidation number and the coordination number of the central atom (in this case B and Pb). In stable ionic lattices, the sum of the bonding forces of the bonds formed between the central atom and the anions (here oxygen) is numerically equal, or nearly equal, to the charge on the anions. In the case of $O_2B–O–Pb$, the charge on the oxygen is 2 (B–O, 3/3; Pb–O, 2/2). In the $[BO_4]$ tetrahedron and a non-linear $[PbO_2]$ group, however, oxygen has a charge of only 1.75 (B–O, 3/4; Pb–O, 2/2). Oxygen can have a charge of 2 if some of the O atoms assume a coordination number greater than 2. On the other hand, this is known to be unfavorable for glass formation.

This does not exclude that lead forms further weak bonds with other O atoms, as *e.g.* in yellow PbO. If, however, it is assumed that the lead atoms in $PbO–B_2O_3$ glasses with a high PbO content as in red PbO and $Pb_3O_4$ are surrounded by, respectively, four or three O atoms having a pyramidal configuration, the coordination number of the oxygen must again exceed 2. This is unfavorable for glass formation, but its occurrence cannot be excluded, provided that a sufficient number of Pb atoms with a coordination number of 2 is present in the glass.

The fact that lead easily can change its coordination number and the form of the coordination polyhedra permits the rearrangement of atoms, provided that oxygen can increase its coordination number. This may account for the ready softening of lead glasses. The glasses formed by $Bi_2O_3$ resemble lead glasses [51,55].

## 4. Glasses Containing Hydrogen Bonds

Molecules containing hydrogen bonds are good glass formers. Thus, on being cooled with solid $CO_2$, ethanol forms a glass which X-ray studies [56] suggest to contain long chains built up as follows:



This glass formation is due to the chain structure and the possibility of free rotation about the hydrogen bonds. In the case of water, each molecule is surrounded by four (sometimes three) neighbors. Water can form a glass only when it is subjected to sudden cooling with liquid air [57]. However, glass formation is facilitated by the addition of substances that can form hydrogen bonds with water, since this enhances the degree of disorder.

It is well-known that concentrated solutions of $H_2SO_4$, $H_3PO_4$, and sugar readily form glasses, as do also ethylene glycol, glycerol, and aqueous phenol.

## 5. Glasses Formed by Metals and Salts

In contrast to the above glasses, obtained by cooling of a melt, there are many similar substances – glasses in the wider sense of the word – which are prepared differently [58], *e.g.* by the condensation of vapors on cooled surfaces [59].

The condensation of vapors of pure metals or alkali halides onto a surface cooled to 20 °K leads, with the exception of a few metals, to a crystalline deposit. In the presence of impurity vapors (*e.g.* KI containing 10 % of KF, or Sn containing Cu) condensation in the vitreous state is obtained under the same conditions. Likewise, the condensation of a Bi vapor containing some Ga yields a glass which is stable at room temperature. Whereas CuCl, AgCl, and AgBr behave like the alkali

[51] *M. Imaoka*, Adv. in Glass Technol., 4th Congress on Glass, Washington 1962; Plenum Press, New York, 1962, p. 149.

[52] *P. J. Bray et al.*, Physics Chem. Glasses *4*, 47 (1963); *6*, 113 (1965).

[53] Cf. *R. V. Adams* and *R. W. Douglas*, Glastechn. Ber. *32 K*, VII 12 (1959).

[54] *L. Pauling*: The Nature of the Chemical Bond. 2nd Edit., Cornell University Press, Ithaca 1948, p. 384.

[55] Gmelins Handbuch der anorganischen Chemie. Verlag Chemie, Weinheim/Bergstr., 8th Edit., Suppl. Vol. 19 (Bi, 1964), p. 844.

[56] *A. Prietzschk*, Z. Physik *117*, 483 (1941).

[57] Gmelins Handbuch der anorganischen Chemie. Verlag Chemie, Weinheim/Bergstr., 8th Ed., Vol. 3, 5th Issue (O, 1963), p. 1224.

[58] *J. D. Mackenzie* in [1c], p. 149; J. Amer. ceram. Soc. *48*, 487 (1965).

[59] *R. Hilsch* in [21], p. 351.

metal halides when deposited from the vapor phase, TlCl, TlBr, and TlI form amorphous deposits, the last two crystallizing only at 110 and 140 °K. This difference in behavior is probably connected with the fact that thallium halides tend to form complicated lattices (cf. the lamellar structure of TlI)[60].

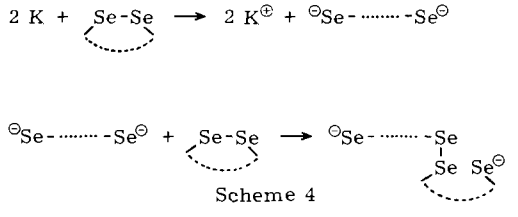
## 6. Chalcogenide Glasses

These glasses are formed when oxygen is replaced by S, Se, or Te. The name is not quite correct, since the chalcogens include oxygen.

### a) Vitreous Elements

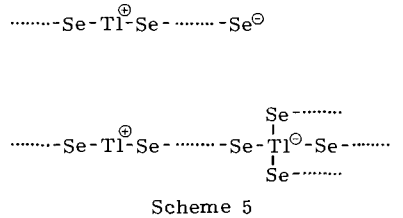
Vitreous selenium is formed when a selenium melt is subjected to moderately slow cooling. The formation of a state characterized by rubber-like elasticity at 70 °C is followed at 30 °C[61] by solidification to a glass which is usually thought to have a chain structure, though it contains about 40 wt-% of $Se_8$ rings which can be extracted with $CS_2$. The remainder consists of large rings containing on an average about 500 Se atoms. The presence of rings of different shape and size inhibits crystallization[62–64].

When traces of an alkali metal, particularly potassium, are added to the selenium melt, the latter assumes a highly mobile state because the large rings are broken up with formation of polyselenide ions, the extremely reactive ionic chain-ends of which attack neighboring selenium rings (Scheme 4).



Scheme 4

A potassium-containing selenium melt is so highly reactive that even quenching leads to well developed hexagonal selenium crystals. The effect of thallium is similar to that of potassium, but is much less pronounced. Scheme 5 shows the atomic arrangement presumably present in the melt[63,64].



Scheme 5

Owing to the fact that they rupture the network, alkali metals and thallium often lower the softening points of binary and ternary chalcogenide glasses.

Similarly to selenium, plastic sulfur also solidifies to a glass on cooling[65]. It consists of a mixture of smaller rings (predominantly $S_8$ and $S_6$ rings) and large rings with an average molecular size of 5000 atoms[64]. A mixture of rings containing 20 to 30 sulfur atoms has recently been isolated[66].

The glasses formed by $(PNF_2)_n$ and $(PNCl_2)_n$ are presumably built in a similar manner of rings of different sizes[63,67].

Vitreous tellurium cannot be obtained by cooling of a melt, but only by condensation of tellurium vapor on a surface[63].

The trivalent and the tetravalent elements adjacent to the chalcogens in the periodic table (*e.g.* As, Sb, C, Si, and Ge) do not form glasses in the strict sense of the word, since the cooling of their melts leads to the formation of crystals. However, they can be obtained in the vitreous state by condensation of their vapors. These glasses devitrify at the following temperatures: As, 270 °C[62]; Sb, 20 °C[62]; Si, 700 °C[62]; Ge, 400 °C[68]. Prolonged heating of molten white phosphorus leads to polymerization into glassy red phosphorus devitrifying at 550 °C. The crystallization temperature of P, As, Sb, Si, and Ge decreases with increasing atomic weight owing to the fact that the bond between the atoms becomes progressively weaker as the atomic number is increased.

The atoms in glassy phosphorus[69], arsenic[70], and antimony[70] form such an extensive network that they cannot be melted without basic structural changes, and cannot, therefore, be obtained from the melts.

Red phosphorus melts at about 600 °C, the process being accompanied by depolymerization into $P_4$ molecules. The structure of molten arsenic is not yet known[71]. The antimony melt is characterized by an octahedral arrangement of the atoms[72], as is molten germanium at 300 °C above its melting point, the Ge–Ge distance being 2.81 Å. In this case, however, the structure is so disordered that the maximum of the atomic distribution curve is hardly noticeable for next nearest neighbors, and the structural disorder is even stronger as the melting point is approached. Each atom is then surrounded by six neighbors, but four are situated at 2.70 Å and two at 3.15 Å[73].

[60] *L. Helmholtz*, Z. Kristallogr., Mineralog. Petrogr. *95*, 129 (1936).

[61] *K. H. Meyer* and *J. F. Sievers*, Naturwissenschaften *25*, 171 (1937); Gmelins Handbuch der anorganischen Chemie. Verlag Chemie, Weinheim/Bergstr., 8th Ed., Vol. 10 (Se, 1953), p. 181, 183.

[62] *H. Krebs*, Z. anorg. allg. Chem. *265*, 136 (1951).

[63] *H. Krebs*, Angew. Chem. *65*, 293 (1953).

[64] *H. Krebs*, Z. Naturforsch. *12b*, 795 (1957).

[65] *M. L. Huggins*, *K. H. Sun*, and *A. Silverman*, J. Amer. ceram. Soc. *26*, 393 (1943); Colloid. Chem. *5*, 308 (1944); *K. H. Sun*, Glass Ind. *27*, 552, 580 (1946).

[66] *H. Krebs* and *H. Beine*, unpublished results.

[67] *O. Schmitz-DuMont*, Angew. Chem. *50*, 415 (1937).

[68] *J. R. Parsons* and *R. W. Balluffi*, J. Physics Chem. Solids *25*, 263 (1964).

[69] *H. Krebs* and *H. U. Gruber*, unpublished results.

[70] *H. Krebs* and *R. Steffen*, Z. anorg. allg. Chem. *327*, 224 (1964).

[71] *W. Klemm* and *H. Niermann*, Angew. Chem. *75*, 508 (1963), Angew. Chem. internat. Edit. *2*, 523 (1963); *W. Klemm*, *H. Spitzer*, and *H. Niermann*, Angew. Chem. *72*, 985 (1960).

[72] *H. K. F. Müller* and *H. Hendus*, Z. Naturforsch. *12a*, 102 (1957).

[73] *H. Krebs* and *L. Winkler*, unpublished results.

As antimony and germanium are heated, the nature of the bonds is changed. This comes from the fact that the valence electrons are in pure p-quantum states (Sb, Ge at high temperatures), or in p-states which are slightly hybridized with s-states (Ge just above the melting point). Now, p-orbitals are known to be symmetrically disposed on either side of the nucleus; when the contribution of s-character increases on hybridization, one lobe of the orbital increases and the other decreases. In the case of pure p-orbitals, bonding is ensured in two opposite directions along each coordinate axis. When sp-hybridization takes place, on the other hand, bonding is possible in one direction only, while the other bond ceases to exist. The mobility of the atoms and their high reactivity in the melt are due to the ready hybridization in this sense [74]. As a result of this, structural ordering, *i.e.* crystallization, can occur even on rapid cooling.

In their stable modifications, As, Sb, Bi, Se, and Te have three or two nearest and, respectively, three or four more distant neighbors, all of which form a distorted octahedron (Fig. 6). This geometrical arrangement cannot be explained on the basis of the classical

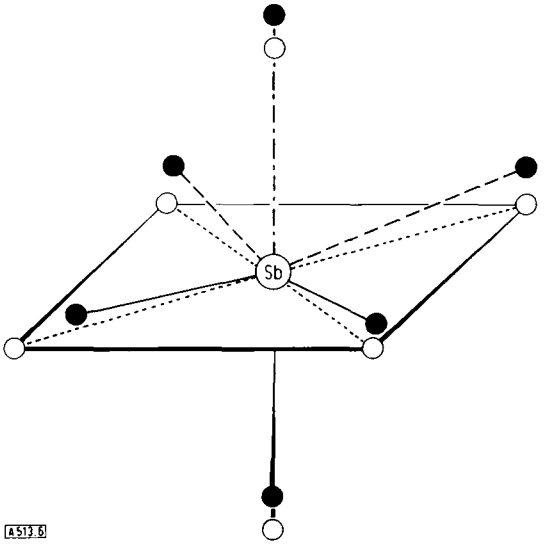



Fig. 6. Typical distortion of the coordination polyhedron incorporating As, Sb, or Bi.

Regular octahedron: ○ ligands; - - - bonds.
Distorted octahedron: ● ligands; ——— strong bonds; — — — weak bonds.

concept of bonding. According to the quantum-mechanical explanation, incomplete hybridization permits not only the preferred bond orientations (corresponding to the valence of the element), but also three or four weak and unfavored bonds [74,75]. Generally, the heavier the atom and the higher the temperature, the smaller is the difference between favored and unfavored bond orientations. In the case of heavy atoms, furthermore, these two types of bond orientation are present not only in the crystalline state and the melt, but also in the vitreous state. This has been confirmed by X-ray investigations on explosive antimony containing some chlorine. It has thus been found that each Sb atom is surrounded by three nearest neighbors situated at 2.90 Å and two more distant ones situated at 3.64 Å. This configuration appears to be similar to that in black phosphorus [70].

[74] *H. Krebs*, Angew. Chem. *70*, 615 (1958).

[75] *H. Krebs*, Acta crystallogr. *9*, 95 (1956); Z. Elektrochem. Ber. Bunsenges. physik. Chem. *61*, 925 (1957).

### b) Binary Chalcogenide Glasses

Table 1 shows the behavior of compositions of the type $M_2X_3$ on cooling at a rate of about 200 °C/sec (corresponding to quenching in water) [76,83].

Table 1. Solidification of compounds of the type $M_2X_3$.

| M \ X | S | Se | Te |
|---|---|---|---|
| P | — | + | |
| As | + | + | — |
| Sb | — | — | — |
| Bi | — | — | — |

+ glass formation.
— no glass formation.

Glass formation becomes progressively more difficult as the atomic weight increases. This has the following two reasons:

a) The bonds formed by the heavy atoms are weaker and can readily dissociate. The atoms can thus be arranged into a crystal lattice.

b) As mentioned before, the heavy atoms are able to bind loosely other atoms in addition to those bound closely according to the valence. At higher temperatures and, especially, in the melt the roles of closely and loosely bound atoms are readily interchanged as the atom of reference moves away from a close neighbor and approaches another one. Thus, rearrangement of the atoms and, thereby, crystallization is possible.

The cooling of a melt of $P_2S_3$ does not lead to a glass, since several definite compounds can arise in this system ($P_4S_3$, $P_4S_5$, $P_4S_7$, and $P_4S_{10}$). When a melt is heated to *e.g.* 900 °C, these compounds are formed to an extent of about 50 wt-%. When the melt is cooled, these compounds crystallize and can be extracted with $CS_2$. However, annealing for several hours at 270 °C promotes polymerization. In this case, cooling to room temperature leads to substances that can be drawn into threads, and glasses are formed on further cooling. Then only about 25 wt-% is soluble in $CS_2$ [77].

The composition of binary chalcogenide glasses can vary within wide limits [78,79]. Thus, in the As/Se and the As/S systems, the proportion of Se and S may be up to 100 and about 90 atom-%, respectively, but the As content cannot be increased to over 60 atom-%. As in the case of the oxide glasses, it is important here, too, that the coordination number of the chalcogen be 2 and the bond angle smaller than 180 °, since irregular linking is again due to free rotation and some flexibility of the bond angle of the bivalent bridging atoms.

[76] *N. A. Goryunova* and *B.T. Kolomiets*: The Structure of Glass II. Proceedings of the Third All-Union-Conference on the Glassy State, Leningrad, 1959. Consultants Bureau, New York 1960, p. 58.

[77] *A. R. Hilton, H. Jarman*, and *H. Krebs*, unpublished results.

[78] *S. S. Flaschen, A. Pearson*, and *W. R. Northover*, J. Amer. ceram. Soc. *42*, 450 (1959); *43*, 274 (1960).

[79] *N. A. Goryunova, B.T. Kolomiets*, and *V. P. Shilo*, Soviet Physics, Tech. Physics *3* [5] 912 (1958).

## c) Ternary Chalcogenide Glasses

Since they have found technical importance, ternary chalcogenide glasses have recently been subjected to extensive investigations [80,81]. These glasses are generally obtained by melting together the components.

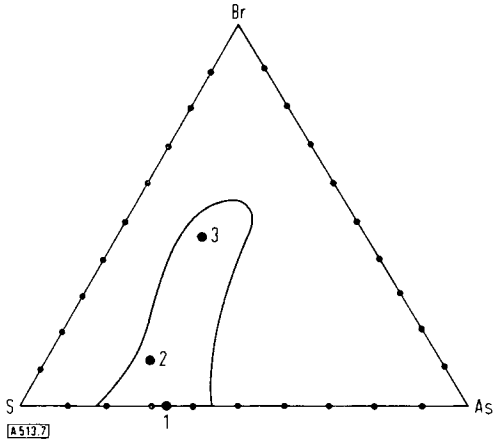



Fig. 7. Region of glass formation in the system As–S–Br [82].
1-$AsS_2$; 2-$AsS_{2.7}Br_{0.6}$; 3-$AsS_{1.8}Br_{2.5}$.

Fig. 7 shows the composition region in which glass formation occurs in the system As–S–Br [82]. Point 3 corresponds to the approximate composition $AsS_{1.8}Br_{2.5}$. This glass has a softening point of −60 °C and flows like water at room temperature. The glass formation is probably due to a mixture of small molecules whose composition is still unknown. When the bromine content is decreased and the sulfur content is raised, the molecules grow in size, since sulfur always links two atoms. As a result, the softening point increases: it is 90 °C for a glass with the approximate composition $AsS_{2.7}Br_{0.6}$ (point 2) and 200 °C for $AsS_2$ (point 1).

The region of glass formation of the chalcogenides of As, Sb, and Bi mixed with those of metals has been investigated by *Pearson* [82] and *Kolomiets* [83]. The addition of germanium and thallium chalcogenides results in large glass-forming regions. These regions generally decrease with increasing atomic weight, but thallium represents an exception. It appears that trivalent thallium can be incorporated in the network, in a state characterized by coordination numbers of 2 and 4. Thallium additions lead to decreased softening points of glasses.

*Hilton*, *Jones*, and *Brau* recently prepared some ternary chalcogenide glasses which are distinguished by relatively high softening points and, in some cases, transparency to infrared radiation [84,85]. Fig. 8 shows the glass-forming regions in the systems Ge-P-S, Ge-P-Se, and Ge-P-Te; the corresponding regions for the systems Si-As-Te, Ge-As-Te, Si-P-Te, and Ge-P-Te are shown in Fig. 9. The following deductions can be made from these figures:

a) Glass formation necessitates a relatively large proportion of the bivalent component (chalcogenide). The importance of the bridging atoms in the three-dimensional network of glasses in the strict sense of the word is again evident.

b) As the atomic weight increases along the series Si, Ge as well as in S, Se, and Te, the region of glass formation decreases. Systems containing Sn and Bi have only small glass-forming regions [86].

The relatively high softening points (up to 500 °C) indicate that the glasses included in Figs. 8 and 9 contain networks. It must also be born in mind, however,

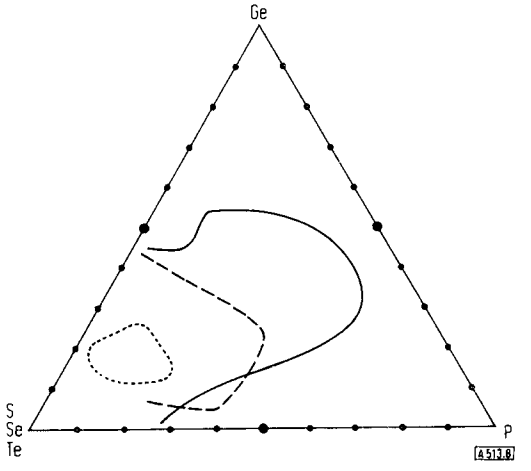



Fig. 8. Regions of glass formation in several systems.
——— Ge–P–S; – – – Ge–P–Se; · · · · Ge–P–Te [85,86].

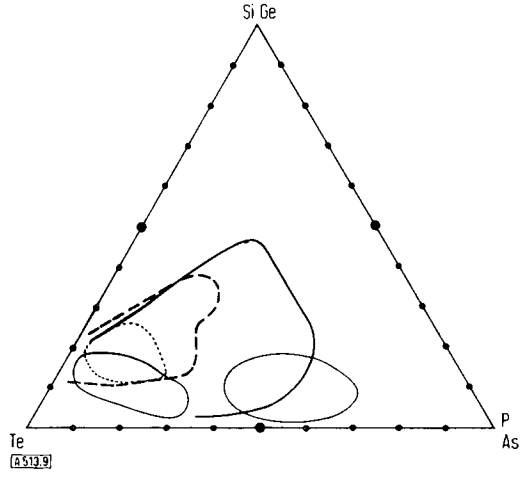



Fig. 9. Regions of glass formation in several systems.
▬▬ Si–As–Te; ——·—— Ge–As–Te; - - - - Si–P–Te;
····· Ge–P–Te [84,86].

that molecules such as $P_4S_{10}$ and $As_4S_4$ may be embedded in the networks of the systems containing P and S or As and S. Similarly to plasticizers in plastics, these molecules lower the softening point of the systems.

[80] Cf. *A. D. Pearson* in [1c], p. 29.

[81] *B.T. Kolomiets*, Physica status solidi *7*, 359, 713 (1964).

[82] *A. D. Pearson*, *W. R. Northover*, *J. F. Dewald*, and *W. F. Peck Jr.* in [51], p. 357.

[83] *B.T. Kolomiets*, *N. A. Goryunova*, and *V. P. Shilo* in [76], p. 410.

[84] *A. R. Hilton* and *M. J. Brau*, Infrared Physics *3*, 69 (1963).

[85] *A. R. Hilton*, *C. E. Jones*, and *M. J. Brau*, Infrared Physics *4*, 213 (1964).

[86] *A. R. Hilton* and *M. J. Brau*, personal communication.

Glass formation in regions with high tellurium contents is surprising, since it does not occur in binary chalcogenide glasses. It can be calculated from the density of these glasses that, similarly to the Sb atoms in explosive antimony, the Te atoms are linked to two strongly-bound neighbors and several loosely-bound ones, so that the coordination polyhedron can assume the form of a distorted octahedron. The loosening effect of Te is counterbalanced by the formation of a stronger network with tetravelent elements (Si or Ge).

Fig. 9 shows that the regions of glass formation are smaller with phosphorus than with the heavier arsenic. This contradicts the observation that the ease of crystallization increases with increasing atomic weight, and is probably due to the fact that Si and Ge form definite compounds with As, but not with P and Sb [87]. It can be assumed, therefore, that Si and Ge do not form bonds with P in glasses either, and that they prefer instead chalcogenides as neighbors. This renders the formation of a three-dimensional network more difficult.

The chalcogenide glasses discussed above must have the same short-range order as their melts, since they can be easily obtained from the latter. If we ignore the additional weak bonds, we see that the bridging atoms permit mobility in the melt even when the molecules are larger. This mobility in the melt is greatly enhanced by the addition of halogens. In the absence of a sufficient number of monovalent or bivalent atoms in the melt, mobility can be ensured only by disruption of the network. This means that the atoms are forced to assume significantly higher coordination numbers. The difference between the preferred and the unfavored bond directions more or less disappears, as it does in the melting of Ge or Sb. Melts of a more highly metallic nature are thus formed, and this should be manifested in the electric conductivity. These atomic arrangements are unstable when the melts are cooled. In fact, extensive rearrangement must take place, which gives rise to the favored crystalline form.

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Translated by Express Translation Service, London

[87] *M. Hansen*: Constitution of Binary Alloys. McGraw-Hill, New York 1959, p. 1124.

# An Apparatus for Titrations in Liquid Ammonia

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*To Prof. Dr. F. Patat on the occasion of his 60th birthday*

*An apparatus for titrations in liquid ammonia is described. The titrations can be carried out in the absence of air, and the utility of the apparatus is demonstrated for a number of conductometric and potentiometric titrations.*

The growing importance of water-like solvents has created the need of being able to follow reactions in these solvents quantitatively. In the case of low-boiling solvents of this type, such as liquid ammonia, the experimental requirements are greater since special care must be devoted to the exclusion of moisture, and sometimes also of air. As long as 30 years ago *E. Zintl, J. Goubeau,* and *W. Dullenkopf* [1], and more recently *G. W. Watt et al.* [2], described devices that permit titrations in liquid ammonia and other volatile solvents. A number of disadvantages associated with these devices led us to develop a new apparatus for our investigations, some of which are reported elsewhere [3]. Efficient cryostats that have recently become commercially available have made it possible to maintain a sufficiently constant low temperature (−50 to −60 °C) in the important parts of the apparatus over long periods with the aid of a circulating coolant (methanol).

[1] *E. Zintl, J. Goubeau,* and *W. Dullenkopf*, Z. physik. Chem. A *154*, 1 (1931).

[2] *G. W. Watt* and *I. B. Otto*, J. electrochem. Soc. *98*, 1 (1951); *G. W. Watt* and *D. M. Sowards*, *ibid. 102*, 46 (1955); *G. W. Watt* and *C. W. Keenan*, J. Amer. chem. Soc. *71*, 3833 (1949).

[3] *P. W. Schenk, E. Krone,* and *H. Kartono-Soeratman*, Mh. Chem. *95*, 710 (1964).

## Description of the Apparatus

A reservoir *a* (Fig. 1) for liquid ammonia is connected *via* $b_{10}$ to the calibrated flask *c*, which has a capacity of 250 ml up to the mark *d*. The reagent used for the preparation of the titrant solution is introduced through $e_2$. Nitrogen is used to force the solution through *f* into the buret *g*. The buret tap $b_3$ is a standard ground-glass tap with a polished sleeve and interchangeable keys. In titrations with potassamide, an ungreased Teflon key is used. $KNH_2$ solution attacks Teflon, causing it to swell slightly with the result that the tap seizes if the sleeve is not polished. However, if the solution is not allowed to remain in contact with the tap longer than necessary, the Teflon key need only be renewed from time to time.

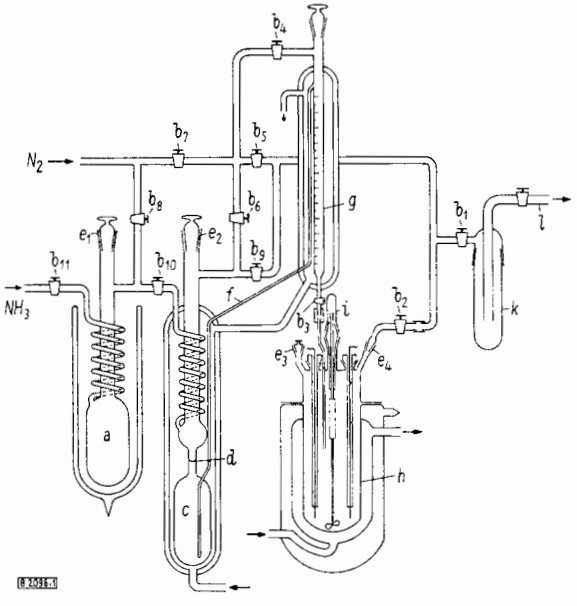


Fig. 1. Diagram of the apparatus for titration in liquid ammonia. *a* reservoir, $b_1$ *to* $b_{11}$ taps, *c* calibrated flask, *d* calibration mark, $e_1$ to $e_4$ ground-glass sockets, *f* tube, *g* buret, *h* titration vessel, *i* ground-glass cap, *k* cold trap, *l* line to mercury pump.

The titration vessel *h* is closed by a flat ground-glass cover fitted with six sleeve joints. Two of these accommodate the electrodes for the electrochemical indication. The middle joint carries the bronze sleeve bearing for the stirrer. This sleeve can be sealed with a glass cap *i* during evacuation of the apparatus. The cup is removed before the titration, and the steel stirrer shaft is connected to the motor by a flexible shaft. A glass sleeve with the spiral stirrer fused to its lower end is cemented over the stirrer shaft inside the vessel. Another socket in the cover holds the glass tube through which the titrant solution flows. This tube is connected to the buret by a length of plastic tubing or by a ball joint. The substance to be titrated is introduced through the joint $e_3$, and $e_4$ connects the titration vessel, *via* $b_2$, to the vacuum pump and the rest of the apparatus, so that it is possible to distil ammonia from *a* into *h*, if necessary. The calibrated flask *c*, the buret *g*, and the titration vessel *h* are insulated by evacuated jackets, and the cooling liquid from the cryostat circulates from one vessel to another between the jacket and the vessel.

The reservoir vessel *a* is separately cooled with acetone/dry ice. If the cryostat has two separate circulating pumps, this vessel may also be cooled by the cryostat. A small immersion heater introduced through the joint $e_1$ supplies the heat required for distillation of ammonia into *c* or *h*. The ammonia is preferably taken from a steel cylinder containing a little sodium [4]. If it is taken directly from the commercial cylinder, it is passed through drying tubes containing soda lime, barium oxide, and sodium wire. A little sodium is placed in *a* to ensure that the ammonia is really dry.

Before the titration, $b_3$ is fitted with a greased glass key, and the entire apparatus is evacuated for several hours with a mercury pump. Oxygen-free nitrogen from a Meyer-Ronge tower is then admitted. The required quantity of ammonia is distilled into *a*, and while a current of nitrogen is passed through, the glass key is removed from $b_3$, the grease is removed with an ether-soaked cotton pad, and a Teflon key is inserted. The cooling of *a* is stopped, and *c*, *g*, and *h* are cooled to cause ammonia to distil into *c* until it reaches the mark *d*. The weighed titrant reagent can then be introduced through $e_2$. The principal parts of the apparatus are shown in Figure 2.

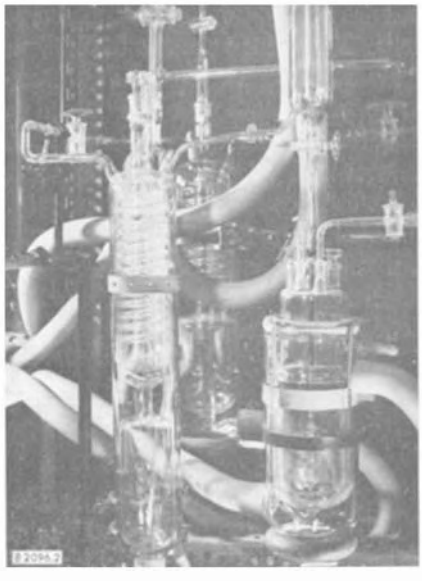

Fig. 2. Principal parts of the apparatus (rear: reservoir for liquid ammonia; front left: calibrated flask; front right: titration vessel with stirrer, electrodes removed).

## Preparation of Standard Potassamide Solutions

For titrations with potassamide solution, a weighed amount of oxide-free potassium is introduced. With the aid of the simple device shown in Fig. 3, a glass tube $n_1$ about 50 cm long and 6 to 7 mm in diameter is filled with oxide-free potassium by the following method.

The ampoule *m* is attached by the horizontal ground-glass joint *o* (which projects backwards) to a horizontal socket (not shown in Fig. 1) fitted to the main apparatus

[4] *F. Feher, J. Cremer,* and *W. Tromm,* Z. anorg. allg. Chem. *287,* 175 (1956).

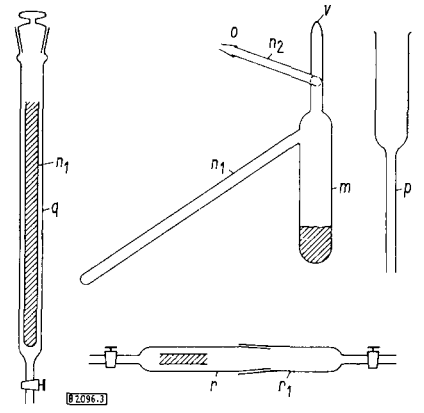


Fig. 3. Weighing accessories for oxide-free potassium.
*m* ampoule, $n_1$, $n_2$ glass tubes fused to the ampoule, *o* ground-glass cone, *p* funnel, *q* glass tube with tap and ground-glass stopper, *r* weighing tube.

between $b_1$ and $b_2$, and is thoroughly baked out in the mercury-pump vacuum. Nitrogen is then admitted, the tip *v* of the ampoule is cut open, and the funnel *p*, into which 8 to 10 g of pure potassium is placed, is inserted into the ampoule in a current of nitrogen. A loosely fitting stopper is inserted and the potassium is melted with a fan-shaped flame and allowed to run into *m*, still under nitrogen. The tip *v* of the ampoule is sealed, the ampoule is evacuated, *m* and $n_1$ are heated, and the ampoule is rotated about *o* to allow the potassium to run into the tube $n_1$. When the metal solidifies, nitrogen is admitted and the tube *q* is pushed over $n_1$, nitrogen being led in *via* the tap. The tube $n_1$ is then cut near the surface of the potassium and immediately pushed inside *q*, the top end of which is closed with a stopper. A suitable length of tube containing potassium is cut off in a "nitrogen bag" or dry box[5] and placed in the weighing tube *r*. Blank experiments have shown that if the joint of the weighing tube is only sparingly greased,

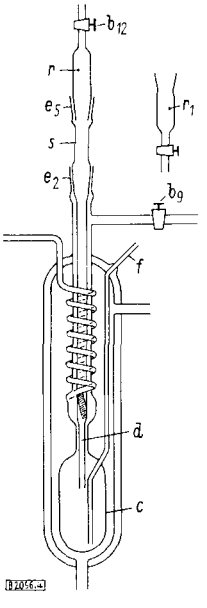


Fig. 4. Equipment for the introduction of a weighed sample of oxide free potassium into the calibrated flask.
*s* tube with ground-glass cone and socket, *r*, $r_1$ weighing tubes with ground-glass cap and tap $b_{12}$ (other symbols as in Fig. 1).

[5] Cf. *G. Brauer*: Handbuch der präparativen anorganischen Chemie. Enke, Stuttgart 1960, Vol. 1, p. 73.

weighing errors caused by the grease are negligible. After the nitrogen-filled weighing tube has been weighed, the ground glass cap $r_1$ is removed in a current of nitrogen and replaced by the tube *s* (Fig. 4). When *s* is full of nitrogen, the assembly is mounted in the socket $e_2$ of the main apparatus (Fig. 1) in a countercurrent of nitrogen ($e_5$ also is only sparingly greased). The pressure is now released at $b_{12}$ (Fig. 4), and *c* is placed under a slight pressure of nitrogen. The liquid ammonia rises in the tube *s* and dissolves the potassium out of the piece of tube, which is open at both ends. The operation must be repeated several times. When all the potassium has dissolved, the tube *s* is removed and placed in a glass tube of sufficient length and width, the lower end of which is closed. A few mg of $Fe_2O_3$ is added to catalyse the conversion of the blue potassium solution into $KNH_2$, and $e_2$ is immediately closed. A weak current of nitrogen is bubbled through the solution overnight *via f* to agitate the $Fe_2O_3$. The apparatus is sealed off from the outside air by a mercury relief valve, which prevents the entry of air and moisture. By the following day, the color of the solution is generally discharged. (The quality of the $Fe_2O_3$ appears to be important). By addition or removal of ammonia the meniscus in *c* is adjusted to the mark *d*. It should be ensured that the height in *f* is the same.

The potassium adhering to the tube *s* is washed down with alcohol and then with water, and the resulting solution is titrated. The length of glass tube is dried and weighed together with the weighing tube. The quantity of potassium titrated is added as a correction. Though the solubility of $KNH_2 \cdot 2NH_3$ (which is stable only below $-42\,^{\circ}C$) decreases rapidly with decreasing temperature[6], 1 N $KNH_2$ solutions can be used at temperatures down to $-60\,^{\circ}C$. As in aqueous systems it is advisable to use fairly dilute solutions. This is particularly desirable here, since after each addition of titrant, the solution between the tip of the buret and the tap runs out, so that dropwise titration as in aqueous systems is impossible, although this is no disadvantage when electrochemical indication is used.

For conductometric titrations we used two platinized platinum electrodes of the usual size, with a "Konduktoskop" (Metrohm AG., Herisau, Switzerland) as measuring instrument; in potentiometric titrations the indicator electrode was a platinum or silver electrode, while the reference electrode was a *gebremste Elektrode* as described by *Müller*[7]. The reference electrode was used in two forms. One of these, the usual form, has already been used in liquid ammonia by *Zintl*[1]. It consists of a glass tube about 3 mm wide, with a fine capillary about 2 cm long at the bottom. The tube is sealed about 2 cm above the capillary. A platinum wire projects into the resulting electrode compartment through the seal. For longer response times, the differential potentiometric method is recommended. In the reference electrode used in this case, the solution is drawn into the electrode compartment by means of a suction ball before each addition of reagent, and forced

[6] *P. W. Schenk* and *H. Tulhoff*, Angew. Chem. *74*, 943 (1962).
[7] *E. Müller*, Z. physik. Chem. A *135*, 102 (1928).

out again after the reading has been taken. The indicating instrument used was a "pH-Meter 260" (Knick, Berlin) with a titration attachment.

### Titration Procedure

The substance to be titrated is introduced into the titration vessel through $e_3$ (Fig. 1) in a stream of nitrogen, and rinsed down with a little ether. When a sufficiently large sample is used, a measured amount of titrant solution is run in as solvent, or alternatively, ammonia may be distilled over from *a*, so that the electrodes are covered. (The *gebremste Elektrode* must first be filled with ammonia gas to enable the liquid to enter). The stirrer is then switched on, and addition of the titrant is commenced. The portions added should not be too small. The reading generally becomes constant within 5 minutes.

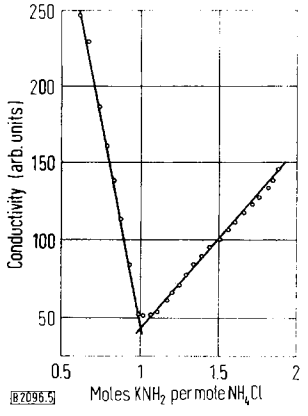


Fig. 5. Conductometric titration of $NH_4Cl$ with $KNH_2$.

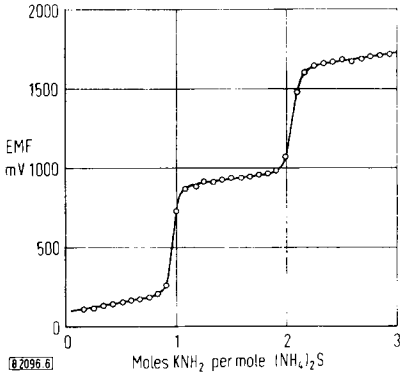


Fig. 6. Potentiometric titration of $(NH_4)_2S$ with 0.44 M $KNH_2$ (Pt indicator electrode, Pt *gebremste Elektrode* as reference electrode); temperature −51 °C, response time 5 min.

Figure 5 shows a conductometric titration curve of $NH_4Cl$ with $KNH_2$, and Figure 6 shows a potentiometric titration curve of $(NH_4)_2S$ with $KNH_2$. The latter clearly shows the two stages of dissociation of $H_2S$ in liquid ammonia. The titration of $(NH_4)_2S$ with

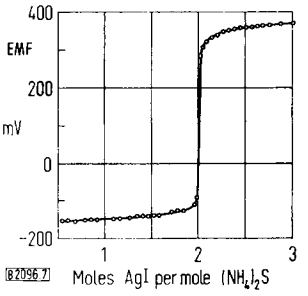


Fig. 7. Potentiometric titration of $(NH_4)_2S$ with 0.6 M AgI solution; indicator electrode Ag wire; reference electrode Pt *gebremste Elektrode*; temperature −50 °C; response time 5 min.

AgI solution (Fig. 7) naturally gives only one inflection, since this is a precipitation titration. The potential curve for the differential titration of $(NH_4)_2S$ with AgI solution is shown in Fig. 8. The apparatus has already

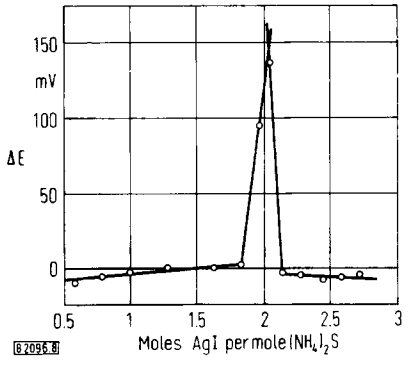


Fig. 8. Differential potentiometric titration of $(NH_4)_2S$ with 0.3 M AgI solution (ΔE EMF difference); Pt indicator electrode, Pt *gebremste* reference electrode.

proved its value in the hands of numerous workers. The results obtained were reported earlier [3]; further results will be published elsewhere.

*E. Krone, I. B. P. Tripathi, K. Huste, D. Gerlatzek, D. Lautenbach, and Frau E. Tulhoff contributed to the development of the apparatus. The author is grateful to the Senator für Wirtschaft des Landes Berlin and to the Fonds der Chemischen Industrie for their financial support.*

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# Progress in the Chemistry of Casein

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*Casein from cow's milk is not a single substance, but can be resolved into numerous components. These include κ-casein, which is the only fraction that contains appreciable quantities of sugars. This component plays a very important role in the clotting of milk by rennin, when it is split into an almost sugar-free fraction, para-κ-casein, and a fraction containing sugars, κ-caseinoglycopeptide. Caseinoglycopeptides have been isolated not only from the casein of cow's milk, but also from the caseins of sheep, goat, and human milk. The second part of the paper deals with the clotting of milk by rennin and the amino acid sequence in caseinoglycopeptides.*

## I. Caseins

The proteins in milk belong to two groups: phosphoproteins or caseins (78% in cow's milk), which are insoluble in acidic media, and milk serum proteins (17%), *i.e.* β-lactoglobulin, α-lactalbumin, globulins, serum albumins, *etc.* 5% of the substances are non protein nitrogen (NPN) containing components such as peptides. In this paper, the percentages indicated are percentages of the dry substances (by weight).

### A. Casein from Cow's Milk

#### 1. Number of Fractions and Their Names

Casein from cow's milk is one of the few substances isolated and studied as early as the first half of the 19th century [1–5]. It was later found [6–9] that casein is not a pure substance. Studies of solubility in dilute hydrochloric acid and in ethanol enabled *Linderstrøm-Lang* and *Kodama* [10] to characterize seven fractions in casein. These observations were confirmed by *Cherbuliez* and *Schneider* [11] by fractional salting out, and later by *Pedersen* [12] and in particular by *Mellander* [13] by physical investigations. Using electrophoresis, *Mellander* isolated three fractions, which he called α-, β-, and γ-casein, names that are still used.

New chromatographic and electrophoretic methods of separation and the use of buffers containing urea, which reduce the interactions between protein components, have made it possible to characterize up to 20 casein fractions. However, as *Waugh et al.* [14] have pointed out, it must be asked which of these fractions are synthesized directly by the cells in the mammary gland ("primary caseins"), and which are artefacts, produced, for example, by enzymatic breakdown of primary caseins. Some fractions might also be genetic variants, or complexes or mixtures of several proteins. The four principal fractions of casein ("primary caseins") are the $\alpha_{s1}$, $\alpha_{s2}$, β, and κ components. The main fractions of casein and the names of these encountered in the literature are listed in Table 1.

#### 2. Study of the Four Principal Fractions

##### a) $\alpha_{s1}$- *and* $\alpha_{s2}$-*Casein*

Nomenclature and Purification. Though α-casein initially appeared to be electrophoretically homogeneous (soluble in 6.6 M, insoluble in 4.6 M urea solution), it was later resolved into two main fractions: κ-casein, which is soluble in the presence of $Ca^{2+}$, and $\alpha_s$-casein, which is insoluble in the presence of $Ca^{2+}$ (0.03 M) at normal (20–40 °C) and low temperatures (1–5 °C). These fractions were named by *Waugh* and *v. Hippel* [15]. The $\alpha_s$ fraction is very similar to the $\alpha_1$ fraction reported by *McMeekin et al.* [16] and to the $\alpha_r$ fraction reported by *Long* [17].

$\alpha_s$-Casein can also be obtained by precipitation of casein with $CaCl_2$ [15]. Chromatography of $\alpha_s$-casein on

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Table 1. The principal fractions of the casein complex.

| [13] | | [15] | | [14] | | [33] | Other names for similar fractions | Subsidiary fractions | Genetic variants |
|---|---|---|---|---|---|---|---|---|---|
| Name | [%] | Name | [%] | Name | [%] | Name | | | |
| $\alpha$ | 70 | | | | | | | | |
| | | $\alpha_s$ | 55 | $\alpha_{s1}$ $\alpha_{s1,2}$ $\alpha_{s2}$ | 38 | | $\alpha_1$ or $\alpha_r$ | "$\alpha_s$" (10%) | $\alpha_{s1}$-A, -B, -C, -BC, -D |
| | | $\varkappa$ | 15 | $\varkappa$ | 15 | | $\alpha_3$ | | $\varkappa$-A, -B |
| | | | | | | | $\alpha_2$, "m" ← | $\lambda$ (3%) | |
| $\beta$ | 27 | | | $\beta$ | 27 | $\beta_{slow}$ $\beta_{fast}$ [a] | | | $\beta$-A, -B, -C, recently -D, -E [39a] |
| $\gamma$ | 3 | | | | | | | | $\gamma$-A, -B |

[a] $\beta_{fast}$ is probably contained in $\lambda$.

DEAE-cellulose with a buffer containing 4.5 M urea yielded two fractions, both of which could be further purified by starch gel electrophoresis [14]. The first chromatographic fraction consists of a mixture of $\alpha_{s1}$- and $\alpha_{s2}$-casein (= $\alpha_{s1,2}$-caseins). The migration of the $\alpha_{s1}$ component at pH 8.4 is faster than that of the $\alpha_{s2}$ component. The second fraction was given the rather confusing name "$\alpha_s$-casein" (*i.e.* the fraction that contains other "$\alpha_s$-like" components).

Table 2. Properties of various casein fractions.

| Casein fraction | Molecular weight | $pH_i$ | Solubility in presence of 0.03 M $Ca^{2+}$ | | Sugar [%] | P [%] | Cys [%] | N [%] | Terminal amino acids or sequences | | Effect of rennin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | [a] | 4 °C | 25 °C | | | | | N | C | |
| $\alpha$ [13] | 24800—27600 | | | | | | 0.44 | | | | |
| $\alpha_s$ [15] | 16500—27000 | 4.4 | — | — | 0 | 1.1 | | 15.10 | Arg | | — |
| $\alpha_{s1,2}$ [14] | 27000 | | | | 0 | 1.03 | 0 | 14.70 | | (Try, Leu, Tyr) | — |
| $\alpha_{s1}$-A [29, 30] | *ca.* 30000 | | | | | 1.01 | | 15.10 | Arg | Leu-Try | — |
| $\alpha_{s1}$-B [29, 30] | *ca.* 30000 | | | | | 1.01 | | 15.34 | Arg | Leu-Try | — |
| $\alpha_{s1}$-C [29, 30] | *ca.* 30000 | | | | | 1.01 | | 15.40 | Arg | Leu-Try | — |
| $\alpha_{s1}$-D [22] | | | | | | | | | Arg | | |
| $\varkappa$ [15] | probably 19000 ± 1000 [56, 58] [b] | 3.7 | + | + | 5.0 | 0.2 | 1.4 | 14.5 | ? | (Ser, Thr, Ala)-Val | + |
| | | | | | | (0.19—0.35) | | (13.5—15.4) | | | |
| $\lambda$ [17] | | | + | + | | 1.2 | | | | | ? |
| $\beta$ [13] | 18000—25000 | 4.9 | + | — | 0—0.2 | 0.48—0.6 | *ca.* 0.1 | 15.35—15.47 | | Ileu-(Val, Ileu) | — |
| $\beta_{fast}$ [33] | | | | | | 1.11 | | | | | — |
| $\beta_{slow}$ [33] | | | | | | 0.68 | | | | | — |
| $\beta$-A [27, 39a] | | | | | | 0.59 | | 15.18 | | | — |
| $\beta$-B [27, 39a] | | | | | | 0.57 | | 15.33 | | | — |
| $\beta$-C [27, 39a] | | | | | | 0.50 | | 15.45 | | | — |
| $\gamma$ [13] | 30000 | 6.4 | | | | 0.14 | 0 | | | | — |

[a] Isoelectric point. [b] Value formerly accepted: 2 × 28000 [65].

Genetic Variants. Three genetic variants, $\alpha_{s1}$-A, $\alpha_{s1}$-B, and $\alpha_{s1}$-C, were identified by *Thompson et al.* [18–21, 27, 28]. The last two are probably very similar to or identical with *Waugh*'s $\alpha_{s1,2}$ fractions. *de Koning* [22] described the variants $\alpha_{s1}$-B, $\alpha_{s1}$-C, $\alpha_{s1}$-BC, and $\alpha_{s1}$-D.

Molecular Weight. $\alpha$-Casein forms aggregates in neutral media, but the size of these aggregates decreases with increasing pH; in molecular weight determinations by sedimentation and diffusion methods, *McKenzie* and *Wake* [23] obtained values of 27600 ± 1000 at pH 7.3 and 24800 ± 1000 at pH 11 in the presence of 6 M urea. The value found for $\alpha_{s1,2}$-caseins by *Waugh et al.* [14] was 27300, and that found by *Schmidt* and *Payens* [24] was 16500; *Manson* [25] found a molecular weight of at least 31000 for $\alpha$-casein (see Table 2), while *de Koning* [22] obtained a value of 30000.

Analyses (Amino Acids, Sugars, Phosphorus). The amino acid compositions of the $\alpha_{s1}$- and $\alpha_{s2}$-caseins were reported by *Hipp et al.* [26]. $\alpha_{s1,2}$-Caseins contain 14.7% N, 1.03% P, 2.3 tryptophan residues, and 11 tyrosine residues per molecule of molecular weight 27000 [14].

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α-Casein (mainly a mixture of $\alpha_{s1,2}$- and κ-casein) contains sugars, but these are confined to the κ component. *de Koning* [22] analysed the genetic variants $\alpha_{s1}$-B, -C, -BC, and -D and found that $\alpha_{s1}$-B contains one glutamic acid residue more and one glycine residue less than $\alpha_{s1}$-C-casein.

Structure studies. Arginine is the only *N*-terminal amino acid, not only in $\alpha_s$-casein (3.25 mole/$10^5$ g of protein) [25], but also in the variants $\alpha_{s1}$-A, -B, -C [29], and -D [22]. These components also have the same *C*-terminal sequence, *viz.* leucyltryptophan, provided they all consist of a single polypeptide chain (molecular weight *ca.* 31000); if on the other hand there are two peptide chains [24], one must have a *C*-terminal leucine and the other a *C*-terminal tryptophan residue. These results do not quite agree with those obtained by *Waugh et al.* [14], who found tryptophan, leucine, and tyrosine as *C*-terminal amino acids in $\alpha_{s1,2}$-caseins.

Many investigations have been carried out on peptides, particularly phosphopeptides, from α-casein. *Österberg* described a peptide containing 35 amino acids, and in this connection reviewed most of the phosphopeptides of casein studied up to that time [31]. The phosphorus in casein is mainly in the form of monoesters of phosphoric acid (phosphoserine, phosphothreonine).

b) *β-Casein*

Purification. In 1962, *Groves et al.* [32] described a purification method using chromatography on DEAE-cellulose, the starting material being the casein soluble at pH 4 and 2 °C. The product obtained seemed to be electrophoretically pure (soluble in 4.6 M, insoluble in 3.3 M urea solution at pH 4.6). However, *Gehrke et al.* [33] showed in 1964 by similar methods that β-casein of this kind consists of two components: "$\beta_{slow}$-casein", the principal component, which is soluble in water at 5 °C, and "$\beta_{fast}$-casein". *Garnier et al.* [34], also in 1964, published a process for the production of β-casein.

Genetic variants of β-casein have also been observed in milk samples [27,28,35–37], *viz.* β-A-, β-B-, and β-C-forms [39]. A new nomenclature based on variations of the histidine content was quite recently proposed [39a].

Molecular Weight. *McKenzie* and *Wake* [23] reported molecular weights of 17300 ± 800 at pH 11 and 19800 ± 1000 at pH 7 for slightly impure samples of β-casein in 6 M urea solution. *Groves et al.* [32] found a sedimentation constant of 1.17 S at pH 7 (0.05 M phosphate buffer, 0.1 M NaCl) and 0.8 °C, while *Gehrke* [33] obtained a value of 1.6 S at pH 8.6 (0.076 M tris buffer, 0.005 M citrate) for $\beta_{slow}$). Association and dissociation were observed in the presence of 0.1 M KCl.

Analyses. $\beta_{fast}$-Casein contains as much phosphorus as λ-casein and the two exhibit a similar electrophoretic behavior; $\beta_{fast}$-casein is probably a fraction of λ-casein (or of λ-caseins). The amino acid composition of β-casein was reported by *Gordon et al.* [38] and by *Pion et al.* [39]. Sugars were detected only in traces.

Structure studies. A number of investigations have been carried out on the isolation of phosphopeptides and on the products of trypsin hydrolysis of total β-casein [39–41]. The genetic variants β-B and β-C contain respectively one arginine and one lysine residue more, and one glutamic acid residue less than β-A [39].

β-Casein can be photo-oxidized at pH 8.6 and 37 °C; this leads in particular to the modification and/or destruction of the histidine, tryptophan, and tyrosine residues. Oxidized β-casein (18 moles of oxygen per 30000 g of casein) is not precipitated by a $CaCl_2$ solution [42].

c) *κ-Casein*

In the presence of 0.3 M $Ca^{2+}$, the complex between $\alpha_s$-, β-, and γ-caseins is broken down; only κ-casein remains in solution [15]. Another unusual property of κ-casein is its ability to stabilize other casein fractions; moreover, κ-casein is the only casein fraction that is attacked by rennin, and the only casein fraction that contains sugars.

Purification. κ-Casein, which forms part of *Mellander*'s α-casein, owes its name to *Waugh* and *v. Hippel* [15]; it is very closely related to the $\alpha_3$-component reported by *Hipp et al.* [26] and can be obtained by fractionation of total casein [43–55], *e.g.* with trichloroacetic acid and urea [44] or by chromatography [46].


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The behavior of κ-casein in starch gel electrophoresis shows that it is not a single substance. *Woychik* [56,57], *Wake* [58], and *Schmidt* [59] found two main fractions and a number of subsidiary fractions following the reduction of κ-casein to "SCM-κ-casein". On chromatography on DEAE-cellulose with buffers containing 20% dimethylformamide, SCM-κ-casein was resolved into two (faster-moving) sugar-rich fractions and two sugar-free fractions. Since all these components are attacked by rennin, the sugar moiety seems to play no part in the clotting of milk by rennin. The heterogeneity of κ-casein (from the milk of several animals) is due to genetic variants (see below) and to the presence of more or less large quantities of sugars mainly in the caseinoglycopeptide part. Seasonal variations in the amino acid composition have also been observed [60].

Molecular Weight. At pH 7 (0.1 M phosphate buffer), the sedimentation constant $s_{20} = 12.9$ S (polymeric form; aggregates), while the value at pH 12.2 (0.19 M phosphate/KOH buffer) is $s_{20}^{c=o} = 1.4$ S (monomeric form) [43,44]. The values given in the literature for the molecular weight of κ-casein range from 26000 ± 3000 [23,61,66] to 160000 [62], even 280000 [47]. *Swaisgood* and *Brunner* [63] accepted a value between 50000 and 60000, while *Beeby* [64] postulated the presence of three sub-units with a molecular weight of 16000 that differ in their neuraminic acid and cystine contents. In 1964, *Swaisgood et al.* [65] concluded from studies on reduced κ-casein that it probably consists of two sub-units of molecular weight 28000. The same molecular weight was also deduced from its sulfur, phosphorus, and neuraminic acid contents. Very recent experiments by *Woychik* [56,57] (analysis of genetic variants, sedimentation constants of carbamoylmethyl-κ-casein) and by *Wake* [58] (investigation of fractions obtained from SCM-κ-casein) have shown that the molecular weight is very probably about 19000 ± 1000. This value is also in agreement with the first results obtained by *Jollès et al.* [67] in connection with the structure of κ-casein.

Genetic variants of κ-casein were detected by *Woychik* [56,68,69], *Neelin* [70], and *Schmidt* [59,71] with the aid of starch gel electrophoresis.

Analyses. The composition of κ-casein was studied by *Jollès et al.* [72] and *Swaisgood et al.* [63,65]. Special mention should be made of the high content of hydroxy-substituted amino acids, glutamic acid, and proline, as well as of the presence of cystine. The amino acid analyses of genetic variants (κ-A and κ-B) have been reported by *Woychik* [56] and *Schmidt* [59]. The two variants differ by one residue each of aspartic acid, threonine, alanine, and isoleucine.

κ-Casein is the only fraction of the total casein complex that contains appreciable quantities of sugars: galactose, galactosamine (not glucosamine, as was formerly believed), and *N*-acetylneuraminic acid were detected and assayed by *Alais* and *Jollès* [73]. The neuraminic acid contents reported differ very widely, either because some of this sugar is lost during the purification process, or because the milks contain κ-caseins with different sugar contents [48,49,73–79]. The phosphorus content (0.22%) is lower than in the other principal fractions.

Structure studies. During the clotting of milk by rennin the only significant alteration occurs in κ-casein. For this reason the structure of κ-casein will be reported in the second part of this article.

Biological Activity. *Yaguchi et al.* [80] found that several casein fractions containing the κ-component behave as lipases towards milk fat at pH 9.

κ-Casein as a Protective Colloid. – Interactions with Other Casein Fractions. – Micelle Formation. In the presence of calcium ions, $\alpha_S$-casein and β-casein are insoluble in water at room temperature, whereas κ-casein is soluble. κ-Casein stabilizes colloidal dispersions of calcium caseinate. According to *Waugh* [81] stable suspensions of micelles are formed when $\alpha_S$- and κ-caseins are present in the ratio of 4:1 by weight (0.03 M $Ca^{2+}$ at 37 °C). When this ratio is greater than 4:1, the excess $\alpha_S$-casein precipitates out, while if the ratio is smaller than 4:1, smaller micelles are formed. This association between κ- and $\alpha_S$-caseins has been studied in neutral solution [82]. Interactions can also occur between κ- and β-caseins [83] or κ-, $\alpha_S$-, and β-caseins [83–88]; β-

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casein remains in solution at high temperatures in the presence of κ-casein. During the clotting of milk by rennin, part of the κ-casein is split off, and the κ-casein can then no longer act as a protective colloid (see Part II).

The chemical bonds in the micelles (*e.g.* ester linkages) and the behavior of calcium and phosphate ions towards the micelles have been studied by *Schipper* [87] and *Pyne* [89]. These authors found that colloidal calcium phosphate is either adsorbed on or chemically bonded to the casein.

Finally, it should be noted that interactions also occur between κ-casein and other proteins, *e.g.* β-lactoglobulin [90].

### 3. Study of Some Subsidiary Fractions

The $\alpha_s$ fraction that accompanies $\alpha_{s1,2}$-caseins was mentioned in Section IA2a [88,91]. The only other acidic phosphoprotein obtained from the casein complex is λ-casein [17] (or m-casein [87]), which often occurs together with κ-casein and which is also present in $\alpha_2$-casein [26]. λ-Casein has a high (1.2%) phosphorus content (see Table 2). A number of proteins with relatively high isoelectric points (6.4–8.0) have been isolated from the casein complex, but they contain very little or no phosphorus.

A new purification method was recently developed [32] for *Mellander*'s γ-casein [13]. The amino acid composition is known only for an earlier sample [92]. The sedimentation constant is 1.15 S at 1.3 °C for a 1% solution in 0.1 M phosphate buffer of pH 7, and the molecular weight is about 30000. *Aschaffenburg* detected two genetic variants [35].

When the pH of a solution of total casein is adjusted to 4, centrifugation gives a supernatant containing two proteins which are insoluble at pH 7–9. These are "red protein", which is a metalloglycoprotein belonging to the transferrin group [93], and a basic protein, lactollin [94].

Finally, it should also be mentioned that some enzymes, *e.g.* protease and lipase, are firmly bonded to casein [95].

None of the subsidiary fractions with relatively high isoelectric points are really caseins, since they are probably not synthesized in the mammary gland.

## B. Caseins from Sheep and Goat Milk. – Casein from Human Milk

Whereas casein from cow's milk and its fractions have been intensively studied, similar data for other caseins are almost completely lacking [97–99]. *Sloan et al.* [96] compared the caseins of 40 animals (eight species), though only by electrophoresis; three types of electropherograms were obtained.

It was shown by *Alais* and *Jollès* [73,99] that caseins from sheep, goat, and human milk contain galactose and galactosamine. While only *N*-acetylneuraminic acid (0.80% [99] or 2.1% [100]) was found in casein from human milk, the caseins from sheep and goat milk contain a mixture of *N*-acetylneuraminic and *N*-glycolylneuraminic acids (0.09 and 0.13%, respectively) [73].

Since the clotting of sheep milk by rennin follows a course similar to that of cow's milk (see Part II), it was assumed that a "κ-like" fraction was present. *Alais* and *Jollès* [98] tried to isolate this fraction and obtained a casein that remained soluble in the presence of 0.4M $CaCl_2$ and was attacked by rennin without added $Ca^{2+}$.

By electrophoretic studies with buffers containing urea, *Malpress* [100] and *Alais* and *Jollès* [101] showed that human casein consists of a very large number of fractions. It was not possible in each case to obtain preparations that could be digested with rennin [99]. *Malpress* and *Seid-Akhavan* [102] carried out chromatographic experiments on CM-C50 Sephadex with buffers containing urea and isolated a fration that has the same properties as the κ-casein of cow's milk.

It should be noted finally that the composition and properties of human casein do not appear to be constant. They are influenced by the composition of the milk from which the casein was obtained and by the changes in the activities of certain enzymes (*e.g.* protein-synthesizing enzymes) in the cells in which the milk is formed [103]. Human casein contains an alcohol-soluble fraction (25% of the total weight; only 5% in the casein from cow's milk), which has been resolved into five fractions by chromatography on DEAE-cellulose [104]. The alcohol-soluble fraction seems to consist mainly of lipids.

## II. The Clotting of Milk by Rennin

Two coagulation processes occur in nature: the clotting of blood, which involves the cleavage of an arginylglycine linkage, and the clotting of milk. *Hammarsten* [7] found that rennet contains an enzyme (rennin) [105–108] and that the treatment of casein with rennin leads to the liberation of peptide-like substances (substances containing non-protein nitrogen, *e.g.* peptides). It is now

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believed that the interaction of casein with rennin includes three reactions [109–110]: A glycomacropeptide (caseinoglycopeptide [111]) is first split off ("primary reaction"), then coagulation takes place, and finally all the casein components are slowly broken down by rennin into smaller peptides [112].

According to *Waugh* [15], the substrate for the primary reaction is the κ-casein that stabilizes the colloidal dispersion of calcium caseinate. This was confirmed by *Jollès* and *Alais* [113], and simultaneously by *Nitschmann et al.* [114], who found that the glycopeptide obtained from a solution of κ-casein on treatment with rennin is the same as that obtained from solutions of total casein or α-casein. Following treatment with rennin, κ-casein gives a particularly high percentage of substances containing non-protein nitrogen, which are soluble in trichloroacetic acid [115]. The primary reaction can be represented as follows:

$$\kappa\text{-casein} \xrightarrow[\text{pH } 6.8]{\text{rennin}} \underset{\text{(insoluble)}}{\text{para-}\kappa\text{-casein}} + \underset{\text{(readily soluble)}}{\kappa\text{-caseinoglycopeptide}}$$

We shall first consider rennin and the structures of κ-casein and para-κ-casein and then deal in detail with the caseinoglycopeptide.

## A. Primary Reaction

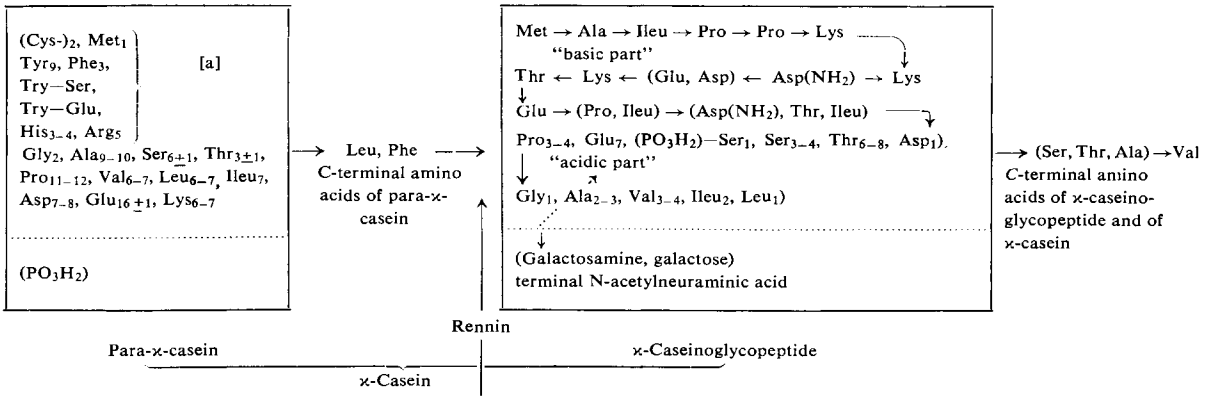
### 1. Rennin

Rennin is an enzyme which occurs in the fourth stomach of calves. It was first isolated and crystallized by *Berridge* [116]. Its specificity is similar to that of pepsin, but its optimum pH is much higher, at about 4 [117]. Rennin attacks not only casein, but also other proteins such as hemoglobin [116] or the B chain of oxidized insulin [118]. *Foltmann* [119,120] has recently studied the structure of rennin.

### 2. κ-Casein

It is now accepted that κ-casein has a molecular weight of 19000 ± 1000 [57,59,67] and that it has a homogeneous peptide skeleton of 165 ± 5 amino acid residues. A few changes are attributable to the genetic variants; these latter and the variations in the sugar composition are ultimately responsible for the heterogeneity observed on electrophoresis. The *N*-terminal amino acids have not yet been identified, but with the aid of carboxypeptidase, *Jollès et al.* [72] were able to liberate valine, together with some alanine, threonine and serine from the *C*-terminal end. Some data on the structure of κ-casein, which were mainly obtained in studies on para-κ-casein and on κ-caseinoglycopeptide, are summarized in Scheme 1 [67, 121,122,132]. Preliminary results obtained in the study of the tryptic units [67] are in agreement with Scheme 1. Clotting by rennin still occurs after treatment of κ-casein with neuraminidase [62], even when 50% of the galactose is subsequently oxidized [67]. Thus the sugar moiety does not appear to be essential to the action of rennin. A sugar-free fraction recently obtained by chromatography from a reduced κ-casein (*S*-carboxymethyl-κ-casein) [123] can also be digested with rennin. However, it is not yet known whether the soluble peptide obtained under these conditions is the same as the "normal" caseinoglycopeptide.

Scheme 1. Composition of cow's κ-casein (molecular weight 19000 ± 1000): cleavage by rennin into para-κ-casein and κ-caseinoglycopeptide.




[a] All the aromatic and basic amino acids (except lysine) and all the cystine of κ-casein are situated in this part of the molecule [67,72,121,122,132].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### 3. Para-κ-casein

Para-κ-casein is the insoluble fraction obtained after the action of rennin on κ-casein. It contains all the aromatic amino acids and all the arginine and cystine residues of κ-casein (see Scheme 1) but its sugar content is very low. The amino acid composition and the terminal amino acids were first reported by *Jollès et al.* [72, 121], who also showed that the sum of the amino acid residues in para-κ-casein and in κ-caseinglycopeptide is equal to the number of amino acids in κ-casein. *Kalan* and *Woychik* [57] recently also analysed para-κ-casein. As in the case of κ-casein, the *N*-terminal sequence has not yet been characterized. A *C*-terminal phenylalanine residue (together with a little leucine) was identified by digestion with carboxypeptidase [121]; this result has been confirmed by *Dennis* and *Wake* [124]. Casein is attacked not only by rennin, but also by other enzymes such as pepsin [125], chymotrypsin [124], and callicrein [126], as well as by chemicals (alkalis, reducing agents) [67, 121]; an insoluble "para-κ-casein-like" part, usually (but not always) with phenylalanine (together with a little leucine) in the *C*-terminal position, is obtained [67].

### 4. κ-Caseinoglycopeptide (from the κ-Casein of Cow's Milk)

Isolation and Molecular Weight. After treatment of κ-casein with rennin for a short time, paper electrophoresis of the soluble supernatant material revealed the presence of four fractions [127, 128]; the caseinoglycopeptide accounts for 80% of this soluble material, and one of the other fractions (10%) is probably a degradation product. The caseinoglycopeptide can be isolated either from the trichloroacetic acid extract of casein that has been treated with rennin, or by chromatography of the supernatant material on DEAE-cellulose [111, 114, 128]; it is very readily soluble, even in 12% trichloroacetic acid, and is non-dialysable. Electrophoresis and ultracentrifugation have shown that this is a single substance (molecular weight about 7500 ± 500 [129]).

Amino Acid Composition. Special mention should be made of the high contents of the hydroxy amino acids, glutamic acid, and proline, and of the absence of aromatic amino acids, cystine, histidine, and arginine [57, 111, 113, 130–132]. A methionine residue has recently been identified [122]. The peptide moiety of the caseinoglycopeptide amounts to about 65%, and the P content is 0.37% (phosphoserine residue [73]).

Sugar Composition. Galactosamine, galactose, and *N*-acetylneuraminic acid have been detected [73, 129, 133], the quantities present accounting for 75, 68 and 77%, respectively, of the quantities present in κ-casein; some authors even report that all the *N*-acetylneuraminic acid of κ-casein is contained in this part [62, 64]. The sugar moiety of κ-caseinoglycopeptide is approximately 30%. (As with many other substances with high sugar contents, some of the sugar escapes detection, probably because of imperfections in the methods used).

Structure Studies. *Jollès et al.* [111] showed by chemical and enzymatic methods that κ-caseinoglycopeptide contains a methionine residue as the *N*-terminal amino acid [122] and that this is followed by an alanine residue. The *C*-terminal sequence is the same as that of κ-casein [72], *viz.* (Ser, Thr, Ala)-Val; it may therefore be assumed that κ-caseinoglycopeptide is situated at the *C*-terminal end of κ-casein. The structure of the *N*-terminal octadecapeptide was elucidated by degradation with trypsin and chymotrypsin [132] (see Scheme 1).

Experiments with neuraminidase from *Vibrio cholerae* have shown that the *N*-acetylneuraminic acid occupies a terminal position in the sugar moiety [73, 134]; partial hydrolyses with $H_2SO_4$ led to the belief that the sugar directly attached to the peptide moiety (probably by an *N*-glycosidic linkage) is not galactose, but galactosamine [134]

Mention should also be made of a shorter but very similar glycopeptide from the colostrum of the cow [135].

### 5. The Linkage Cleaved in κ-Casein by Rennin

As mentioned above, after rennin has been allowed to act on κ-casein, no new *N*-terminal amino acids can be detected in the para-κ-casein produced [72] although a new *N*-terminal residue (methionine) is found in the caseinoglycopeptide [122]; a new *C*-terminal amino acid (phenylalanine), which comes from the para-κ-casein portion, has also been identified [121]. The question arises whether it can therefore be assumed that it is a Phe-Met linkage that has been cleaved.

*Garnier et al.* [137] followed the formation of the caseinoglycopeptide by titration of the carboxyl groups liberated at a constant pH, and found that one carboxyl group was liberated per 55000 molecular weight units (the molecular weight of κ-casein is now thought to be 19000 ± 1000). This and the following facts suggest the cleavage of an ester linkage. *Jollès et al.* [121] reduced κ-casein with $LiBH_4$ and then obtained an insoluble "para-κ-casein-like" part, which was found to contain a 2-amino-3-phenyl-1-propanol

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(phenylalaninol) residue; this also suggests an ester linkage between the *C*-terminal phenylalanine residue and a hydroxylated residue (a sugar, serine, or threonine); this experiment does not, however, rule out another kind of labile linkage, such as a labile peptide linkage [67].

*Cheeseman et al.* [138] disagreed with this "ester" hypothesis, since they were unable to observe any liberation of protons during the action of rennin. *Beeby* and *Nitschmann* [139] expressed the opinion that rennin first cleaves linkages like hydrogen bonds, with the result that part of the κ-casein dissolves afterwards; the rennin liberates the glycopeptide from the dissolved material.

Finally, *Dennis* and *Wake* [124] have shown that sugar-free reduced κ-casein is cleaved by rennin, so that an ester linkage between phenylalanine and a sugar can be ruled out.

Further investigation will be necessary in order to elucidate the nature of the linkage that is cleaved by the action of rennin (possibly a Phe-Met linkage as shown in Scheme 1; for earlier theories see [136]).

*N*-acetyl- and *N*-glycolylneuraminic acids, while the human glycopeptide contains only *N*-acetylneuraminic acid; the latter is the only glycopeptide in which fucose and glucosamine have been found [102].

*C*- and *N*-Terminal Amino Acids. The action of carboxypeptidase on sheep, goat, and human caseinoglycopeptides led to the liberation of valine [99, 111]. The *N*-terminal amino acid was studied only in the case of the sheep caseinoglycopeptide; as in cow's κ-caseinoglycopeptide, it was found to be methionine [122].

Structure Studies. The caseinoglycopeptide from total sheep casein consists of three parts: 1. an *N*-terminal sequence, which contains the three lysine residues of the peptide; 2. a decapeptide containing the only histidine unit of the peptide; and 3. an "acidic" part, which has not yet been completely purified by column chromatography. This last-named part contains the phosphorus and most of the sugar [122, 132, 140] (see Table 3).

Table 3. Data on the structure of sheep caseinoglycopeptide [122, 132, 140].

1. *N*-Terminal sequence containing the three lysine residues present in the molecule:
Met → Ala → Ileu → Pro → Pro → Lys → Lys → ($Asp_2$, Glu) → Lys → Thr → ($Ileu_2$, Ala, Pro, Glu, Asp)

2. Decapeptide containing the unic histidine residue in the molecule:
Thr → Ileu → Ala → Ser → Ala → Glu → Pro → Thr → Val → His

3. "Acidic" part:
phosphorus +
sugars +
*C*-terminal amino acid: Val
$Asp_5$, $Thr_8$, $Ser_6$, $Glu_7$, $Pro_3$, $Ala_6$, $Val_5$, $Ileu_1$.

## 6. Caseinoglycopeptides from Total Sheep, Goat, and Human Caseins

The total casein, α-casein, and κ-casein from cow's milk all give the same caseinoglycopeptide [113]. Since pure κ-casein fractions have not yet been isolated from sheep, goat, and human milk, *Alais* and *Jollès* [99, 111] used the total caseins for the preparation of caseinoglycopeptides.

Purification. The caseinoglycopeptides were isolated from the trichloroacetic acid extract of caseins that had been treated with rennin [111]; it was not always possible to obtain a glycopeptide from human total casein [99].

Amino Acid Composition. The three new caseinoglycopeptides contain large quantities of serine, threonine, glutamic acid, and proline, but no aromatic amino acids, cystine or arginine [111]. This composition appears to be characteristic of caseinoglycopeptides. The peptide contents are about 80% [73].

Sugar Composition. The sugar contents of caseinoglycopeptides from sheep, goat, and human milk are 7.1, 11.6, and 16%, respectively [73, 99]. All three substances contain galactosamine and galactose. The glycopeptides from sheep and goat milk contain a mixture of

The neuraminic acids occur in a terminal position in sheep and goat caseinoglycopeptides; galactosamine, but not galactose, appears to be directly attached to the peptide chain [134]. *Malpress* [102] believes that *O*-glycosidic linkages are formed between the sugars and the serine and threonine residues.

## 7. "Caseinoglycopeptide-like" Substances

As mentioned in Section II A 3, casein is attacked not only by rennin, but also by other enzymes [125, 126] and by chemical reagents [67, 121]. During the primary reaction between casein from cow's milk and pepsin, the peptide split off is the same as with rennin [125]; that split off by callicrein is slightly different [126]. A slightly different peptide is also obtained in good yields either with 0.1 N NaOH at 20 °C [67] or by reduction [121]. All these caseinoglycopeptide-like substances, such as the glycopeptide obtained by the action of rennin, are soluble in 12% trichloroacetic acid and are not dialysable; no aromatic amino acids or arginine are present.

When casein is heated to 100 °C not only neuraminic acid, but also "caseinoglycopeptide-like" substances are liberated [104, 141, 142] (regarding the action of heat on casein, see also [142, 143]).

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## B. Secondary and Tertiary Reactions

The second phase in the clotting of milk involves several reactions (deaggregation, reaggregation, coagulation, syneresis of the gel), during which the degree of dispersion of the casein micelles changes. Coagulation is the easiest of these to be followed by physical methods (ultramicroscopy [144], ultrasonics [145], viscometry [146]). The clotting of milk can be represented by the following reactions [147] (see also Section IA2c):

$$\text{Micelles} \overset{Ca^{2+}}{\rightleftharpoons} \text{soluble complex } (\alpha_s, \varkappa, \beta, \ldots) \quad (1)$$

$$\text{Soluble complex } (\alpha_s, \varkappa, \beta, \ldots) \xrightarrow{\text{rennin}} \text{soluble complex } (\alpha_s, \text{para-}\varkappa, \beta, \ldots) + \text{caseinoglycopeptide} \quad (2)$$

$$\text{Soluble complex } (\alpha_s, \text{para-}\varkappa, \beta, \ldots) \xrightarrow{Ca^{2+}} \text{coagulum} \quad (3)$$

It is assumed that Reaction (1) is established very quickly, and does not affect Reaction (2). In the absence of $Ca^{2+}$, only Reaction (2) occurs, and no coagulation takes place. The rate of Reaction (3) increases rapidly with rising temperature; it is therefore possible to distinguish this reaction from Reaction (2) at low temperatures [148].

*Cheeseman* [149] showed that some substances can shorten or lengthen the coagulation time (*e.g.* $Ca^{2+}$ reduces the coagulation time, urea increases it). After coagulation, the syneresis of the casein gel is completed.

This reaction can be followed by the change in the weight of the gel or by measurement of the emerging liquid [149]. Syneresis according to Reaction (2) begins already during the hydrolysis of the $\varkappa$-casein. Hydrogen bonds are first formed between the casein aggregates, and bridges are finally also established between thiol groups [149, 150]. The rates of the second phase and of the clotting by rennin were recently studied [151, 152].

The existence of a tertiary phase was shown by *Alais et al.* [112]. The primary reaction involves aspecific digestion of casein by rennin, while the tertiary reaction involves a non-specific digestion. High molecular weight substances derived from the various casein components are formed first; the final products are a large number of polypeptides which are more or less resistant to rennin.

In conclusion, it should be mentioned that the digestion of casein by various enzymes (particularly pepsin) often leads to substances that are very similar to those obtained during the tertiary phase of the clotting by rennin [31, 153–157].

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[153] *B. Lindqvist* and *T. Storgards*, Acta chem. scand. *14*, 1432 (1960).

[154] *P. Baudet*, *R. Rössler*, and *E. Cherbuliez*, Helv. chim. Acta *43*, 1795 (1960).

[155] *L. Strid*, Acta chem. scand. *15*, 1423 (1961).

[156] *J. Schormüller* and *R. Fresenius*, Z. Lebensmittel-Unters. u. -Forsch. *114*, 279 (1961).

[157] *M. Derechin*, Biochem. J. *82*, 42 (1962).

# Force Constants and Bond Orders of Nitrogen Bonds

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*The force constants and the corresponding bond orders of nitrogen bonds have been calculated from the vibrational spectra (infrared and Raman spectra) of a great number of nitrogen compounds. Plotting the maximum bond order of stable nitrogen bonds against the sum of Pauling's electronegativities of the bonding partners ($\Sigma x$) leads to one continuous curve for the N–X bonds where X represents elements of the first and the second short period of the periodic table. Furthermore, when the bonds formed between these elements are arranged in a coordinate system in such a way that the position of each bond is determined by the difference between the electronegativities of the bonding partners ($\Delta x$ along the ordinate) and the sum of the electronegativities of the bonding partners ($\Sigma x$ along the abscissa), the bonding partners capable of forming multiple bonds all lie within a closed domain, where their position can be correlated with their polymerizability and other reactivities of the multiple bonds. Also discussed are the orders of bonds between nitrogen and some transition elements. In an appendix, the present methods used to calculate force constants and bond orders are surveyed.*

## A. Introduction

The conditions for the formation of π-bonds have been previously summarized as follows [1]:

1) electron deficiency on both bonding partners;

2) the sum of the Pauling electronegativities of the partners must be at least 5;

3) the difference between the Pauling electronegativities of the bonding partners must be small.

We have endeavored in the past few years to verify these conditions on further examples and, in particular, to define more accurately condition 3). Condition 2) has recently been confirmed by *Herber* and *Stöckler* [2], who investigated the Mössbauer effect of tin compounds and showed that the isomeric shift is invariably proportional to the sum of the electronegativities of all bonding partners involved.

We have chosen nitrogen for our investigations, since it forms a great number of compounds and has the high electronegativity of 3,0, enabling it to form bonds with numerous elements in such a way that the sum of the electronegativities is at least 5. Unlike the halogens, and like oxygen, nitrogen can form π-bonds without the accumulation of high formal charges. The types of bonds that nitrogen can form are summarized in Table 1.

Table 1. Types of bond formed between nitrogen and a partner X.

| | |
|---|---|
| Ammines | $X \leftarrow NH_3$ |
| Amines, amides | $X-\ddot{N}H_2 \leftrightarrow X \leftarrow NH_2$ |
| Imines, imides | $X-\ddot{N}-H \leftrightarrow X=\ddot{N}H \leftrightarrow X \equiv NH$ |
| Nitrides | $X-\ddot{N}: \leftrightarrow X=\dot{N}: \leftrightarrow X \equiv N:$ |

In addition to the preferred bonds, in which the two atoms involved have a low formal charge (cf. Table 1), bonds in which the nitrogen carries a formal positive charge are also important. This formal positive charge is to some extent compensated by the fact that nitrogen is at the same time the negative end of the polar bonds which it forms in most cases.

## B. Calculation of Bond Order

The following discussion is based on vibrational spectra (infrared and Raman spectra) furnishing data for the force constants, which in turn are used for the calculation of the bond orders. In these calculations, the geometry of the molecule and the assignment of the observed frequencies to the fundamental vibrations is also accounted for. *Fadini*, *Sawodny*, and *Ballein* [3] have used a new method of calculation, enabling them to obtain the force constants and all interaction constants directly from the measured frequencies without a trial-and-error procedure [4]. The resulting valence bond constants, the only ones discussed below, have the advantage of being mutually comparable, since they are obatined by the same method. Deviations of more than 5–10 % correspond to actual changes in the nature of the bonding.

*Siebert*'s rule [4,5] has been used for the calculation of the force constants of single bonds. This rule gives good results, suitable for a general comparison of all force constants. *Siebert*'s values for single bonds correspond

[1] *J. Goubeau*, Angew. Chem. *69*, 77 (1957).

[2] *R. H. Herber* and *A. Stöckler*, Chem. Engng. News *42*, No. 28, 66 (1964).

[3] *A. Fadini*, Z. angew. Math. Mechan. *44*, 506 (1964); *W. Sawodny*, *A. Fadini*, and *K. Ballein*, Spectrochim. Acta *21*, 995 (1965).

[4] *J. Goubeau*, Angew. Chem. *73*, 305 (1961).

[5] *H. Siebert*, Z. anorg. allg. Chem. *273*, 170 (1953).

to $sp^3$ hybridization. Since differences in the hybridization can lead to large (up to 50 %) variations in the force constants of single bonds, it has been found necessary to introduce an empirical correction factor [11].

Using these theoretical force constants for single bonds, we can calculate the bond order, b. It is assumed that higher force constants are essentially due to $\pi$-bonds. *Siebert* has given two equations for the bond order. One is based on the assumption that the bond is proportional to the force constant up to about b = 1.5, the other being an empirical formula (giving good results) for b > 1.5 (see Appendix III). The calculations are generally based on direct proportionality even in the case of higher bond orders. It is further possible to correlate, on a theoretical basis, the bond orders of single and double bonds in certain compounds with the force constants, and then to find the bond orders corresponding to the other force constants, as has been done in Tables 3 and 5 (column $b_{II}$).

## C. Order of Bonds between Nitrogen and Elements of the First Period

The parameters of the N–O, N–N, and the N–C bonds are well known and need no further discussion. In all three cases, the bond order can be between 1 and 3 according to the force constants.

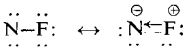
### I. The N—F Bond

Although, on the basis of the sum of electronegativities, the formation of multiple bonds should be possible in nitrogen trifluoride, this compound possesses no electron deficiency (condition 1 in Section A), and can, therefore, form no $\pi$-bonds. In the compounds $NF_2$ [6] and NF [7], which have recently been described together with their vibrational spectra, the nitrogen does not attain an electronic octet (*i.e.* it is electron deficient), and, therefore, it can form multiple bonds (at the most a three-electron bond in $NF_2$). Distributed over two N–F bonds, this leads to a maximum bond order of 1.25, while in NF the bond order may reach 2.0.

Table 2. Force constants f and bond orders b of the N–F bonds in various nitrogen fluorides.

| | $NF_3$ | $NF_2$ | NF |
|---|---|---|---|
| $f_{exp.}$ [mdyne/Å] | 4.38 | 4.85 | 5.90 [7] |
| $f_{calc.}$ (single bond) [mdyne/Å] | 4.26 | 4.05 [8] | 3.87 [8] |
| | | | 4.05 [8] |
| b | 1.03 | 1.20 | 1.45 [8a] |

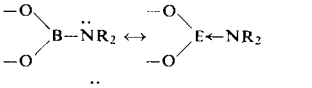
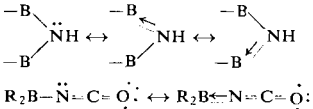
The experimental force constants and bond orders increase in a parallel direction, which confirms the importance of electron deficiency for the formation of multiple bonds. Whereas the bond order in $NF_2$ is close to theoretical, it is appreciably lower than the theoretical value in NF. This is in agreement with the observation that the positive charge on fluorine in N=F opposes the formation of a $\pi$-bond:



### II. The N—B Bond

The most important results concerning force constants and bond orders of N–B bonds in various compounds are listed in Table 3 [9], together with the possible

Table 3. Force constants f and bond orders b of N–B bonds (X = H, $CH_3$, F, Cl; Y = H, $CH_3$)

| Formula | Ref. | Canonical forms | f [mdyne/Å] | $b_I$ | $b_{II}$ |
|---|---|---|---|---|---|
| $X_3BNY_3$ | [10] | $X_3B{\leftarrow}NY_3$ | 2.8 | 0.7 | 1.0 |
| $(O_3B_3NR_2)_3$ | [11] |  | 4.0 | 1.0 | 1.3 |
| $B(NR_2)_3$ | [12] | $(R_2N)_2B{-}\ddot{N}R_2{\leftrightarrow}(R_2N)_2{\leftarrow}NR_2B$ | 6.0 | 1.5 | 1.7 |
| $(HBNH)_3$ | [13] |  | 6.3 | 1.6 | 1.8 |
| $R_2BNCO$ | [3,14] | $R_2B{-}\ddot{N}{=}C{=}\dot{O}: \leftrightarrow R_2B{\leftarrow}N{=}C{=}\dot{O}:$ | 6.6 | 1.7 | 1.9 |
| $X_2BNY_2$ | [15] | $X_2B{-}\ddot{N}Y_2 \leftrightarrow X_2B{\leftarrow}NY_2$ | 7.0 | 1.8 | 2.0 |
| $BN_2^{3\ominus}$ | [16] | $[:\dot{N}{=}B{=}\dot{N}:]^{3\ominus}$ | 7.0 | 1.8 | 2.0 |
| BN | [17] | $B{-}\ddot{N} \leftrightarrow \overset{\ominus}{B}{=}\overset{\oplus}{N}: \leftrightarrow B{\equiv}N:$ | 8.3 | 2.1 | 2.3 |

mesomeric limiting structures. The bond orders $b_I$ are based on *Siebert*'s value for the single bond (f = 3.9 mdyne/Å). In calculating thebond order $b_{II}$, it was assumed that compounds of the type of $X_3BNY_3$ are characterized by a single bond, while $BN_2^{3-}$ contains a

[6] *F. A. Johnson* and *C. B. Colbuin*, Inorg. Chem. *1*, 431 (1962); *M. D. Harmony* and *R. J. Myers*, J. chem. Physics *37*, 636 (1962).

[7] *M. E. Jacox* and *D. E. Milligan*, J. chem. Physics *40*, 2457 (1964).

[8] In such a case, the value for the $\sigma$-bond represents an intermediate value, since the number of free electron pairs changes in the transition from single bond to double bond. For NF two values are obtained (3.87 and 4.05).

[8a] The bond orders were determined by a simple averaging method, the extreme values being b = 1.39 and b = 1.52.

[9] Cf. *J. Goubeau*, Advances Chem. Ser. *42*, 87 (1964). *H. Nöth*, *G. Schmid*, and *Y. Chung* (IUPAC Congress, Vienna, 1964) have found another example of a B–N bond with high bond order in the adduct $B(NR_2)_3{\cdot}TiCl_4$. However, since the force constant has not been calculated, this example could not be included in Table 3.

double bond. The intermediate bond orders were found on the basis of an assumed proportionality between the bond orders and the force constants. The difference between $b_I$ and $b_{II}$ (about 0.2) is of little significance for the subsequent discussion; the $b_I$ values are preferred for purposes of comparison. The maximum bond order has thus been found to be 1.8 for the N–B bond in compounds that are stable at room temperature.

### III. The N—Be Bond

Beryllium compounds, like boron compounds, form adducts with ammonia and amines [18]. The reaction between beryllium alkyls and amines leads to substituted beryllium amides [19] which could not be prepared from adducts of the type $BeCl_2 \cdot 2HN(CH_3)_3$ by the abstraction of HCl [20]. Unlike the boron compounds, these beryllium amides are known only in polymeric form.

The force constants have been calculated from the spectra of berylliumdi-[bis-(trimethylsilyl)] amide [13] and the adducts formed of ammonia, dimethylamine, and trimethylamine with $BeCl_2$ and $BeBr_2$ [21]. In the first case, the value f = 2.96 mdyne/Å has been obtained for the N–Be bond, while in the other cases, calculations on the basis of the antisymmetric vibrations of the $BeN_2$ group (600–785 $cm^{-1}$) led to f = 1.2 to 1.4 mdyne/Å. Using these values and taking, with *Siebert*, f = 3.1 mdyne/Å for the single bond, we obtain b = 0.95 and b = 0.39 to 0.45, respectively. Since the beryllium amides are polymeric, we cannot expect them to have appreciably higher force constants. In fact, there is no indication at the present of higher bond orders in N–Be compounds.

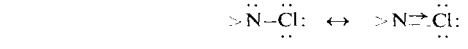
### IV. The N—Li Bond

Only one very broad infrared band has been observed for each of the simple compounds available, $LiNH_2$, LiNH, and $Li_3N$. These bands are situated, respectively, at 403, 465, and 430 $cm^{-1}$ and can be attributed to antisymmetric vibrations [22]. The resulting force constants (0.44, 0.61, and 0.55 mdyne/Å, respectively) are probably too high. On the assumption that the single bond has a force constant of 2.3 mdyne/Å, the average bond order for the N–Li bond is 0.23.

## D. Order of Bonds of Nitrogen with Elements of the Second Short Period

### I. The N—Cl Bond

Owing to the presence of vacant d-orbitals in elements of the second short period, electron deficiency exists here even when the electronic octet is reached. This means that double bonds can be formed, *e.g.* in $NCl_3$, unlike the case of $NF_3$:



The experimental data for the N–Cl bonds are listed in Table 4.

Table 4. Force constants and bond orders of N–Cl bonds in various compounds [*].

| | f [mdyne/Å] | b | Ref. |
|---|---|---|---|
| $H_2NCl$ | 3.1 | $1.2_6$ | [23] |
| $HNCl_2$ | 3.0 | $1.2_1$ | [23] |
| $NCl_3$ | 2.5–3.0 | $1.0_4$–$1.2_1$ | [23,24] |
| NCl | 4.0 | $1.7_2$ | [7] |
| $NClO_3^{2\ominus}$ | 8.9 | 2.2 | [25] |

In nitrogen trichloride, the calculated force constant varies with the Cl–N–Cl angle; the lower value corresponds to a tetrahedral angle, the higher to an angle somewhat smaller than 120°. However, the geometry of the molecule is not yet known. The bond orders in chloramine and dichloramine confirm the prediction based on the presence of vacant d-orbitals. These are also partly responsible for the fact that chlorine is the negative end in the N–Cl dipole [26]. The bond order in NCl is seen to be high; it is higher than in NF, probably because of the smaller difference between the electronegativities of the bonding partners. The highest force constant (f = 8.9 mdyne/Å) is exhibited by $NClO_3^{2-}$, this value being greater than that corresponding to a double bond.

### II. The N—S Bond

Out of the reliable data for the force constants of N–S bonds, some characteristic examples are listed in Table 5.


[10] *J. R. L. Amster* and *R. C. Taylor*, Spectrochim. Acta *20*, 1487 (1964); *J. Goubeau* and *W. Sawodny*, Z. physik. Chem. N.F. *44*, 227 (1965).

[11] *J. Goubeau* and *H. Keller*, Z. anorg. allg. Chem. *272*, 303 (1953).

[12] *H.-J. Becher*, Z. anorg. allg. Chem. *287*, 283 (1956).

[13] *B. L. Crawford* and *J. T. Edsall*, J. chem. Physics *7*, 223 (1939); *H. Watanabe*, *M. Narisada*, *T. Nakagawa*, and *M. Kubo*, Spectrochim. Acta *16*, 78 (1960).

[14] *J. Goubeau* and *H. Gräbner*, Chem. Ber. *93*, 1379 (1960).

[15] *J. Goubeau* and *H.-J. Becher*, Z. anorg. allg. Chem. *268*, 133 (1952).

[16] *J. Goubeau* and *W. Anselment*, Z. anorg. allg. Chem. *310*, 248 (1961).

[17] *A. E. Douglas* and *G. Herzberg*, Canad. J. Res., Sect. A *18*, 179 (1940).

[18] *e.g. R. Fricke* and *F. Röbke*, Z. anorg. allg. Chem. *170*, 25 (1928).

[19] See, *e.g.*, *G. E. Coates* and *F. Glocking*, J. chem. Soc. (London) *1954*, 22.

[20] *N. Th. Rakintzis*, Dissertation, Technische Hochschule Stuttgart, 1957.

[21] *Ch. Forker*, Dissertation, Technische Hochschule Stuttgart, 1964; *H. Bürger*, *Ch. Forker*, and *J. Goubeau*, Mh. Chem. *96*, 597 (1965).

[22] *V. Dorn*, Dissertation, Technische Hochschule Stuttgart, 1964.


[*] According to *Siebert*, the $sp^3$ single bond has a force constant of 4.0 mdyne/Å.


[23] *G. M. Moore* and *R. Badger*, J. Amer. chem. Soc. *74*, 6076 (1952).

[24] *E. Allenstein*, Dissertation, Technische Hochschule Stuttgart, 1953.

[25] *E. Kilcioglu*, Diploma Thesis, Technische Hochschule Stuttgart, 1965; together with *E. Jacob*.

[26] *E. Allenstein*, Z. anorg. allg. Chem. *308*, 3 (1961).

Table 5. Force constants and bond order of N–S bonds in various compounds.

| | f [mdyne/Å] | $b_I$ | $b_{II}$ | Ref. |
|---|---|---|---|---|
| $(CH_3)_3NSO_3$ | 3.0 | 0.8 | 0.8 | [27] |
| $H_3NSO_3$ | 3.1 | 0.8 | 0.8 | [28] |
| $(CH_3)_2NSCH_3$ | 3.1 | 1.2 | 1.1 | [29] |
| $H_3CN(SCH_3)_2$ | 4.3 | 1.5 | 1.3 | [29] |
| $(H_3CN)_2S$ | 8.1 | 2.5 | 1.9 | [30] |
| HNSO | 8.3 | 2.6 | 2.0 | [31] |
| NSF | 10.7 | 3.4 | 3.0 | [32] |
| $NSF_3$ | 12.5 | 3.4 | 3.0 | [32] |

With *Siebert*'s value of f = 3.7 mdyne/Å for the single bond, we obtain bond orders between 0.8 and 3.4, taking into account the hybridization and assuming a direct proportionality between f and b. However, since the bond order cannot exceed 3, it is better to ascribe the values b = 3 and b = 2 to $NSF_3$ and HNSO, respectively, and to recalculate the other values on this basis ($b_{II}$). The corrected *Siebert* formula gives b = 2.70 and b = 2.2 in these cases. The properties of these compounds confirm the presence of the double and triple bonds deduced from the bond orders.

## III. The N—P Bond

Only a few examples have been selected from the chemistry of N–P compounds [33] to illustrate the range of the force constants. Discounting the band spectrum of PN in the gaseous state, which would probably give b = 3, we find that the bond order for normal compounds varies between 0.8 and 2.0.

The force constants in $[Cl_3P{-}N{-}PCl_3]^+$ [*] depend on the P–N–P angle (which is again unknown):

| Angle | 120° | 140° | 160° | 180° |
|---|---|---|---|---|
| f [mdyne/Å] | 6.2 | 6.9 | 7.8 | 9.1 |

Table 6. Force constants and bond orders of N–P bonds in various compounds [**].

| | f [mdyne/Å] | b | Ref. |
|---|---|---|---|
| $H_3NPO_3^{\ominus}$ | 3.1 | 0.8 | [35] |
| $(CH_3)_2NPCl_2$ | 3.5 | 1.3 | [36] |
| $(NPCl_2)_3$ | 4.2 | 1.2 | [37] |
| $H_2NPO_3^{\ominus}$ | 4.3 | 1.2 | [35] |
| $HNP(CH_3)_3$ | 6.1 | 1.7 | [38] |
| $[N(PCl_3)_2]^{\oplus}$ | 6.9 | 2.0 | |
| NP | 10.6 | 3.4 | [39] |

On the basis of calculations [33], the most likely value for the angle is 140 °C; it is associated with the highest force constant known to us (f = 6.9). It should be added that compounds such as $RNPCl_3$, $RNPF_3$, $NPCl_2$, and $NPF_2$, for which high bond orders are expected, exist only in polymeric form at room temperature.

## IV. The N—Si Bond

The reported values of the force constants vary, probably because the bond angle exerts a strong influence on the value of f.

Table 7. Force constants and bond orders of N–Si bonds in various compounds.

| | f [mdyne/Å] | b | Ref. |
|---|---|---|---|
| Single bond | 3.3 | | *Siebert* |
| $HN[Si(CH_3)_3]_2$; 140° | 3.5 | 1.1 | [40] |
| $HN(SiCl_3)_2$; 140° | 4.0 | 1.2 | [41] |
| $N(SiH_3)_3$ | 4.1 | 1.2 | [42] |
| $N[Si(CH_3)_3]_2^{\ominus}$; 160° | 4.2 | 1.3 | [43] |
| NSi | 7.3 | 2.2 | [44] |

Discounting molecular SiN which exist only at high temperatures, we find that the maximum bond order is 1.3 for the N–Si bond in compounds stable at ordinary temperatures. The maximum value of f = 4.8 mdyne/Å reported for the compound $S{=}C{=}N{-}SiH_3$ [45] is not included in Table 7, since, on recalculation, we have obtained a considerably lower value. However, even for the published value the bond order would be only 1.45. In the case of silicon, compounds of the type >Si=NR, which are monomeric in the case of sulfur and phosphorus, exist here only in polymeric form. Although we have taken b = 1.3 as the maximum value, the bond order may be somewhat higher in certain compounds.

## V. The N—Al Bond

In this case and in the following ones, spectroscopic data that may be used for the calculations are relatively scarce, except perhaps for aluminum nitride [22] and the ammonia and amine adducts of aluminum com-

[**] *Siebert*'s value for the $sp^3$ single bond is f = 3.5.


[27] *F. Watari*, Z. anorg. allg. Chem. *332*, 322 (1964).

[28] *H. Siebert*, Z. anorg. allg. Chem. *292*, 167 (1957); *J. Nakagawa, S. Mizushima, A. J. Saraceno, T. J. Lave*, and *J. V. Quagliano*, Spectrochim. Acta *12*, 239 (1958) (calculated by present author).

[29] *W. Bubeck*, Dissertation, Technische Hochschule Stuttgart, 1962.

[30] *B. v. Cramon*, Staatsexamen Thesis, Technische Hochschule Stuttgart, 1958; *F. Räuchle*, Diploma Thesis, Technische Hochschule Stuttgart, 1962.

[31] *H. Richert* and *O. Glemser*, Angew. Chem. *72*, 585 (1960).

[32] *H. Richert* and *O. Glemser*, Z. anorg. allg. Chem. *307*, 328 (1961).

[33] *R. Baumgärtner, W. Sawodny*, and *J. Goubeau*, Z. anorg. allg. Chem. *340*, 246 (1965).

[*] The author thanks Frau Prof. Dr. *M. Becke-Goehring* [34] (Heidelberg) for these data.

[34] *M. Becke-Goehring* and *W. Lehr*, Z. anorg. allg. Chem. *327*, 128 (1964).

[35] *E. Steger*, Z. anorg. allg. Chem. *309*, 304 (1961).

[36] *N. Lönhoff*, Dissertation, Technische Hochschule Stuttgart, 1964.

[37] *J. v. Iriborne* and *D. G. de Kowalewski*, J. chem. Physics *20*, 346 (1952).

[38] Calculated by the author from data communicated by *R. Appel*.

[39] *J. Curry, L. Herzberg*, and *G. Herzberg*, Z. Physik *86*, 348 (1933).

[40] U.a. *H. Kriegsmann*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *61*, 1088 (1957).

[41] *G. Gudmundsson*, Dissertation, Technische Hochschule Stuttgart, 1964.

[42] *E. A. V. Ebsworth, J. R. Holl, M. J. Mackilon, D. C. McKean, N. Sheppard*, and *L. A. Woodward*, Spectrochim. Acta *13*, 202 (1958); *H. Kriegsmann* and *W. Förster*, Z. anorg. allg. Chem. *298*, 212 (1959).

[43] *H. Bürger, W. Sawodny*, and *U. Wannagat*, unpublished work.

[44] *F. A. Jenkins* and *H. de Laszlo*, Proc. Roy. Soc. (London), Ser. A *122*, 103 (1929).

[45] *K. Sathianandan* and *J. C. Margrave*, J. molecular Spectroscopy *10*, 442 (1963).

pounds [10, 46]. The calculated force constants are between 1.9 and 2.5 mdyne/Å, to which correspond bond orders between 0.6 and 0.8 (*Siebert*'s force constant of the single bond is f = 3.0).

### VI. The N—Mg and the N—Na Bond

Infrared spectra have been recorded for $Mg_3N_2$, $Mg(NH_2)_2$, and $NaNH_2$ [22], and the force constants for the MgN (1.33 and 2.00) and NaN bonds (0.53) calculated only from antisymmetric vibrations on the basis of the two-body model now appear to represent upper limits. The resulting bond orders, b = 0.47 and 0.70 for MgN and b = 0.21 for NaN, are compatible with the high polarity of these bonds.

Basically the same curve is obtained by plotting b against $\Sigma x$ for the nitrogen bonds formed with elements of the first short period and elements of the second short period (Fig. 1; $\Sigma x$ denotes the sum of the electronegativities of the bonding partners, and the b values represent the maximum bond orders). Whenever $\Sigma x > 5$, double bonds can be formed (except in the case of F). Recalling condition 2 which states that, for the formation of double bonds, the sum of the electronegativities of the bonding partners must be at least 5, we note that, when this condition is not fulfilled (*i.e.* for the nitrogen bonds to Li, Be, B and Na, Mg, Al, and Si) the bond orders do in fact lie below b = 2 (b = 1 at $\Sigma x \approx 4.5$). Bond orders below 1 are due to the fact that the polarity of the bonds increases with decreasing value of $\Sigma x$ [3]. The bond orders of 0.42 and 0.72 for the "single bond" adducts of Be and B, respectively, fit in well with this series. The coincidence of the curves for the two short periods may be regarded as a confirmation of the second condition stated in Section A.

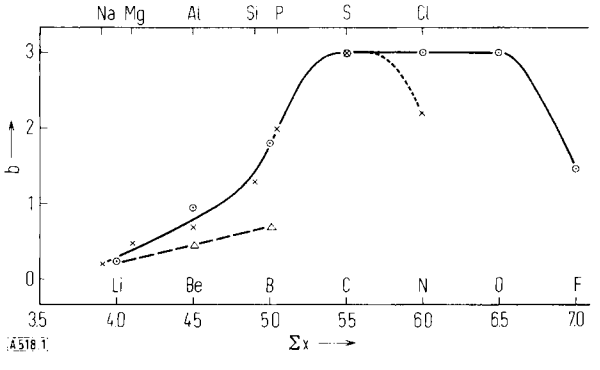



Fig. 1. Maximum bond order of the nitrogen bonds of elements of the first (○) and the second (×) short period and adducts (△), as a function of the sum of Pauling's electronegativities of the bonding partners ($\Sigma x$). The full curve refers to the maximum bond order.

### E. Order of Bonds between Nitrogen and Elements of Higher Periods Including Transition Elements

The bond order for NBr is 1.7 [7], and the bond is, therefore, similar to that in NCl. The compound RN=Se=O does not exist as a monomer and even its dimer (probably a four-membered ring) is stable only at temperatures below −10 °C [47], further polymerization occurring at higher temperatures. The N=Se bond is, therefore, less stable than the analogous N=S bond. Approximate calculations based on the assumption that the dimer forms a four-membered ring have given f = 3.4 and b = 1.3 for the N–Se bond.

In addition to insufficient experimental data on the nitrogen bonds of the transition elements, calculations are made difficult by the fact that the electronegativities are not accurately known and the electrons can occupy various orbitals. The force constants and the bond orders of the nitrogen bonds of the transition elements are listed in Table 8.

None of the elements has been subjected to exhaustive investigations concerning their bond parameters. Instead, ranges of single values are given in Table 8 for the force constants of azides, since the $N_3$ group was treated as a point mass in the simplified approximation. The lower limit corresponds to mass 14, the upper to mass *ca.* 30.

Table 8. Electronegativities (x), stretching frequencies (ν), force constants (f), and bond orders (b) of the nitrogen bonds of transition elements.

| | Ref. | x | ν [cm⁻¹] | | f acc. to *Siebert* | $f_{exp.}$ | b |
|---|---|---|---|---|---|---|---|
| (ClTiN)n | [48] | 1.6 | 406 | | 3.2 | 1.1 | 0.3 |
| $Cl_3TiN_3$ | [48] | | 565 | | | 2.0–3.1 | 0.6–1.0 |
| $Cl_4VN_3$ | [49] | 1.8 | 555 | | 3.7 | 2.0–3.1 | 0.5–0.8 |
| $Cl_2OVN_3$ | [48] | | 560 | | | 2.0–3.1 | 0.5–0.8 |
| VN | [22] | | 615 | | | 2.5 | 0.7 |
| $Cl_3VNCl$ | [49] | | | 1110 | | 8.0 | 2.2 |
| $Cl_2W(NH)_2$ | [50] | 1.9 | 475 | | 3.6 | 1.8 | 0.5 |
| $F_2W(NH)_2$ | [50] | | 470 | | | 2.1 | 0.6 |
| | | | 530 | | | | |
| $[Cl_2W(NH_3)_3]Na_2$ | [50] | | 715 | | | 4.8 | 1.3 |
| | | | 815 | | | | |
| $Cl_3WN$ | [49] | | | 1073 | | 8.8 | 2.4 |
| $Cl_4MoN_3$ | [49] | 2.0 | 552 | | 3.8 | 2.2–3.7 | 0.6–1.0 |
| $Cl_3MoN$ | [49] | | | 1045 | | 7.9 | 2.2 |
| $ClO_2CrN_3$ | [48] | 2.1 | 495 | | 4.1 | 1.6–2.5 | 0.4–0.6 |
| CrN | [22] | | 565 | | | 2.1 | 0.5 |
| $Cl_3ReNR{\cdot}PR_2R'$ | [51] | 2.1 | 780 | | 3.8 | 4.9 | 1.3 |
| $O_3ReN^{2\ominus}$ | [52] | | | 1025 | | 8.0 | 2.1 |
| $O_3OsN^{\ominus}$ | [53] | 2.2 | | 1023 | 3.9 | 8.0 | 2.1 |
| $Cl_5OsN^{2\ominus}$ | [53] | | | 1084 | | 9.0 | 2.4 |

The higher values, which are more probable, lead to bond orders of 0.6 and 1.0 in accordance with expectations. When the values of $b_{max}$ for Ti, V, Mo, W, Re and Os are plotted against $\Sigma x$ (Fig. 2), the points for Ti, Re, and Os lie on the curve, while Mo, and particularly W and V (the last two in their chloronitrides with b > 2) lie above the curve. The O-V bond in oxygen-containing compounds has a similar anomalous position.


[46] *H. Roszinski, R. Dautel*, and *W. Zeil*, Z. physik. Chem. N.F. *36*, 26 (1961).

[47] *J. Goubeau* and *U. Weser*, Z. anorg. allg. Chem. *319*, 276 (1963).

[48] *K. Dehnicke*, Habilitation Thesis, Technische Hochschule Stuttgart, 1964.

[49] *J. Strähle*, Dissertation, Technische Hochschule Stuttgart, 1964.

[50] *M. Schober*, Dissertation, Technische Hochschule Stuttgart, 1964.

[51] *J. Chatt* and *G. A. Rowe*, J. chem. Soc. (London) *1962*, 4019.

[52] *G. Wilkinson*, Inorganic Syntheses VI, 169.

[53] *J. Lewis* and *G. Wilkinson*, J. inorg. nuclear Chem. *6*, 12 (1958); *L. A. Woodward* and *J. A. Creighton*, Trans. Faraday Soc. *56*, 1266 (1960); *U. Hübler*, Staatsexamen Thesis, Technische Hochschule Stuttgart, 1962.

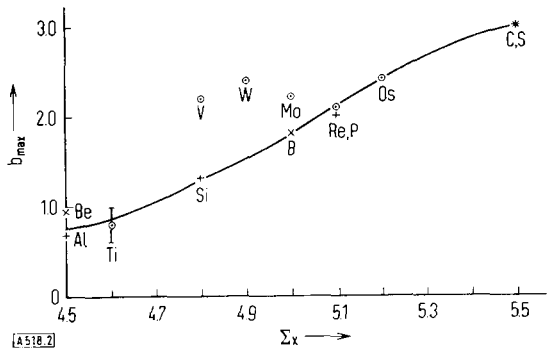



Fig. 2. Maximum bond order $b_{max}$ of the nitrogen bonds of transition and other elements as a function of the sum of *Pauling*'s electronegativities of the bonding partners (Σx).

It cannot yet be decided whether the electronegatitivies [*] and/or force constants belonging to the single bonds are incorrect, or whether the transition metal bonds are in fact different. A more accurate knowledge of the hybridization may throw some light on this problem.

## F. Comparison with Bonds Involving no Nitrogen

In order to compare the polarities of all possible bonds that may be formed within the first short period, we have constructed Fig. 3 by plotting the sum of the electronegativities against the difference of electronegativities of all such combinations. The three apexes of the triangle represent the three types of bond in pure form.

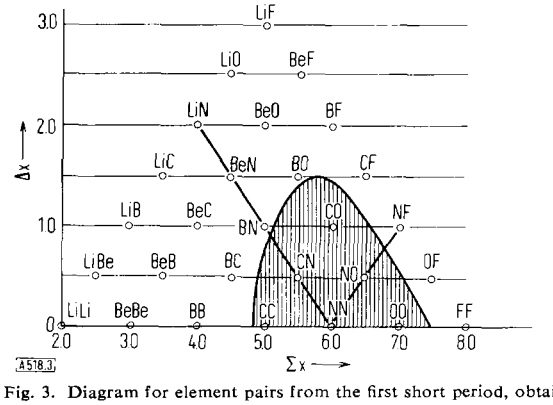



Fig. 3. Diagram for element pairs from the first short period, obtained by plotting the sum of the electronegativities (Σx) against the difference of electronegativities (Δx) of the bonding partners. The shaded area comprises bonds with b ≥ 2 in compounds stable at ordinary temperatures.

The shaded area contains the element-pairs that can form multiple bonds (b ≥ 2.0) in compounds stable at ordinary temperatures. The boundary to the top right is determined by the electron deficiency (condition 1), that to the top left by the difference, and to the left by the sum of the electronegativities (conditions 3 and 2, respectively).

Fig. 4 has been obtained in the same way for element pairs formed in the first and second short periods, the range being now set by Σx = 4.5 and 7.0 and by Δx = 0 and 2.0 comprising the more interesting combinations.

[*] The literature values of these electronegativities differ by 0.1 to 0.2 eV. We have taken the mean values, but the highest ones would bring V, W, and Mo nearer to the curve.

Most element pairs lying within the boundaries drawn for the first short period (shaded area) can similarly reach a bond order of 2, the exceptions being the chlorine bonds of P, S, and C [owing the polar bonding (halogen effect)] and the S–S bond. The latter, however, is clearly a limiting case, since S=S bonds do exist in $S_2$ molecules at 800 °C [54]. These anomalies indicate that, as expected, *Pauling*'s electronegativities represent only a rough approximation.

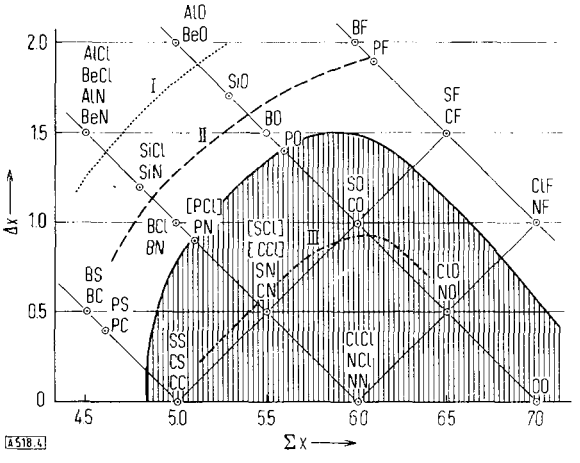



Fig. 4. Diagram for element pairs from the first and second short period, obtained by plotting Σx against Δx. The shaded area comprises bonds with b ≥ 2 in compounds stable at ordinary temperatures (curve I: b ≈ 1; curve II: b ≈ 1.5; curve III: b ≈ 3).

## G. Conclusions

Although it may seem like playing with numbers, the above treatment does lead to significant conclusions concerning the stability and the reactivity of multiple bonds. Thus, we can quote again the following examples (cf. Fig. 1):

| | |
|---|---|
| 3 :N≡N: ← $N_6$ | Σx = 6.0 |
| 3 HC≡N: ⇌ $H_3C_3N_3$ | Σx = 5.5 |
| 3 HB≡NH → $H_3B_3N_3H_3$ | Σx = 5.0 |

In the case of nitrogen with Σx = 6.0, the triple bond is so stable that no polymer is formed. In the case of HCN with Σx = 5.5, both monomeric and polymeric forms exist, while only the polymer is known for HBNH characterized by Σx = 5.0. In terms of the diagram in Fig. 4, the lower right element pairs form very stable multiple bonds with a small tendency to polymerize. The stability of the multiple bonds decreases, and the polymerizability increases, as one proceedes towards the top left, coming to bonds formed by carbon, phosphorus, and boron frequently encountered in polymer chemistry. The element pairs N–O, C–O, and B–O form similar rows, as do Cl–O, S–O, and P–O.

The N–O system affords a further example of the polymerizability increasing with decreasing Σx: having 10 valence electrons, $NO^{\oplus}$ shows no tendency to polymerize. Nitric oxide has 11 electrons, and its Σx value must be lower; accordingly, it dimerizes in the liquid

[54] *R. Maeder*, Helv. physica Acta *21*, 411 (1948).

state at a low temperature. The species $NO^{\ominus}$, having 12 electrons and being formed in the reaction of NO with alkali metals in liquid ammonia, exists only as a dimer [55]. This shows that the position of the element pairs in Fig. 4 is not fixed, but varies according to the type of bond and the other bonding partners. The polymerizability of C=S has recently been confirmed in the case of $F_2CS$ which polymerizes in the presence of fluorides [56].

Among the interesting bonds lying outside the shaded area in Fig. 4, whose boundary is not yet well defined in the low-$\Delta x$ region, we may mention the P–C and the P–S bonds, which have been studied with respect to their reactivities but which require further spectroscopic investigation.

## H. Appendix

### Calculation of Force Constants and Bond Orders (by Dr. W. Sawodny)

### I. Derivation of the Oscillation Equation [57–59]

The theoretical treatment of molecular vibrations starts with the assumption that the atoms can be considered as points of mass and the bonds between them as weightless springs, *i.e.* that we are faced with a mechanical system of coupled oscillators. It is further assumed that the very small motions of the mass points about their rest positions are harmonic vibrations and the potential curve can, therefore, be represented approximately by a parabola. The kinetic energy T and the potential energy V of the oscillating system are given by

$$2\,T = \sum_{ij} b_{ij}\dot{q}_i\dot{q}_j = \dot{\mathbf{q}}'\mathbf{B}\dot{\mathbf{q}} \quad (b_{ij} = b_{ji}) \tag{1a}$$

$$2\,V = \sum_{ij} f_{ij}q_iq_j = \mathbf{q}'\mathbf{F}\mathbf{q} \quad (f_{ij} = f_{ji}) \tag{1b}$$

where the $q_{i,j}$ are displacements of the mass points from their equilibrium positions. The potential energy coefficients $f_{ij}$ are described as force constants, and are a measure of the strength of the springs, *i.e.* of the forces acting between the atoms. For sufficiently small and slow vibrations, the coefficients $b_{ij}$ and $f_{ij}$ can be considered independent of $q_i$.

By substituting expressions (1a) and (1b) into the energy equation

$$T + V = \text{const.} \tag{2}$$

we obtain

$$^1/_2\,(\dot{\mathbf{q}}'\mathbf{B}\dot{\mathbf{q}} + \mathbf{q}'\mathbf{F}\mathbf{q}) = \text{const.} \tag{3}$$

Differentation with respect to time gives the equation of motion

$$\mathbf{B}\ddot{\mathbf{q}} + \mathbf{F}\mathbf{q} = 0, \tag{4}$$

a possible solution of which is

$$\mathbf{q} = \mathbf{a}\sin\omega t; \quad \ddot{\mathbf{q}} = -\omega^2\,\mathbf{a}\sin\omega t = -\omega^2\mathbf{q}. \tag{5}$$

Insertion of this result into Eq. (4) leads to a set of linear algebraic equations:

$$(\mathbf{F}-\lambda\mathbf{B})\mathbf{q} = 0; \quad \lambda = \omega^2, \tag{6}$$

which have non-vanishing solutions for $\mathbf{q}$ only at certain $\lambda$ values (eigenvalues). These eigenvalues are connected with the frequencies of the fundamental oscillations by the relationship $\lambda = 4\pi^2c^2\nu^2$, and they satisfy the secular equation:

$$\det(\mathbf{F}-\lambda\mathbf{B}) = 0. \tag{7a}$$

The substitution $\mathbf{G} = \mathbf{B}^{-1}$, carried out for convenience sake, leads to

$$\det(\mathbf{G}\mathbf{F}-\mathbf{E}\lambda) = 0 \tag{7b}$$

where $\mathbf{E}$ is the unit matrix.

Besides the eigenvalues $\lambda$ (fundamental vibrations) obtained from the vibrational spectra, the determinant contains the matrix $\mathbf{G}$, which is made up of the atomic masses, the bond angles, and the bond lengths of the molecule, and matrix $\mathbf{F}$, which is constructed of the desired force constants [*].

The derivation of the secular equation (7b) is independent of the choice of coordinates for the oscillator displacement, provided that they satisfy conditions (1a) and (1b). On the other hand, the coefficients $b_{ij}$ and $f_{ij}$ are determined by the coordinates used. Instead of Cartesian coordinates, linear transformations of these are generally used.

Most convenient are the internal valence coordinates, which embrace only the internal vibrations of the molecule without its translational and rotational motions (these have zero frequency). The movement of the atoms is thus described in terms of changes in either the bond angle or bond length. The force constants thus assume the following physical meaning: the diagonal elements of the $\mathbf{F}$ matrix represent the valence and the deformation constants, while the non-diagonal members denote the coupling constants between the valence and deformation modes. This is known as the General Valence Force Field (GVFF) model.

The mathematical effort rapidly increases as the order of the determinant (7b) increases, though it may be simplified by virtue of molecular symmetry. Within a symmetry class, the fundamental molecular vibrations are subdivided into various symmetry species. One can find linear combinations of the inner coordinates that correspond to the symmetry properties of the fundamental vibrations. These are called "symmetry coordinates". The overall secular determinant of the molecule can then be factorized into several smaller determinants whose orders are given by the number of fundamental vibrations of the corresponding symmetry species. These smaller determinants can then be solved separately.

Nevertheless, electronic computers generally must be employed in the treatment of the vibration problem, particularly for molecules of low symmetry or containing many atoms [60].

### II. Solution of the Secular Equation

Equation (7b) is termed the characteristic equation of the eigenvalue problem, and can be solved by various methods for the eigenvalues $\lambda$ [58]. This type of calculation presupposes a knowledge of the force constants and can be used to confirm the assignment of the fundamental vibrations for a given

[*] If there is only one fundamental vibration, the determinant reduces to one single equation $gf - \lambda = 0$ which, for a diatomic molecule, leads to $4\pi^2\nu^2 = f\left(\frac{1}{m_1} + \frac{1}{m_2}\right)$.


[55] *J. Goubeau* and *K. Laitenberger*, Z. anorg. allg. Chem. *320*, 78 (1963); *K. Laitenberger*, Dissertation, Technische Hochschule Stuttgart, 1964.

[56] *C. Walter*, US-Pat. 3032537 (1962).

[57] *R. Zurmühl*: Matrizen. Springer, Berlin-Göttingen-Heidelberg 1961.

[58] *E. B. Wilson Jr.*, *J. C. Decius*, and *P. C. Cross*: Molecular Vibrations. McGraw-Hill, New York 1955.

[59] *J. M. Mills* in *M. Davies*: Infrared Spectroscopy and Molecular Structure. Elsevier, London 1963.

[60] *D. E. Mann*, *T. Shimanouchi*, *J. H. Meal*, and *L. Fano*, J. chem. Physics *27*, 43 (1957); *J. Overend* and *J. R. Scherer*, *ibid. 32*, 1289 (1960); *T. Shimanouchi* and *I. Suzuki*, *ibid. 42*, 296 (1965); *J. Aldous* and *I. M. Mills*, Spectrochim. Acta *18*, 1073 (1962); *D. A. Long*, *R. B. Gravenor*, and *M. Woodger*, *ibid. 19*, 937 (1963); *E. W. Schmid*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 533 (1960); *D. Papousek* and *J. Pliva*, Collect. czechoslov. chem. Commun. *28*, 755 (1963).

molecule by using the constants of compounds having a similar structure[61]. However, the problem is generally the reverse: we know the vibrational assignment and seek the coefficients of the F-matrix. The derivation of Eq. (7b) in the manner specified above involves the basic difficulty of having to calculate for each symmetry species n(n+1)/2 GVFF-force constants from n eigenvalues (in the case of a symmetric F-matrix); as a result, the system of equation is insufficiently defined for $n > 1$.

We can now attempt to find further defining equations by the use of additional experimental data, or to reduce the number of required force constants to n by use of simplifying assumptions concerning the force field, or else to employ mathematical approximation methods.

## 1. Additional Experimental Data

To obtain additional information, fundamental vibrations of isotope-substituted molecules can be used. The force field is considered to be independent of the masses of the system, *i.e.* the isotope substitution does not change the F-matrix, but the fundamental vibrations are changed and a new G-matrix results. Thus, additional equations for the force constants are obtained. However, the mass of the isotope-substituted molecule must differ sufficiently from that of the reference molecule, since otherwise the additional equations roughly duplicate the original ones, and the indeterminacy of the F-matrix is retained[62]. Furthermore, as the frequency shifts decrease, their measurement involves an increasing error. Therefore, H–D substitution is the most convenient for the calculation of force constants, although owing to the small masses, the anharmonicity cannot be neglected introducing a further uncertainty. In addition, there are some isotope rules, such as the product rule of *Teller* and *Redlich*[63], which represent relationships independent of the force constants, and decrease the number of independent equations available for the determination of the F-matrix.

The vibration-rotation interaction constants can also be utilized in the determination of the force constants. Both the centrifugal stretching constants $D_J$, $D_{JK}$, and $D_K$[64] and the Coriolis coupling constants $\zeta_i$[65] depend on the F-matrix, Although their relationship is a more complicated one, these constants can still be used successfully.

The force constants are also related to the mean vibration amplitudes obtained from electron diffraction studies[66] as well as to the intensities of Raman and infrared bands[67], although all these measurements are not yet sufficiently accurate for the application of the data in the calculation of the force constants.

Unfortunately, these additional data are at present available only for simple molecules. It may also happen that even the use of such information leads to no unique solution of the GVFF constants, and resort must then be taken to the application of simplified potential fields.

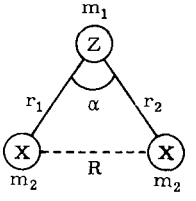
## 2. Simplified Potential Functions

To reduce the number of force constants, we can make certain assumptions concerning the magnitudes of some constants or the relationships between them. One possibility is to borrow some of the constants from other molecules. Particularly suited for this are constants obtained with the aid of the Urey-Bradley field[68]. However, this process becomes questionable when the changes in the bonds caused by the modified surroundings are to be investigated.

Simplification of the potential functions is best illustrated by means of an example: a symmetric non-linear three-body system $ZX_2$ of symmetry $C_{2v}$ executes three fundamental vibrations, two of the type $A_1$ and one of the type $B_1$. The potential energy is given, in accordance with Eq. (1), by

$$2V = f_r(\Delta r_1^2 + \Delta r_2^2) + 2f_{rr}\,\Delta r_1\,\Delta r_2 + f_\alpha\,\Delta\alpha^2 + 2f_{r\alpha}(\Delta r_1\alpha + \Delta r_2\alpha)$$

Therefore, the GVFF contains four constants to be determined.




The following two simplifying assumptions can be made. In one case, we assume that all interaction constants are negligibly small, so that they can be put equal to zero. The potential function then contains only two constants:

$$2V = f_r(\Delta r_1^2 + \Delta r_2^2) + f_\alpha\Delta\alpha^2$$

This model is known as the Simple Valence Force Field (SVFF). In the second case, we assume that the potential energy is a pure square function of all the internuclear distances, *i.e.* that the force acting on an atom is the sum of the attractive and the repulsive forces due to all the other atoms, these forces coinciding with the lines between the nuclei and depending on internuclear distances alone. This is the ionic model of the Simple Central Force Field (SCFF), in which the potential energy is given by:

$$2V = f_r(\Delta r_1^2 + \Delta r_2^2) + f_R\Delta R^2$$

Both the deformation constants and the coupling terms have thus been expressed in terms of the interaction between the two X atoms not bonded to each other. This postulate is inadequate in the case of linear and planar molecules, since it leads to a zero frequency for the out-of-plane vibrations. With certain molecular configurations, such as tetrahedral $ZX_4$ molecules, not only the squared, but also the linear potential energy terms must be taken into account. The rest position of the atoms is then described as a state of equilibrium between the attractive and repulsive forces.

Both the SVFF and SCFF system are characterized by a redundancy of parameters. Thus, in the given example, three fundamental vibrations are available for the determination of two force constants. The third equation can then be used to verify the results. The results reveal that both postulates involve oversimplifications[69]. It appears, therefore, that we cannot neglect all the coupling constants. The SVFF treatment gives the better result when the central atom is heavy in comparison to the ligands (weak coupling), whereas it is the SCFF treatment that leads to the better approximation when the central atom is light and the ligands are heavy (strong coupling).

The results can be improved by the introduction of additional interaction terms, so as to have the same number of force con-

[61] See, *e.g.*, *H.-J. Becher*, *W. Sawodny*, *H. Nöth*, and *W. Meister*, Z. anorg. allg. Chem. *314*, 226 (1962); *H.-J. Becher*, *ibid.* *271*, 243 (1953).

[62] See, *e.g.*, *J. L. Duncan*, J. molecular Spectroscopy *13*, 338 (1964); *L. Beckmann*, *L. Gutjahr*, and *R. Mecke*, Spectrochim. Acta *21*, 141 (1965).

[63] *O. Redlich*, Z. physik. Chem. B *28*, 371 (1935).

[64] *D. Kivelson* and *E. B. Wilson Jr.*, J. chem. Physics *21*, 1229 (1953).

[65] *J. H. Meal* and *S. R. Polo*, J. chem. Physics *24*, 1126 (1956).

[66] *S. J. Cyvin*, Acta chem. scand. *14*, 959 (1960).

[67] *B. L. Crawford*, J. chem. Physics *20*, 977 (1952); *G. W. Chantry* and *L. A. Woodward*, Trans. Faraday Soc. *56*, 1110 (1960).

[68] See, *e.g.*, *J. Overend* and *J. R. Scherer*, J. chem. Physics *32*, 1296, 1720 (1960); *33*, 446 (1960); *34*, 547 (1961).

[69] *G. Herzberg*: Molecular Spectra and Molecular Structure. Vol. II, Infrared and Raman Spectra of Polyatomic Molecules. Van Nostrand, Toronto 1951.

stants to be calculated as the number of the available fundamental vibrations. These modified models have been used in most force-constant determinations. The above mentioned equalization may be achieved by the introduction of the required number of GVFF coupling terms into the SVFF model (Modified Valence Force Field, MVFF). Although the choice of the interaction terms is arbitrary, we can often rely on analogy and past experience. In many cases all interactions between identical internal coordinates are used, since this advantageously leads to a diagonal F-matrix in the derivation of the oscillator equation with symmetry coordinates. The potential energy of the non-linear $ZX_2$ molecule is then given by:

$$2V = f_r(\Delta r_1^2 + \Delta r_2^2) + f_{rr}\,\Delta r_1\,\Delta r_2 + f_\alpha \Delta\alpha^2$$

A model which combines the SVFF and the SCFF concepts is the Urey-Bradley Force Field model (UBFF)[70]. It contains the valence force constants and the deformation constants of the SVFF model and describes all couplings in terms of forces acting between the non-bonded atoms:

$$2V = f_r(\Delta r_1^2 + \Delta r_2^2) + f_\alpha\,\Delta\alpha^2 + f_R \Delta R^2$$

This treatment generally affords valence force and deformation constants that are appreciably smaller than those obtained by the valence force fields, but gives relatively large van der Waals terms. As mentioned above, the force constants can often be transferred from one molecule to another similar one, but in some cases the UBFF model must be further modified to obtain meaningful results[71]. For easy comparison with force constants obtained by other methods, the UBFF model is frequently employed to calculate the potential energy with symmetry coordinates, but the resulting constants are transformed into those of the valence force field.

Attempts have also been made to derive simplified potential fields by considering the coupling from the point of view of bond theory. Thus, *Heath* and *Linnett*[73] have used the change in hybridization that occurs during the vibration, and developed the Orbital Valence Force Field (OVFF). When an atom is displaced from its equilibrium position by a change of the bond angle, the overlap of the orbitals decreases. In certain deformation vibrations, the orbitals of the central atom can follow this motion either by a partial rotation of the system or a rehybridization with change of the s and p contributions. We thus arrive at a new definition of the deformation constants. The OVFF model resembles the UBFF model in describing the coupling forces by the interactions between the non-bonded atoms. Rehybridization of the orbitals of the central atom can give rise to yet another definition of the coupling between valence and deformation modes: an increase in s-character shortens the bond, while an increase in the p-component lengthens it. These considerations have been incorporated in a model by *Mills*[73] called the Hybrid Orbital Force Field (HOFF) model. This treatment has led to good results in force constant calculations[74], but is at present applicable only when d orbitals do not participate in the bond. A similar, though more complicated, model has been developed by *King*[75] for the $NH_3$ molecule; it is known as the Hybrid Bond Force Field (HBFF) model.

We must also mention an attempt at using the interactions of a $\pi$-electron system to describe relations between some of the GVFF force constants. This is called the $\pi$-bond Interaction Valence Force Field ($\pi$-IVFF) concept, and its use has made it possible to reduce the number of constants to be determined in the case of $Ni(CO)_4$ from 17 to 10[76].

Table 9a. Force constants of tetrahedral molecules $ZX_4$ calculated with different potential fields.

| Compd. | Method | $f_r$ | $f_{rr}$ | $f_{r\alpha} - f_{r\alpha}$ | $F_{22}(E)$ | $F_{44}(F_2)$ |
|---|---|---|---|---|---|---|
| $CH_4$ | OVFF | 4.95 | — | — | 0.441 | 0.434 |
| | UBFF (V) | 4.944 | 0.051 | 0.036 | 0.436 | 0.436 |
| | MVFF | 5.37 | — | — | 0.420 | 0.420 |
| | *Fadini* | 5.391 | 0.151 | 0.008 | 0.486 | 0.460 |
| | GVFF (Rot. const., Isotop.) | 5.050 | 0.036 | 0.142 | 0.469 | 0.430 |
| $CF_4$ | OVFF | 4.35 | 0.6 (F) | — | 0.844 | |
| | UBFF | 3.75 (K) | 1.35 (F) | −0.3 (F') | 0.15 (H) | 0.5 (x) |
| | UBFF (V) | 6.15 | 1.00 | 0.50 | 0.62 | 1.331 |
| | MVFF (I) | 9.15 | — | 1.13 | 0.71 | 0.71 |
| | MVFF (II) | 6.72 | 0.81 | — | 0.71 | — |
| | *Fadini* | 6.876 | 0.788 | 0.567 | 0.710 | 1.014 |
| | GVFF (Isotop.) | 6.25 | 0.99 | 0.90 | 0.70 | 1.12 |
| | GVFF (Rot. const.) | 6.97 | 0.75 | 0.59 | 0.71 | 1.01 |
| $CCl_4$ | UBFF | 1.76 (K) | 0.656 (F) | −0.097 (F') | 0.08 (H) | 0.26 (x) |
| | UBFF (V) | 2.98 | 0.45 | 0.24 | 0.33 | 0.46 |
| | *Fadini* | 3.288 | 0.370 | 0.458 | 0.317 | 0.417 |
| | GVFF (El. diffract.) | 3.59 | 0.24 | 0.36 | 0.32 | 0.38 |
| | GVFF (Raman int.) | 3.157 | 0.415 | 0.406 | 0.34 | 0.420 |
| $SiH_4$ | MVFF | 2,77 | — | — | 0.207 | 0.207 |
| | UBFF (V) | 2.743 | 0.034 | 0.021 | 0.190 | 0.225 |
| | *Fadini* | 2.764 | 0.028 | 0 | 0,188 | 0.231 |
| | GVFF (Isotop.) | 2.769 | 0.027 | 0.016 | 0.188 | 0.231 |
| $SiF_4$ | OVFF | 5.9 | 0.15 (F) | | 0.56 | |
| | UBFF | 5.4 (K) | 0.43 (F) | −0.31 (F') | 0.02 (H) | 0.3 (x) |
| | UBFF (V) | 5.95 | 0.39 | 0.26 | 0.26 | 0.50 |
| | MVFF | 5.94 | 0.41 | — | 0.268 | 0.468 |
| | *Fadini* | 6.400 | 0.254 | 0.168 | 0.268 | 0.454 |
| | GVFF (Rot. const.) | 6.16 | 0.33 | 0.03 | 0.27 | 0.47 |
| | GVFF (Isotop.) | 6.57 | 0.21 | 0.19 | 0.26 | 0.44 |
| $SiCl_4$ | MVFF | 2.75 | 0.33 | — | 0.158 | 0.258 |
| | *Fadini* | 3.077 | 0.232 | 0.100 | 0.157 | 0.236 |
| | GVFF (Raman int.) | 3.124 | 0.213 | 0.110 | 0.082 | 0.235 |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## 3. Mathematical Approach

Mathematical approximation methods may be used to eliminate the indeterminacy of the secular equation (7b) caused by the fact that the number of force constants to be calculated exceeds the number of experimental data available. Thus, in one approach, the matrix product $\mathbf{A} = \mathbf{GF}$ is reduced to the Jacobian canonical form, *i.e.* the determinant $|\mathbf{A}|$ now consists only of the product of the diagonal elements. The eigenvalue $\lambda_k$ involving the fundamental vibration $\nu_k$ is considered as characteristic of the coordinate $q_k$, but corrected for the interaction with the rest of the molecule. The fundamental vibrations are first arranged in a series on the basis of their magnitudes, and the individual terms are then successively removed, so that the force constants $f_{ij}$ $(i > j)$ will depend only on eigenvalues between $\lambda_i$ and $\lambda_n$ [77].

A recent method [3] based on the Cayley-Hamilton theorem gives $n(n+1)/2$ equations for $n(n+1)/2$ force constants, but these equations are not mutually independent. However, this mutual dependence can be eliminated by systematic slight alterations of the equations and the use of an approximate solution. In practice, we start with fully uncoupled vibrations as a first approximation. For this case, a fully defined diagonal **F**-matrix from the diagonal **G**-matrix can be obtained. Using this **F**-matrix as a starting point, a complete **F**-matrix containing all the coupling terms can be calculated by the iterative and stepwise build-up of the known, complete **G**-matrix from the diagonal matrix.

Table 9b. Force constants of non-linear symmetric $ZX_2$ molecules calculated with different potential fields.

| Compd. | Method | $f_r$ | $f_{rr}$ | $f_{r\alpha}$ | $f_\alpha$ |
|---|---|---|---|---|---|
| $H_2O$ | MVFF | 8.250 (K) | 0.083 (F) | 0.407 (F') | 0.984(H) |
| | UBFF | 8.437 | −0.118 | — | 0.751 |
| | *Torkington* | 8.330 | −0.225 | 0.104 | 0.772 |
| | *Fadini* | 8.422 | −0.132 | 0 | 0.754 |
| | GVFF (Isotop.) | 8.454 | −0.100 | 0.234 | 0.761 |
| $ClO_2$ | UBFF | 7.150 (K) | −0.441 (F) | 0.014 (F') | 0.823 (H) |
| | MVFF (I) | 7.16 | — | 0.18 | 0.63 |
| | MVFF (II) | 6.78 | −0.22 | — | 0.635 |
| | *Torkington* | 7.144 | 0.724 | 0.328 | 0.778 |
| | *Fadini* | 6.815 | −0.164 | 0.022 | 0.618 |
| $SO_2$ | GVFF (Isotop. and Rot. const.) | 7.018 | −0.170 | 0.006 | 0.651 |
| | UBFF | 10.09 (K) | 0.21 (F) | 0.31 (F') | 0.993 (H) |
| | MVFF | 9.86 | −0.12 | — | 0.81 |
| | *Torkington* | 10.172 | 0.290 | 0.452 | 0.796 |
| | *Fadini* | 9.887 | −0.108 | 0.044 | 0.808 |
| | GVFF (Isotop.) | 10.02 | 0.03 | 0.20 | 0.793 |
| | GVFF (Rot. const.) | 10.006 | 0.024 | 0.189 | 0.793 |
| $O_3$ | MVFF | 4.64 | 0.703 | — | 1.696 |
| | *Torkington* | 6.338 | 2.160 | 0.964 | 1.131 |
| | *Fadini* | 5.624 | 1.440 | 0.297 | 1.308 |
| | GVFF (Rot. const.) | 5.701 | 1.523 | 0.332 | 1.285 |
| $NO_2$ | UBFF | 8.46 (K) | 3.03 (F) | — | 0.395 (H) |
| | MVFF | 10.022 | 1.652 | — | 1.036 |
| | *Torkington* | 10.818 | 2.210 | 0.851 | 0.870 |
| | *Fadini* | 10.111 | 1.741 | 0.068 | 1.021 |
| | GVFF (Isotop.) | 10.406 | 2.024 | 0.535 | 1.097 |
| $F_2O$ | MVFF | 3.08 | — | −0.14 | 1.13 |
| | *Torkington* | 5.320 | −0.252 | 0.680 | 0.788 |
| | *Fadini* | 3.964 | 0.862 | 0.163 | 0.715 |
| | GVFF (Rot. const.) | 3.950 | 0.806 | 0.137 | 0.724 |

The UBFF force constants have the following meaning:

K = stretching force constant

F = repulsive force constant between non bonded atoms

F' = repulsive force constant, linear term

H = bending force constant

$\varkappa$ = internal tension

UBFF(V) denotes constants of valence force field calculated from UBFF.


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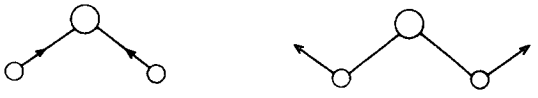
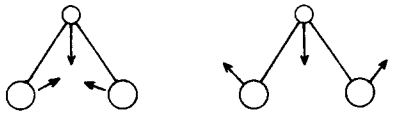
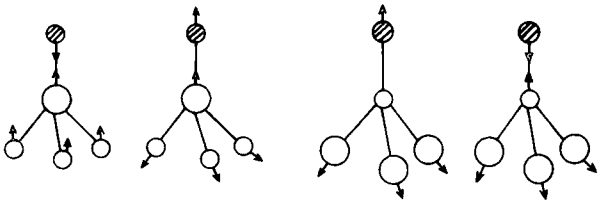
The results of calculations carried out for some simple molecules using various force fields are listed in Tables 9a and 9b, but their discussion must be preceded by brief mention of the concept of coupling. If, in the triangular $ZX_2$ molecule used earlier, the mass of the central atom $m_z$ is large in comparison to that of the ligands $m_x$, then the central atom will remain virtually static during the vibrations:



In this case, the vibrations are practically pure valence or deformation modes, owing to the lack of any coupling *via* the central atom. When, however, the mass relationship is the reverse (*i.e.* $m_z < m_x$), it is predominantly the central atom that oscillates; because of its similar motion in both vibrations, strong coupling between the two modes results.



Although the vibrations are no longer pure stretching and deformation vibrations, they still retain some of their original character, namely, the lower frequency is predominantly the deformation mode and the higher frequency, the valence vibration. On the other hand, in the case of strong coupling between two valence vibrations complete mixing can take place. When, for example, a tetrahedral molecule $YZX_3$ is characterized by the mass relationship of $m_z < m_x \approx m_y$, we can no longer describe the symmetrical valence vibrations as $\nu_{zy}$ and $\nu_{zx_3}$ sym., because these motions actually represent an in-phase and out-of-phase vibration $\nu_{yzx_3}$.



$\nu_{zy}$ $\nu_{zx_3}$ sym. $\nu_{yzx_3}$ sym. $\nu_{yzx_3}$ asym.

In addition to this coupling of masses, the coupling of vibrational energies also plays a part, as for example, in the $NO_2$ molecule. In this case, the relationship $m_z < m_x$ does hold, but the valence vibration of the N–O bond of bond order 1.5 and the deformation vibration differ in their energy so much that they can interact only to a small extent.

Weak coupling does not mean that the coupling constant will be very small. Calculations carried out on $H_2O$, $CH_4$, and $NO_2$ by the GVFF method have given by no means negligible values for the interaction constant $f_{r\alpha}$. However, the coupling constant can vary within wide limits without notable deviations in the valence and the deformation constants. As coupling increases, the system becomes more and more sensitive to changes in the interaction constants. It is, therefore, not surprising that the MVFF method gives poor results in the case of strong coupling. Quite often, no real solutions are obtained at all, as is the case with $F_2O$, $Cl_2O$, $CF_4$, and $CCl_4$; nor can the situation be remedied by neglecting $f_{rr}$, since its value cannot be neglected in most cases (*e.g.* $CF_4$).

By contrast, the UBFF method gives a better approximation for strongly coupled systems, but it leads to erroneous answers in the case of weak coupling. Whereas the constants obtained for $CF_4$ and $CCl_4$ are in good agreement (after transformation of the valence coordinates), the UBFF method

must be modified to result in reasonable values for $CH_4$. Similarly, additional interaction constants must be introduced in the calculations on silicon compounds and molecules with resonance structures (*e.g.* $NO_2$)[71]. The resulting modified model (MUBFF) gives good results, but generally contains more constants than the available number of vibration frequencies[77a].

The force constants obtained by the OVFF method are very similar to those of the UBFF method. The HOFF method on the other hand, represents a considerable improvement. In calculations on $YZX_3$ molecules[74], it was shown to be superior to the MVFF and the UBFF methods, although for tetrahedral $ZX_4$ molecules it again involves more constants than there are vibration frequencies available.

The mathematical method put forward by *Torkington*[77] generally leads to excessively high coupling constants. By contrast, the results obtained by the Cayley-Hamilton theorem[3] for intermediately coupled systems ($CF_4$, $SiF_4$, and $SiCl_4$) are in good agreement with those obtained by the GVFF method. For weak coupling, the resulting coupling constant is practically zero, but as mentioned earlier, this has only a small effect on the valence and deformation constants. The method is not applicable to strongly coupled valence vibrations, since a certain vibration character is a prerequisite for the validity of the first approximation (uncoupled vibrations).

Summing up, we may say that unambiguous answers concerning the coupling constants are available at the present only in very few cases, even with an exact knowledge of the vibrational frequencies and possible additional data as well as all the molecular dimensions (for the influence of the latter, see[78]). Thus, even the values obtained by the GVFF method, using various additional data, show considerable deviations, as for example in the case of $SiF_4$. As regards the valence and the deformation constants, on the other hand, the appropriate choice of the potential function ensures an accuracy of about 10%. Higher accuracy presumably is obtained by the application of a unified method.

Deformation force constants sometimes cannot been given in an explicit form, owing to the presence of "redundant coordinates" (*e.g.* in the case of $ZX_4$ tetrahedra, cf. Table 9a). For the time being, it is reasonable, therefore, to confine the discussion to valence force constants, which, incidentally, are also the most important parameters as regards the properties of bonds.

## III. Empirical Rules for Valence Force Constants

There have been attempts to correlate the valence force constants with other bond properties such as internuclear distance, dissociation energy, and the number of electrons in the bonding partners. The literature contains many such empirical correlations, though they are generally derived and verified only for diatomic molecules (Table 10).

The most important empirical rules are as follows:

*Badger*'s rule[79] correlates the force constant f with the internuclear distance r:

$$f(r-d_{ij})^3 = C_{ij}$$

where $d_{ij}$ and $C_{ij}$ are constants whose values are determined by the position of the bonding atoms in the periodic table.

A similar correlation is given by *Clark*'s formula[80]:

$$fr^6(z_A + z_B)^{1/2} = k_{ij} - k'$$

Table 10. Comparison of valence force constants calculated from empirical rules and from experimental data.

| Bond | Force constants according to: | | | | Group |
|---|---|---|---|---|---|
| | *Badger* | *Gordy* | *Siebert* | exp. | |
| CH | 4.33 | 4.45 | 5.40 | 5.05 | $(CH_4)$ |
| NH | 6.33 | 5.81 | 6.30 | 6.00 | $(NH_4^{\oplus})$ |
| OH | 7.62 | 6.94 | 7.20 | 8.45 | $(H_2O)$ |
| BC | 2.04 | 2.93 | 3.38 | 3.64 | $B(CH_3)_3$ |
| BN | 2.55 | 3.52 | 3.94 | ≈2.8 | $BX_3$—$NR_3$ |
| BO | 2.92 | 4.05 | 4.50 | 4.16 | $B(OH)_4^{\ominus}$ |
| BF | 3.14 | 4.49 | 5.06 | 4.87 | $BF_4^{\ominus}$ |
| CC | 2.93 | 3.76 | 4.05 | 4.45 | $CH_3$—$CH_3$ |
| CN | 3.77 | 4.54 | 4.73 | 4.49 | $N(CH_3)_4^{\oplus}$ |
| CO | 4.31 | 5.25 | 5.40 | 5.22 | $O(CH_3)_2$ |
| CF | 4.78 | 5.85 | 6.08 | 6.97 | $CF_4$ |
| CCl | 2.78 | 3.54 | 3.40 | 3.59 | $CCl_4$ |
| SiH | 2.68 | 2.29 | 3.74 | 2.77 | $SiH_4$ |
| PH | 3.44 | 2.74 | 4.00 | 3.16 | $PH_4^{\oplus}$ |
| SiF | 2.33 | 3.28 | 4.20 | 6.57 | $SiF_4$ |
| SiCl | 1.57 | 2.13 | 2.35 | 3.12 | $SiCl_4$ |
| PCl | 1.99 | 2.50 | 2.52 | 3.52 | $PCl_4^{\ominus}$ |
| AlCl | 1.18 | 1.82 | 2.18 | 1.97 | $AlCl_4$ |
| SiC | 1.53 | 2.20 | 2.80 | 2.93 | $Si(CH_3)_4$ |
| PC | 1.90 | 2.56 | 3.00 | 3.35 | $P(CH_3)_4^{\oplus}$ |
| GeH | 2.82 | 2.17 | 3.60 | 2.61 | $GeH_4$ |
| GeCl | 1.25 | 2.10 | 2.27 | 2.68 | $GeCl_4$ |

where $k_{ij}$ is a constant determined by the position of the bonding atoms in the periodic table, k′ is a correction factor for ions, and $z_A$ and $z_B$ denote the number of valence electrons of the two atoms.

Another relationship involving the number of valence electrons $z_i$ has been put forward by *Guggenheimer*[81] in the form:

$$f = R(z_A z_B)^{1/2}/r^t$$

where R and t are constants whose values depend on the polarity of the bond. *Gordy*'s relationship[82] involving the electronegativities

$$f = ab\left(\frac{x_A x_B}{r^2}\right)^{3/4} + c$$

is a special case of *Guggenheimer*'s formula[83]. The constants a and c here generally have the values of 1.67 and 0.30 (other values have to be assumed when one of atoms involved has only one valence electron); b denotes the bond order.

*Siebert*[5] has devised the particularly simple formula:

$$f_1 = P\,\frac{Z_A Z_B}{n_A^3 n_B^3}$$

where the constant P invariably has the value of 7.20, $Z_i$ is the nuclear charge and $n_i$ is the principal quantum number of the valence electrons of atom i. This formula enables us to calculate the single bond values $f_1$ without knowing any experimental data such as bond lengths. However, this formula is strictly valid only for bonds of $sp^3$ hybridization. It can be shown that the formation of free electron pairs at the bonding partners (*i.e.* the setting-up of overlapping p-orbitals) weakens the bond. This can be taken into account by the introduction of an empirical correction factor in *Siebert*'s formula[1]. Furthermore, the single bond value of the force constants increases with increasing s-character of the bond[84].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[83] *R. L. Williams*, J. physic. Chem. *60*, 1016 (1956).

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[85] *L. Salem*, J. chem. Physics *38*, 1227 (1963); *L. Salem*, J. chem. Physics *38*, 1227 (1963); *P. Phillipson*, ibid. *39*, 3010 (1963); *44*, 633, (1966).

[86] *S. Bratoz* u. *M. Allavena*, J. chem. Physics *37*, 2138 (1962); J. Chim. physique *60*, 1199 (1963).

*Siebert* also gives a formula for the determination of the bond order b from the single-bond value $f_1$:

$$b = r_b f_b / r_1 f_1$$

Moreover, we can use an even simpler relationship

$$b = f_b / f_1$$

up to b = 1.5 whenever the distances $r_1$ and $r_b$ are not known. However, for bond orders over 1.5, we must use the formula

$$b = 0.29 + 0.71\, f_b / f_1$$

containing empirical correction factors; $f_b$ always is the experimental force constant.

Finally, it should be mentioned, that also attempts where made to find relations between quantum mechanical data, as the electron density, and force constants [85]. For small molecules ($H_2O$, $NH_3$) force constants have been calculated from energy values obtained from an approximative wave function [86].


## Acknowledgments

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# COMMUNICATIONS

## Amination of Hydrazines to Yield Triazanes


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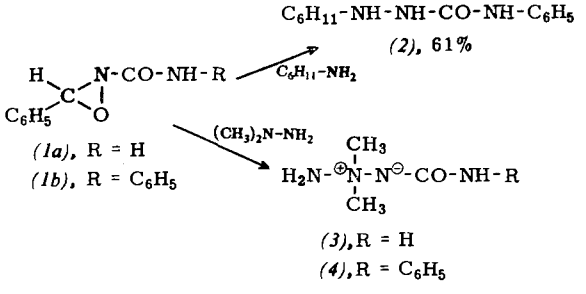
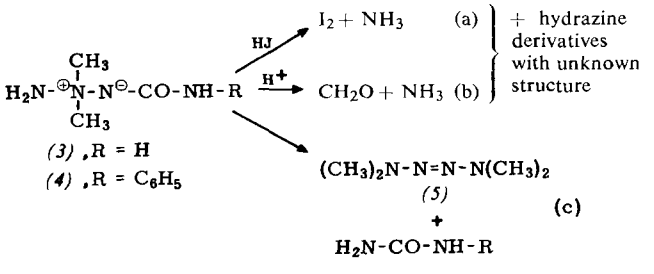
Experiments with $^{15}N$ have shown that hydrazine can be aminated by hydroxylamine-*O*-sulfonic acid, the reaction proceeding by way of triazane [1].

We have found 2-acyloxaziridines [2] to be extremely effective aminating agents. The compound *(1b)* aminates cyclohexylamine at room temperature within one minute, giving the hydrazine derivative *(2)* (m.p. and mixed m.p. [3] 141 °C). This reaction led to attempts to aminate hydrazines to triazanes.



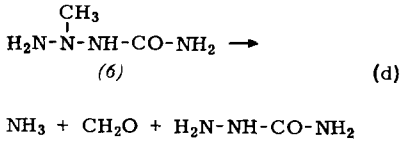

2-Acyloxaziridines, *(1a)* and *(1b)*, suspended in benzene, dissolved immediately on addition of *N,N*-dimethylhydrazine, and crystalline compounds separated in 70–80 % yield in 1–2 minutes at 5–10 °C.

Elemental analyses showed that products containing four N-atoms were formed with loss of benzaldehyde. These products liberated iodine from acidic iodide solution in the cold [reaction (a)]. As with peroxides, oxaziridines, and diaziridines, acid initiates an intramolecular redox reaction,

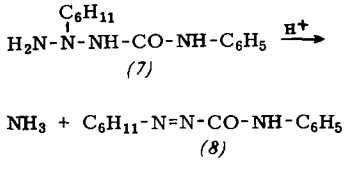



in which fission of the N-N bond is coupled with dealkylation. Dilute acid liberates ammonia (0.7 mol) and formaldehyde (0.5 mol) from compound *(3)* within a second [reaction (b)], and because of this competing reaction the yield of the iodide reaction amounts to only 70–75 %. Neutral aqueous solutions of compounds *(3)* and *(4)* decompose five minutes at room temperature with formation of tetramethyltetrazene *(5)* and urea or phenylurea, respectively [reaction (c)]. Compound *(5)* was identified by gas chromatography, phenylurea by melting point and mixed melting point, and urea by means of xanthydrol. The same products are formed when the crystalline compounds *(3)* and *(4)* are kept at room temperature for one hour. During a melting-point determination, compound *(4)* reacts at 80–85 °C and then shows the melting point of phenylurea.

Compounds *(3)* and *(4)* are formulated as triazanium betaines, in analogy to the 2,2-dialkyltriazanium salts obtained by *R. Gösl* [4] from *N,N*-dialkylhydrazines and hydroxylamine-*O*-sulfonic acid. Final proof of structure was provided for the triazanes prepared analogously from monoalkylhydrazines. A crystalline compound *(6)* (m.p. 63–65 °C) separates in 30 % yield from a solution of *(1a)* and methylhydrazine in tetrahydrofuran; *(6)*, too, oxidizes iodide to iodine. Its thermal or acid-catalysed decomposition leads to ammonia, formaldehyde, and semicarbazide [reaction (d)]; the semicarbazide contains the N–N bond obtained on formation of the triazane.




On reaction with cyclohexylhydrazine, compound *(1b)* affords the triazane *(7)* (yield 70 %). The position of the alkyl group, not rigidly proved for *(6)*, was made certain for this product *(7)*: the colorless crystals *(7)*, when brought into contact with acid, pass within seconds into yellow crystals (m.p. 89 °C), the azo compound *(8)* being formed with loss of ammonia. In *(8)* the cyclohexyl group has the position required by the triazane structure *(7)*.



The structure of product *(8)* follows from its cleavage by acid to cyclohexanone (2,4-dinitrophenylhydrazone, m.p. 162 °C) and 4-phenylsemicarbazide (benzylidene derivative, m.p. and mixed m.p. 180 °C).

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German version: Angew. Chem. *78*, 587 (1966)

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[2] *E. Schmitz, R. Ohme,* and *S. Schramm,* Tetrahedron Letters *1965*, 1857.

[3] *E. Schmitz* and *D. Habisch,* Rev. Chim. (Bucarest) *7*, 1281 (1962).

[4] *R. Gösl,* Angew. Chem. *74*, 470 (1962); Angew. Chem. internat. Edit. *1*, 268 (1962).

## Formation of Tetramethyl Furantetracarboxylate from Dimethyl Acetylenedicarboxylate

By Priv.-Doz. Dr. E. Winterfeldt and cand. chem. G. Giesler

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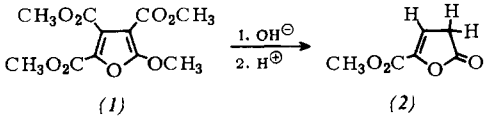
In addition reactions of dimethyl acetylenedicarboxylate we isolated varying yields of the triester *(1)*. We have now found that this ester is also formed when dimethyl acetylenedicarboxylate is heated alone at 180 °C, and that the yield is increased to 25 % if the sealed tube is filled with oxygen and the reaction catalysed with copper powder. Support is thus withdrawn from the rather complicated mechanism proposed by *Huebner et al.*[1] when he isolated *(1)* in diene syntheses with acetylenedicarboxylic esters.

The structure of *(1)* was supported by, *inter alia*, formation of *(2)* on hydrolysis and by the spectral data.

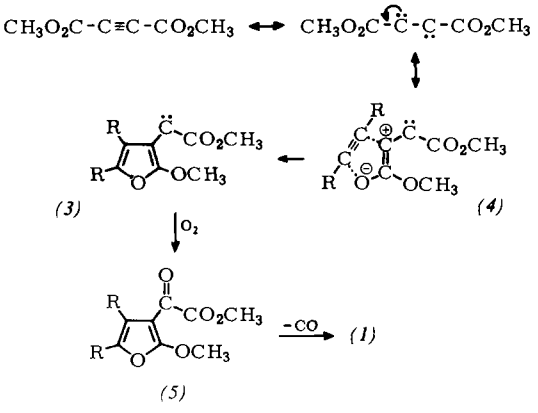



*(1)* *(2)*

*(1)*: M.p. 121 °C
IR: 1750, 1620, 1590, 1160, 1110, 1070 $cm^{-1}$
UV: 273 mμ (ε = 15400), shoulder at 248 mμ (ε = 10900) in ether
NMR: 5.72 τ (3 H), 6.02 (3 H), 6.12 (3 H), 6.17 (3 H).

*(2)*: M.p. 71 °C
IR: 1850, 1830, 1740, 1640 $cm^{-1}$
UV: 232 mμ (ε = 9850)
NMR: 6.22 τ (3 H); 6.60 (2 H), J = 2.5; 2.43 (1 H), J = 2.5

The formation of *(1)* can be understood if it is assumed that acetylenedicarboxylic ester reacts in the 1,3-dipolar form *(4)*.




The trapping reaction leading to the carbene *(3)* has parallels in the investigations of diazo derivatives by *R. Huisgen et al.*[2] The α-keto ester *(5)* can then pass into the triester *(1)* by decarbonylation. The following findings support this assumption: exclusion of oxygen reduces the yield of ester *(1)* to 0.01 %; the carbon monoxide liberated can be identified; the radical *(4)* can be trapped by other acetylenic compounds; and the carbene *(3)* can be trapped by sulfur. The correct order of the two steps is still open to question. The stability of tetramethyl furantetracarboxylate under the reaction conditions has been ascertained.

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[1] *C. F. Huebner, E. Donoghue, L. Dorfman, F. A. Stuber, N. Danieli,* and *E. Wenkert,* Tetrahedron Letters *1966*, 1185.

[2] *R. Huisgen et al.*, Chem. Ber. *97*, 2864 *et seq.* (1964).

## A Simple Method for Selective Acylation of Cytidine on the 4-Amino Group [1]

By Dr. K. A. Watanabe and Prof. Dr. J. J. Fox

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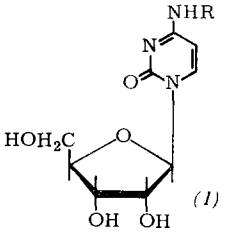
To our knowledge, the only reported procedure[2] for the preparation of *N*(4)-acetylcytidine *(1a)* is the reaction of cytidine with 1-acetoxy-2(1*H*)-quinolones (65 % yield).




*(1)*

*(a)*: R = $CO-CH_3$,
*(b)*: R = $CO-C_6H_5$,
*(c)*: R = $CO-(CH_2)_2-CH_3$

A simple and direct synthesis, giving an almost quantitative yield of the selectively blocked nucleosides *(1)*, consists in treatment of cytidine with aliphatic or aromatic acid anhydrides in boiling methanol.

The structures of products were secured as follows: All gave ultraviolet spectra (details for pH 6.4 in the table) similar to those of poly-*O*-acetylated *N*(4)-acetylcytidine[3] and *N*(4)-acetyl-1-methylcytosine[4]. Elemental analyses agree with monoacetylated products. The compounds have sharp melting points and give only one spot on thin-layer chromatography in two solvent systems[5]. Their infrared spectra (KBr pellets) show no absorption bands in the region 1650 to 1800 $cm^{-1}$ that could be attributed to an ester-carbonyl group.

| | M.p.[°C] [a] | $\lambda_{max}$ [mμ] | $\varepsilon_{max}$ | $\lambda_{min}$ [mμ] | $\varepsilon_{min}$ |
|---|---|---|---|---|---|
| *(1a)* | 208–209 | 294 [b]<br>245<br>212 | (8600)<br>(15100)<br>(18200) | 268 [b]<br>225 | (4400)<br>(6100) |
| *(1c)* | 182–183 | 295<br>245<br>210 | (8500)<br>(17000)<br>(19300) | 278<br>225 | (7500)<br>(7600) |
| *(1b)* | 238–239 | 302<br>257 | (9900)<br>(18000) | 284<br>228 | (7900)<br>(8300) |

[a] Determined on a Thomas-Hoover melting-point apparatus; corrected.

[b] *Mizuno* [2] gives for neutral aqueous solution: $\lambda_{max}$ = 296, 247 mμ; $\lambda_{min}$ = 270, 227 mμ.

*Experimental*:

1 part of cytidine was heated with 1 part of acid anhydride for 5 hrs. under reflux in 100 parts of methanol. Further anhydride was added after 1, 2, and 3 hrs. (1 part each time). Compound *(1)* crystallized from the reaction mixture on cooling. After filtration, the crystals were washed with cold alcohol and then with ether; they were analytically pure (yields: 50 to 70 %). The mother-liquor was concentrated almost to dryness in a vacuum and the residue was rubbed with ether until a crystalline product was formed. The total yields were almost quantitative.

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[1] This investigation was supported by the US Public Health Service, National Cancer Institute Grant CA 08748.

[2] *Y. Mizuno, T. Itoh*, and *H. Tagawa*, Chem. and Ind. *1965*, 1498.

[3] *J. J. Fox, Y. Kuwada, K. A. Watanabe, T. Ueda*, and *E. B. Whipple*: Antimicrobial Agents Chemotherapy. American Society for Microbiology, Ann Arbor, Mich. 1964, p. 518.

[4] *G. W. Kenner, C. B. Reese*, and *A. R. Todd*, J. chem. Soc. (London) *1955*, 855.

[5] On silica gel $HF_{254}$ (Brinkman Instruments, Westbury, N.Y.) in two systems: 1-butanol/acetic acid/water (5:2:3) and 2,6-lutidine/ethanol/water/diethylamine (55:25:20:2). In these systems the products *(1)* migrate faster than cytidine. No cytidine spot is obtained from the reaction solution at the end of the stated time.

[6] *L. J. Bellamy*: The Infrared Spectra of Complex Molecules. Methuen and Co., Ltd., London 1958, p. 178.

## Oxidation of Organoboranes with Amine Oxides

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All B–C groups of organoboranes are smoothly converted into B–O–C groups by anhydrous *N*-oxides of tertiary amines (*e.g.* trimethylamine oxide, pyridine 1-oxide). Trialkyl- and triarylboranes afford the corresponding boric esters quantitatively.

$$BR_3 + 3 \text{ Amine oxide} \rightarrow B(OR)_3 + 3 \text{ Amine}$$

Aliphatic trisorganoboranes with $B-C_{primary}$ and $B-C_{secondary}$ groups (*e.g.* tricycloalkylboranes) are as readily oxidized as alkenyl (*e.g.* vinyl- or allylborane) and cycloalkenylboranes, but alkynyl groups on boron do not react. Dehydroboration, as in the reaction of trialkylboranes with triphenylphosphine oxide[1], does not occur.

Preparation of boric esters from organoboranes with trimethylamine oxide is superior to previously reported methods (*e.g.* those involving hydrogen peroxide, oxygen, or perbenzoic acid), because it is not complicated by protolysis (*e.g.* fission of $B-C_{aryl}$ or $B-C_{C=C}$ bonds) or homolysis of O–O bonds (*e.g.* on oxidation of arylboranes). The trimethylamine arising from trimethylamine oxide on oxidation of trialkyl- or triarylboranes is evolved and its acidimetric determination permits quantitative determination of the B–C bonds in organoboranes[2].

The B–C bonds of trialkylboranes react stepwise and exothermically with trimethylamine oxide, even at room temperature, so that partial oxidation leads to high yields of boric esters of the composition $R_2BOR$ and $RB(OR)_2$. Quantitative conversion of all the B–C bonds of trisorganoboranes is very rapid between 20 and 90 °C. If no solvent is used, it is advisable to add the *N*-oxide portionwise to the trialkylborane. The reactions are particularly smooth in solution (alcohols, chloroform) and when suspensions of trimethylamine oxide are used (*e.g.* in boiling benzene or toluene). Transesterification, *e.g.* with methanol, leads from the borates to the alcohols or phenols with nearly quantitative yields.

The B–C groups of saturated and unsaturated aliphatic as well as of aromatic boron heterocycles are also completely oxidized by *N*-oxides. Some particularly stable organoboranes (*e.g.* those with the $C_4B_2$ skeleton[3]) and organocarboranes[4] do not react in boiling toluene.

BH-containing organoboranes, *e.g.* tetraethyldiborane, react with amine oxides preferentially at the B–H linkages, in contradiction to the results of a spectroscopic study[5] of "borane-pyridine 1-oxide". Most of the BOH groups resulting from oxidation at room temperature react further with unchanged BH groups, with loss of hydrogen:

Relatively small amounts of hydrocarbons are also formed from BOH compounds containing $B-C_{aryl}$ and $B-C_{alkyl}$ linkages.

Further, all the B–C bonds of dialkylchloroboranes and dialkylfluoroboranes are oxidized by trimethylamine oxide. Not only each B–C bond of dialkyl(dialkylamino)boranes and similar compounds, but also each of their B–N bonds yields quantitatively 1 mole of trimethylamine. For example, piperidinodipropylborane consumes 3 moles of the *N*-oxide. BH groups of bis(dialkylamino)boranes and of some borazines also consume 1 mole of *N*-oxide. The B–N groups of some borazines (*e.g.* *N*,*N'*,*N''*-triphenylborazine, are however, not attacked in boiling toluene, though the B–N–B groups of acyclic compounds are completely oxidized. The latter is true also for the B–N bonds and the B–B groups of aminoboranes: tetrakis(dimethylamino)diboron with trimethylamine oxide affords 5 moles of trimethylamine.

*Oxidation of triphenylborane*:

A solution of 10.3 g (42 mmole) of triphenylborane in 150 ml of toluene is dropped into a boiling suspension of 9.6 g (128 mmole) of trimethylamine oxide in 50 ml of toluene. The liberated trimethylamine is led in a stream of inert gas into 1 N sulfuric acid and determined by titration. At the end of the reaction the mixture is filtered from small amounts of unchanged *N*-oxide and on distillation of the toluene affords 12 g (97 %) of triphenyl borate (m.p. 95 °C). 10 g of pure phenol (nearly quantitative yield) are obtained as residue after addition of 10 ml of anhydrous methanol, short heating, and distillation of the trimethyl borate.

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[1] *R. Köster* and *Y. Morita*, Angew. Chem. *77*, 589 (1965); Angew. Chem. internat. Edit. *4*, 593 (1965).

[2] *R. Köster* and *Y. Morita*, unpublished work.

[3] *P. Binger*, Tetrahedron Letters *1966*, in press.

[4] *R. Köster* and *G. W. Rotermund*, Tetrahedron Letters *1964*, 1667; *1965*, 777.

[5] *N. Kulevsky* and *L. Sveum*, J. inorg. nuclear Chem. *27*, 2111 (1965); Chem. Abstr. *63*, 16153e (1965).

## Preparation of Methyl- and Ethyl-Substituted Monocarbahexaboranes(9) and Dicarbaclovoheptaboranes(7)

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Organoboranes can be obtained on a preparative scale by dehalogenation of alkylhalogenoboranes with alkali metals[1]. If the dehalogenation is carried out in tetrahydrofuran with compounds containing more than one halogen atom on a boron atom, then organofluoroboranes are appreciably

better reactants than are the chlorinated compounds[1]. In this way ethyldifluoroborane and lithium in tetrahydrofuran at *ca.* 0 °C afford two types of carboranes, each containing five boron atoms per molecule and carrying alkyl groups on carbon as well as on boron. The total yield amounts to 7 to 8 g per 78 g of $C_2H_5BF_2$. About 25 % of the *B*-ethyl groups of the ethyldifluoroborane used are contained in the organocarboranes. More than 50 % of the *B*-ethyl groups can be recovered as triethylborane; the remaining 20–25 % are found in compounds with B–O bonds (cleavage of tetrahydrofuran) or in non-distillable high-molecular fractions of the product mixture.

*Preparation:*

A solution of 62.4 g (0.8 mole) of ethyldifluoroborane in 150 ml of THF is dropped at 0 to 5 °C into a well-stirred suspension of 11.2 g (1.6 g-atom) of finely divided lithium in 300 ml of THF. The metal is completely consumed in *ca.* 9 h. The LiF (42.6 g, containing 1.9 % of boron) is centrifuged off and washed with hexane. The THF solution is concentrated by distillation of 340 g (containing about 14 g of triethylborane) at 12 mm; the residual 70 ml, together with the hexane wash-liquor, is treated with ethylene at *ca.* 50 atm. for about 1 h at room temperature. Subsequent distillation afforded, first, 54 g of a fraction of b.p. 68–72 °C containing *ca.* 5 % of triethylborane, and then 18.7 g of a fraction of b.p. 41–91 °C/20 mm, which contained mainly compounds with BO bonds (ethylboroxine, cyclic boric esters[2]) and only small amounts of organocarboranes (molecular weights 174, 198). Further distillation gave 10.5 g of a colorless liquid (b.p. 65–106 °C/$10^{-2}$ mm), of which 60–70 % consisted of the alkylated $B_5$-carboranes detailed in the table.

Table 1. Carboranes obtained from $C_2H_5BF_2$ + Li in THF.

| Compound | Mol. wt. [a] | B.p. [°C/mm] | Yield [g] | Yield [%] calc. on $bC_2H_5$ consumed [b] |
|---|---|---|---|---|
| $C_{10}H_{23}B_5$ | 198 | — | little | 1 |
| $C_{12}H_{27}B_5$ | 226 | — | 1.23 | 8.2 |
| $C_{14}H_{31}B_5$ | 254 | 82/$10^{-3}$ | 2.48 | 17.0 |
| $C_{10}H_{27}B_5$ | 202 | — | 0.52 | 3.2 |
| $C_{12}H_{31}B_5$ | 230 | 84/$10^{-3}$ | 2.68 | 17.5 |

[a] Determined by mass spectrometry [3].
[b] b = $^1/_3$ B

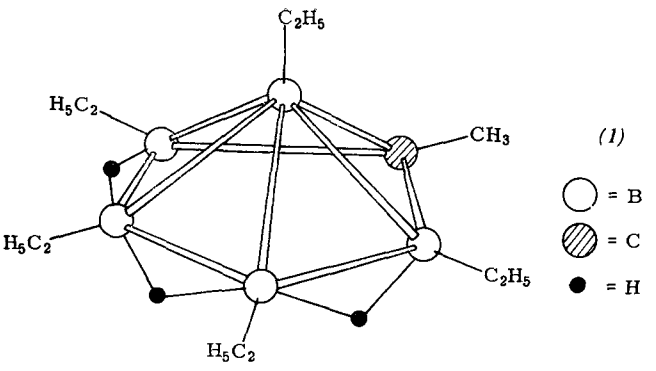
The individual carboranes could be enriched by fractional distillation and isolated in pure form by gas chromatography[4]. The non-distillable residue (17.2 g) also contained boron compounds (12.15 % B).

The compound of molecular weight 254 is considered from its spectroscopic properties ($^1$H- and $^{11}$B-NMR spectrum[5], infrared spectrum, and mass spectrum[3]) to be 1,3,5,6,7-pentaethyl-2,4-dimethyl-2,4-dicarbaclovoheptaborane(7) with the structure of a pentagonal bipyramid[6]. The carborane nuclei of the compounds with molecular weights 226 (three isomers) and 198 have the same structure.

The $^1$H- and $^{11}$B-NMR spectra[5] indicate that the compound with molecular weight 230 is an alkyl derivative of the unknown monocarbahexaborane(9), $CB_5H_9$. Structure *(1)*, a pentagonal pyramid with a boron atom at the apex, follows from consideration of the infrared spectrum and in analogy with hexaborane(10)[7] and dicarbahexaborane(8)[8].

Compound *(1)* is identical with the compound of molecular weight 230 obtained on hydroboration of acetylene with ethyldiboranes[9], the latter having been originally designated a derivative of a $C_2B_5H_{11}$ carborane because of its mode of formation.

The pure compound *(1)* is only slowly oxidized by 30 % $H_2O_2$ in acid solution at room temperature or by atmospheric oxygen. When heated to 200 °C it rearranges, with loss of $H_2$, $CH_4$, $C_2H_6$, and a small amount of triethylborane and




*(1)*

unidentified boron compounds of low molecular weight, into other carboranes among which 2,3,4-triethyl-1,5-dimethyl-1,5-dicarbaclovopentaborane(5)[10] and three isomeric *B*-tetraethyl-*C*-dimethyldicarbaclovoheptaboranes(7) (mass spectrometric molecular weights 226[3]) could be identified.

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[2] *G. Benedikt*, unpublished experiments.

[3] *D. Henneberg*, measurements with a high-resolution mass spectrometer, model CEC 21–110.

[4] *G. Schomburg*, gas-chromatographic separations.

[5] *E. G. Hoffmann*, $^1$H- and $^{11}$B-NMR measurements.

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[9] *R. Köster* and *G. W. Rotermund*, Tetrahedron Letters *1965*, 777.

[10] *R. Köster* and *G. W. Rotermund*, Tetrahedron Letters *1964*, 1667.

## Stabilized Dialkylnickel Compounds

By Prof. Dr. G. Wilke and Dr. G. Herrmann[1]

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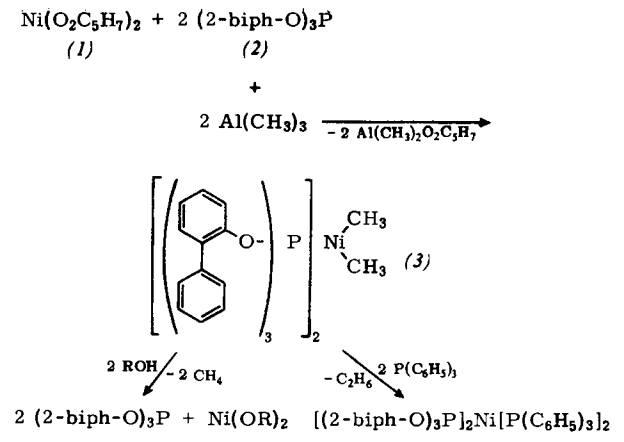
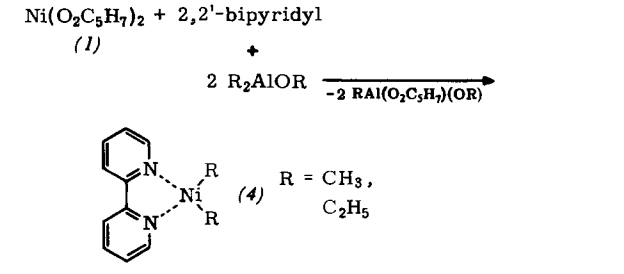
The method[2] for preparation of transition metal complexes which depends on the reaction of transition-metal salts with organometallic compounds (*e.g.* organoaluminum) in the presence of electron donors fails if the usually unstable intermediate alkylmetal is stabilized by electron donors. Such a stabilization has hitherto been observed only with arylmetals such as bis(triethylphosphine)diphenylnickel[3]. Alkylnickel compounds, however, cannot be stabilized by triphenylphosphine; they decompose, and $Ni[P(C_6H_5)_3]_4$[4] is formed. If acetylacetonatonickel*(1)*is treated with trimethylaluminum in the presence of tri-(2-biphenylyl) phosphite *(2)* (molar ratio 1:2:2) in toluene at −45 °C and the mixture is warmed for 8–12 h to 20 °C, subsequent addition of ether precipitates a colorless product that, when redissolved in benzene, reprecipitated with ether, and dried, has the composition of a dimethylbis[tri-(2-biphenylyl phosphito)]nickel : $C_{74}H_{60}O_6P_2Ni$ (yield at least 30 %). The product is stable at 20 °C. Alcoholysis yields the calculated amount of methane. Heating the material with an excess of triphenylphosphine affords 1 mole of ethane per g-atom of nickel.

2,2′-Bipyridyl can also stabilize the Ni–C bond. However, trialkylaluminum compounds are less suitable for the preparation of dialkyl-(2,2′-bipyridyl)nickel compounds because they form adducts with 2,2′-bipyridyl, rendering it unavailable



for complex formation with nickel. The result is that elemental nickel is readily deposited. If alkoxy(dialkyl)aluminum[2] compounds, which do not form stable adducts with 2,2′-bipyridyl, are used for transfer of the alkyl groups dialkyl-(2,2′-bipyridyl)nickel *(4)* compounds are obtained in good yields (70–80 %).



The green compounds *(4)* are crystalline and can be recrystallized from boiling benzene; the solubility rises with increasing length of R[5]. The alkyl groups are quantitatively split off as RH by 5 N HCl or primary alcohols. (2,2′-Bipyridyl)diethylnickel reacts with phenol with liberation of only one ethyl group, and (2,2′-bipyridyl)Ni($OC_6H_5$)($C_2H_5$) is obtained in the form of deep violet crystals. On addition of trialkylaluminum compounds the complexes *(4)* are decomposed with separation of elemental nickel.

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[1] *G. Herrmann*, Dissertation, Technische Hochschule Aachen, 1963.

[2] *G. Wilke*, Angew. Chem. *72*, 581 (1960); German Pat. 1 191 375, Studiengesellschaft Kohle.

[3] *J. Chatt* and *B. L. Show*, J. chem. Soc. (London) *1960*, 1718.

[4] *G. Wilke*, *E. W. Müller*, and *M. Kröner*, Angew. Chem. *73*, 33 (1961).

[5] (2,2′-Bipyridyl)Ni($C_2H_5$)$_2$ was recently described by *A. Yamamoto* [*], *K. Morifuji*, *S. Ikeda*, *T. Saito*, *Y. Uchida*, and *A. Misono*, J. Amer. chem. Soc. *87*, 4652 (1965).

[*] Fellow of the Alexander-von-Humboldt-Stiftung at the Max-Planck-Institut für Kohlenforschung, 1962/63.

## π-Allylmethylnickel

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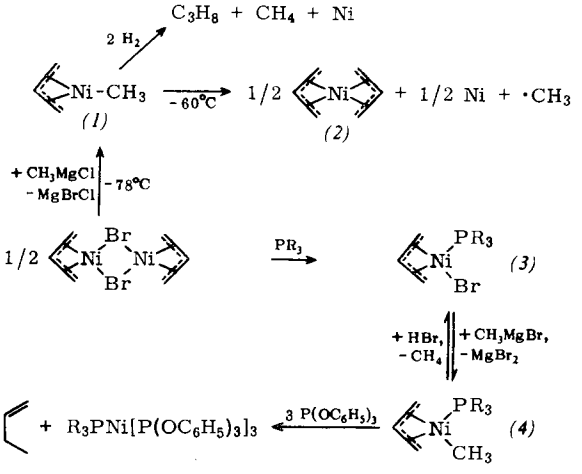
In a study of π-allylcompounds of transition metals[3] the stabilizing effect of a π-allyl group on a M–C bond linked to the same central atom appeared of interest.

π-Allylnickel bromide reacts with methylmagnesium chloride (molar ratio 1:1) in ether at −78 °C. The resulting deep violet solution is freed from MgBrCl by filtration at −78 °C. If the solvent is distilled off at −78 °C and $10^{-4}$ mm, violet crystals of composition $C_4H_8Ni$ are obtained (96 % yield). π-Allylmethylnickel *(1)* decomposes at −40 to −35 °C, even in an inert atmosphere, yielding a mixture of butenes, propene, ethane, and methane, together with elemental nickel. Compound *(1)* is somewhat volatile even at −78 °C, indicating that it is monomer; the molecular weight could not be determined mass-spectrometrically, owing to decomposition.

The following reactions, which also prove the constitution, characterize the π-allylmethylnickel *(1)*:



Hydrogenation of *(1)* at −40 °C yields, in addition to metallic nickel, methane and propane with small amounts of ethane and butane. Compound *(1)* disproportionates in solution at −60 to −50 °C quantitatively within a few hours, yielding bis-(π-allyl)nickel *(2)* and dimethylnickel, the latter at once decomposing into metallic nickel and methyl radicals. The coordinatively unsaturated compound *(1)* reacts with phosphines and phosphites, giving well defined, crystalline 1:1 adducts *(4)*. Adducts with R = ethyl, cyclohexyl, phenyl, phenoxy, and *o*-phenylphenoxy were isolated and, except for the $(C_6H_5O)_3P$ adduct, were stable at room temperature. The same compounds are obtained by treating the 1:1 adducts *(3)* of phosphines or phosphites and π-allylnickel bromide with methylmagnesium chloride. On reaction with HBr, methane is split off from compounds *(4)*, and π-allylnickel bromide·$PR_3$ *(3)* is again formed. Use of an excess of triphenyl phosphite leads to junction of the allyl and methyl radicals in *(4)*, affording butenes and, *e.g.* Ni[$P(OC_6H_5)_3$]$_4$.

The $^1$H-NMR spectrum of π-allylmethylnickel (at −60 °C in tetramethylsilane as solvent) shows four signals (relative intensities 1:2:2:3). Those of relative intensity 1:2:2 at 4.67, 7.24, and 7.75 τ are typical of the π-allyl group. The singlet at 12.1 τ arises from the methyl protons, and its unusually strong shielding is probably to be ascribed to interaction with the non-bonding d-electrons of the nickel. The low stability of compound *(1)* is apparently also connected to this effect[4]. The interaction is weakened by phosphines. Indeed, the signals of the $CH_3$ protons in the stable phosphine adducts *(4)* lie at lower field strengths (9.7 τ). In the spectrum of the triphenylphosphine adduct it can be seen that the *syn*- and *anti*-protons of the π-allyl group are no longer equivalent in pairs[5]: there are four signals, at 6.39 and 7.12 τ (*syn*), and 7.29 and 8.09 τ (*anti*). Thus the π-allyl group is not symmetrically bound to the central atom. The signal of the central allyl proton lies at 5.00 τ[*].

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[2] *H. Bönnemann*, Diploma Thesis, Technische Hochschule Aachen, 1965.

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[4] *J. Chatt* and *B. L. Shaw*, J. chem. Soc. (London) *1959*, 705.

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[*] We thank Dr. *E. G. Hoffmann* for measurement and discussion of the $^1$H-NMR spectra.

## Bistritylnickel and Tritylnickel Chloride

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According to all previous information, pure alkyl- and arylnickel compounds are stable only when stabilized by further ligands[2]. If, for instance, acetylacetonatonickel is treated with triethylaluminum in toluene at −78 °C, the diethylnickel formed as an intermediate decomposes rapidly with formation of elemental nickel. The nickel atoms can be trapped, *e.g.* by 1,5-cyclooctadiene, as bis-(1,5-cyclooctadiene)nickel(0)[3].

We have found that, for instance, bis-(1,5-cyclooctadiene)-nickel(0) *(2)* reacts with hexaphenylethane at 20 to 70 °C with loss of cyclooctadiene to yield stable bistritylnickel *(1)*, as deep violet crystals. This product can be recrystallized from benzene (solubility *ca.* 1 g/l at 20 °C). It is obtained in more than 90 % yield when acetylacetonatonickel is reduced with $(C_2H_5)_2AlOC_2H_5$ in benzene at about 0 °C in the presence of an excess of hexaphenylethane.

$$\underset{(2)}{Ni(C_8H_{12})_2} + (C_6H_5)_3C\text{-}C(C_6H_5)_3 \xrightarrow{-2\ C_8H_{12}} \underset{(1)}{(C_6H_5)_3C\text{-}Ni\text{-}C(C_6H_5)_3}$$

$$-2\ C_2H_5Al\begin{matrix}O_2C_5H_7\\OC_2H_5\end{matrix} \xrightarrow{-2\ \cdot C_2H_5}$$

$$Ni(O_2C_5H_7)_2 + 2\ (C_2H_5)_2AlOC_2H_5 + (C_6H_5)_3C\text{-}C(C_6H_5)_3$$
*(3)*

Compound *(1)* is also obtained by reaction of $NiBr_2$ with tritylsodium in ether at −78 °C (yield ≥ 40 %).

Pure bistritylnickel decomposes under argon at about 120 °C. If it is added to molten triphenylphosphine at 80 °C, a deep red color appears within a few minutes; addition of benzene precipitates $Ni[P(C_6H_5)_3]_4$ (yield 89 %):

$$Ni[C(C_6H_5)_3]_2 + 4\ P(C_6H_5)_3 \rightarrow Ni[P(C_6H_5)_3]_4 + (C_6H_5)_3C\text{–}C(C_6H_5)_3$$

Bistritylnickel *(1)* does not change visibly in air at 20 °C during several days, yet a slow oxidation occurs in solution. On treatment with pure oxygen, exactly 2 moles of $O_2$ are taken up per mole of *(1)*. Decomposition of the oxidation product is approximately described by the scheme:

$$(1) \xrightarrow{O_2} Ni[O\text{–}O\text{–}C(C_6H_5)_3]_2$$

10 mmoles

| $(C_6H_5)_2CO$ | $(C_6H_5)_3COH$ | $[(C_6H_5)_3C\text{–}O\text{–}]_2$ | $C_6H_5OH$ |
|---|---|---|---|
| 4.7 mmoles | 7.5 mmoles | 1.65 mmoles | 2.3 mmoles |

Bistritylnickel reacts only very slowly with non-oxidizing acids under argon, even in solution; *e.g.* in conc. HCl it takes ≥ 20h before tritylnickel chloride appears in the form of a blue insoluble product. Pure tritylnickel chloride *(4)* is obtained on treatment of 1,5,9-cyclododecatrienenickel(0) with triphenylmethyl chloride in ether at −78 °C:

$$Ni(1,5,9\text{-Cyclododecatriene}) + (C_6H_5)_3CCl \rightarrow \underset{(4)}{(C_6H_5)_3CNiCl} + 1,5,9\text{-Cyclododecatriene}$$

The product *(4)* is appreciably less stable than *(1)*. Suspensions in benzene decompose in a few hours:

$$2\ (C_6H_5)_3CNiCl \rightarrow (C_6H_5)_3C\text{–}C(C_6H_5)_3 + NiCl_2 + Ni$$
*(4)*

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[1] *H. Schott*, Dissertation, Technische Hochschule Aachen, 1965.

[2] *G. Wilke* and *G. Herrmann*, Angew. Chem. *78*, 591 (1966), Angew. Chem. internat. Edit. *5*, 581 (1966).

[3] *G. Wilke*, Angew. Chem. *72*, 581 (1960); *M. Kröner*, Dissertation, Technische Hochschule Aachen, 1961.

## Preparation of Carbonyl(chlorodifluorophosphine)nickel Complexes [1]

By Prof. Dr. O. Glemser, cand. chem. E. Niecke, and Dr. A. Müller

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The compounds $Ni(PF_2Cl)_4$ *(1)*, $Ni(CO)(PF_2Cl)_3$ *(2)*, $Ni(CO)_2(PF_2Cl)_2$ *(3)*, and $Ni(CO)_3(PF_2Cl)$ *(4)* can be prepared by direct reaction of nickel tetracarbonyl and $PF_2Cl$ in a Carius tube (molar ratio 1:4; about 80 hr at 30–90 °C)[*]. Mixtures of *(1)* to *(4)* are always obtained in this reaction, formation of products with higher phosphine content being favored by higher temperatures. The products *(1)* to *(4)* were separated by fractional distillation in a high vacuum. Except for *(1)*[2], they were all obtained pure and were characterized by mass spectra, elemental analyses, and infrared spectra between 4000 and 300 $cm^{-1}$.

In the region of ν(CO), ν(PF)[3], ν(PCl)[3], and ν(NiC) vibrations, the infrared spectra of the pure substances *(2)*, *(3)*, and *(4)* in the gaseous state showed the number of vibrations bands expected from group theory [$C_{3v}$ symmetry assumed for *(2)*, $C_{2v}$ for *(3)*, and $C_s$ for *(4)*]. The compounds are most easily characterized by their ν(CO) vibration frequencies:

$Ni(CO)(PF_2Cl)_3$: $\nu(A_1)$ at 2079 $cm^{-1}$

$Ni(CO)_2(PF_2Cl)_2$: $\nu(A_1)$ at 2097 and $\nu(B_1)$ at 2059 $cm^{-1}$

$Ni(CO)_3(PF_2Cl)$: $\nu(A_1)$ at 2114 and $\nu(E)$ at 2058 $cm^{-1}$ (assignment according to the symmetry of the $NiP_x(CO)_{4-x}$ skeleton)

The position of the ν(CO) frequency corresponds to experience in that the ν(CO) frequencies of substituted carbonyls are lowered when the ligands are not π-acceptors and are constant or even raised when the ligands are π-acceptors ($PF_2Cl$)[4]. In the present case the frequency of the symmetrical stretching vibration increases with increasing number of $PF_2Cl$ ligands as a result of the increased proportion of π-bonding in the CO linkage. Similar observations have been made for complexes of the type $Ni(CO)_x(PF_3)_{4-x}$[5].

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[*] All the products are colorless liquids at room temperature. Determination of their boiling points was difficult because of their ready decomposition.

[1] Part V of Studies on PF Compounds. – Part IV: *A. Müller, E. Niecke*, and *O. Glemser*, Z. anorg. allg. Chem., in press.

[2] Separation of *(1)* and *(2)* – for preparation of pure *(1)* – failed because of the low vapor pressures below the decomposition temperatures.

[3] For infrared spectra of $PF_2Cl$ see *A. Müller, O. Glemser*, and *E. Niecke*, Z. Naturforsch., in press.

[4] *F. A. Cotton*, Inorg. Chem. *3*, 702 (1964).

[5] *M. Bigorgne*, Bull. Soc. chim. France *1960*, 1986.

## New Catalyst Systems for the Dimerization of Ethylene and Propene

By Dr. J. Ewers

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According to *Wilke* and *Bogdanovic*[1], allylnickel halide systems catalyse the dimerization of ethylene and propene. These catalysts are particularly active if the halogen is bound in a complex by addition of Lewis acids, *e.g.* $AlCl_3$, and if phosphines are added to them.

We have found catalysts for the dimerization of ethylene and propene that are probably π-complexes of Ni(0) and substantially exceed the system named above in activity (based on nickel content).

The catalyst is formed when a nickel salt (*e.g.* bisacetylacetonatonickel) is reduced with a chlorine-containing organoaluminium compound in toluene. The most suitable reducing agent is $Al_2(C_2H_5)_3Cl_3$. Catalytic activity appears only when at least one mole of $Al_2(C_2H_5)_3Cl_3$ is added per mole of nickel salt. A yellow to orange solution is formed, which absorbs propene greedily. The activity of the catalyst is increased by electron-donors, *e.g.* triphenylphosphine.

The catalyst can be used over a wide temperature range and has a high activity even at −30 °C. A catalyst prepared from 1 mole of bisacetylacetonatonickel, 45 moles of $Al_2(C_2H_5)_3Cl_3$, and 16 moles of triphenylphosphine converts $5.7 \times 10^5$ moles of propene in 2 hours at 60 °C and 10 atm. 91 % of the product consists of:

2-Methyl-1-pentene 17.4 %

2-Methyl-2-pentene 26.5 %

4-Methyl-2-pentene 37.0 %

4-Methyl-1-pentene 1.6 %

2,3-Dimethyl-1-butene 6.0 %

2,3-Dimethyl-2-butene 0.5 %

2-Hexene 5.6 %

3-Hexene 5.3 %

Ethylene is dimerized even faster and with a higher conversion. A catalyst prepared from 1 mole of bisacetylacetonatonickel, 32 moles of $Al_2(C_2H_5)_3Cl_3$, and 8 moles of triphenylphosphine converts $8.3 \times 10^5$ moles of ethylene in 15 minutes and is still fully active at the end of this time. 94 % of the product consists of butenes, of which 95 % is 2-butene.

Catalysts for the dimerization of propene can also be obtained from:

1 Mole of di-(π-allyl)nickel + 32 moles of $Al_2(C_2H_5)_3Cl_3$

1 Mole of π-allylnickel chloride + 32 moles of $Al_2(C_2H_5)_3Cl_3$

1 Mole of di-(π-allyl)nickel + 32 moles of $Al_2(C_2H_5)_3Cl_3$ + 8 moles of triphenylphosphine

1 Mole of π-allylnickel chloride + 32 moles of $Al_2(C_2H_5)_3Cl_3$ + 8 moles of triphenylphosphine

1 Mole of di-(π-allyl)nickel + 32 moles of $AlCl_3$ + 8 moles of triphenylphosphine

These systems are, however, less active than those without the allyl group.

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[1] *G. Wilke et al.*, Angew. Chem. 78, 157 (1966); Angew. Chem. internat. Edit. 5, 151 (1966).

## Synthesis of Alkynylamines from α-Halogeno Iminium Salts and Ketene S,N-Acetals [1]

By Dr. R. Buijle, Dr. A. Halleux, and Dr. H. G. Viehe

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Ynamines react with an excess of anhydrous hydrogen halide with formation of α-halogenoiminium salts[2]. The ynamines are regenerated therefrom by lithium dialkylamides. Ketene *N,N*-acetals, which can be separated by distillation, are also formed in this reaction, so that the total yields range between 50 and 75 %. An ethereal solution of the amide is dropped during 30 min into an ethereal solution of the iminium salt at 0 °C; the solution is then decanted from the precipitated salts and distilled.

α-Halogenoiminium salts are readily obtained from carboxamides and phosgene[3], so that this synthesis of ynamines has preparative interest. Pure *N,N*-diethyl-1-butynylamine is obtained from crude *N,N*-diethyl-1-chlorobutylideneiminium chloride in 77 % yield. A summary of the results is given in Table 1.

Table 1. Ynamines from α-halogenoiminium salts.

$$[R^1\text{-}CH_2\text{-}CCl{=}\overset{\oplus}{N}R^2_2]\ Cl^{\ominus} \underset{2\ HCl}{\overset{LiNR_2}{\rightleftharpoons}} R^1\text{-}C{\equiv}C\text{-}NR^2_2$$

| Ynamine | Base | B.p. [°C/mm Hg] | Yield [%] |
|---|---|---|---|
| $CH_3-C{\equiv}C-N(C_2H_5)_2$ | $LiN(C_2H_5)_2$ | 60–62/90 | 39 |
| | $LiN(C_6H_{11})_2$ | | 58 |
| $CH_3-C{\equiv}C-NC_5H_{10}$ | $LiN(CH_3)_2$ | 72–73/15 | 12 |
| | $LiN(C_2H_5)_2$ | | 39 |
| | $LiN(C_3H_7)_2$ | | 0 |
| | $LiN(C_6H_{11})_2$ | | 46 |
| $C_2H_5-C{\equiv}C-N(C_2H_5)_2$ | $LiN(C_2H_5)_2$ | 50–51/30 | 38 |
| | $LiN(C_6H_{11})_2$ | | 77 |
| $n\text{-}C_4H_9-C{\equiv}C-N(C_2H_5)_2$ | $LiN(C_2H_5)_2$ | 77–78/15 | 29 |
| $HC{\equiv}C-N(C_2H_5)_2$ | $LiN(C_2H_5)_2$ | | [a] |

[a] Obtained only in solution and identified by infrared spectroscopy.

Ynamines can also be prepared from ketene S,N-acetals[4]. 4-Phenylethynylmorpholine is obtained by slow addition of β-methylthio-β-morpholinostyrene under nitrogen to lithium diethylamide in tetrahydrofuran at 20 °C or to sodium amide in boiling piperidine. After 3 hr the mixtures are fractionally distilled. The same ynamines arise when the ketene S,N-acetal is led over solid sodium amide at 150–165 °C and 1 mm.

Table 2. Ynamines from ketene S,N-acetals.

$$R^1\text{-}CH{=}C(SR)\text{-}NR^2_2 \xrightarrow[-HSR]{Base} R^1\text{-}C{\equiv}C\text{-}NR^2_2$$

| Ynamine $R^1$ | Ynamine $R^2$ | Base | B.p. [°C/mm Hg] | Yield [%] |
|---|---|---|---|---|
| $C_6H_5$ | Morpholino | $LiN(C_2H_5)_2$ | 99–100/0.01 | 40 |
| | | $NaNH_2$ | | 50 |
| | | $NaNH_2/C_5H_{11}N$ | | 50 |
| H | Morpholino | $NaNH_2/C_5H_{11}N$ | | [a] |

[a] Obtained only in solution and identified by infrared spectroscopy.

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[1] Part XII of Heterosubstituted Acetylenes. – Part XI: *H. G. Viehe, R. Merenyi*, and *J. F. Oth*, Angew. Chem. 76, 922 (1964); Angew. Chem. internat. Edit. 3, 755 (1964).

[2] *H. G. Viehe*, Lecture on June 5th, 1964, in Paris.

[3] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Chem. Ber. 96, 2671 (1963).

[4] *R. Gompper* and *W. Elser*, Tetrahedron Letters *1964*, 1971.

## Condensation of Alkynylamines with 1,3-Dipolar Compounds, Carbonyl Compounds, and Schiff Bases [1]

By Dr. R. Fuks, Dr. R. Buijle, and Dr. H. G. Viehe

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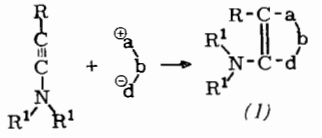
Only two examples of cycloaddition to ynamines have so far been reported [2]. By 1,3-dipolar cycloaddition under the conditions described previously [3], ynamines readily afford dialkylamino-substituted heterocycles *(1)* (Table 1). The structure of the products follows from analytical data and in analogy to earlier results [3].

Table 1. Heterocycles from ynamines.



*(1)*

| R | $R^1$ | $^{\oplus}a-b-d^{\ominus}$ | Adduct M.p. [°C] | Adduct Yield [%] |
|---|---|---|---|---|
| $C_6H_5$ | $CH_3$ | $N{=}N{-}N{-}C_6H_5$ | 180 | 59 |
| $C_6H_5$ | $CH_3$ | $C_6H_5{-}CH{-}N(C_6H_5){-}O^{\ominus}$ | 151 | 95 |
| $CH_3$ | $R^1 + R^1 = -(CH_2)_5-$ | $C_6H_5{-}CH{-}N(C_6H_5){-}O^{\ominus}$ | 144 | 89 |
| $C_6H_5$ | $CH_3$ | $C_6H_5{-}C{=}N{-}N{-}C_6H_5$ | 128 | 63 |
| $C_6H_5$ | $CH_3$ | $N{=}N{-}N{-}CO{-}C_6H_5$ | 143 | 71 |
| $(i\text{-}C_4H_9)_2N$ | $i\text{-}C_4H_9$ | $p\text{-}(O{-}N{-}C)_2\text{-}C_5H_4$ | 144 | 45 |

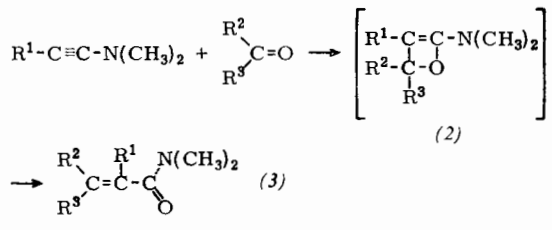
Ynamines condense surprisingly easily also with aldehydes and ketones. Although this addition occurs without catalysis when the components are heated [4], catalysis with 1 to 5 mole-% of boron trifluoride-ether is preferable.

Addition of this catalyst to an etheral solution of equivalent amounts of the reactants leads to exothermal condensation that is usually complete in a few minutes but at latest after refluxing for half an hour.

The four-membered ring system *(2)* probably formed as intermediate rearranges to the α,β-unsaturated carboxamides *(3)*.

$BF_3$-catalysed addition of Schiff bases to ynamines occurs less easily and gives lower yields. Reaction times are about 24 hr under the conditions described for the carbonyl compounds (heating under reflux). Acrylamidines *(5)*, whose structures are proved by independent syntheses, are obtained, probably by way of azetines *(4)*.

Table 2. α,β-Unsaturated carboxamides formed from ynamines.



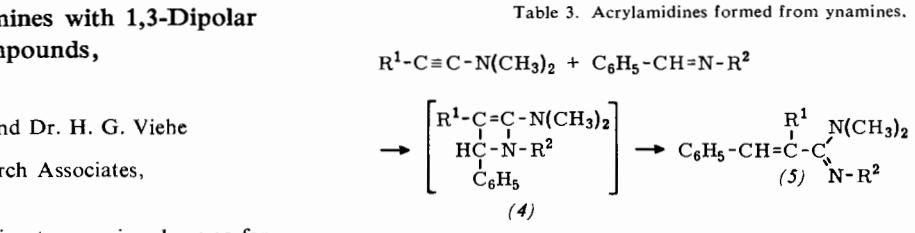
*(2)*

*(3)*

| $R^1$ | $R^2$ | $R^3$ | *(3)*, M.p. [°C] | Yield [%] |
|---|---|---|---|---|
| $C_6H_5$ | $C_6H_5$ | H | 84–85 [a] | 82 |
| $C_6H_5$ | $C_6H_5$ | $CH_3$ | 106–107 [a] | 84 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | 56–57 | 83 |
| $C_6H_5$ | $-(CH_2)_4-$ | | 65–66 | 90 |
| $C_6H_5$ | $-(CH_2)_5-$ | | 75–76 | 72 |
| $t\text{-}C_4H_9$ | $C_6H_5$ | H | 70–71 | 85 |

[a] Melting point and yield of the *cis*-isomer formed exclusively.

Table 3. Acrylamidines formed from ynamines.



*(4)*

*(5)*

| $R^1$ | $R^2$ | *(5)* M.p. [°C], B.p. [°C/mm Hg] [a] | *(5)* Yield [%] |
|---|---|---|---|
| $C_6H_5-$ | $-C_6H_5$ | 87–88 | 43 |
| $C_6H_5-$ | $-(CH_2)_3-CH_3$ | 140/0.3 | 70 |
| $t\text{-}C_4H_9-$ | $-C_6H_5$ | 145/0.1 | 30 |

[a] See footnote to Table 2.

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[1] Part XIII of Hetero-substituted Acetylenes. – Part XII: *R. Buijle, A. Halleux*, and *H. G. Viehe*, Angew. Chem. *78*, 593 (1966); Angew. Chem. internat. Edit. *5*, 584 (1966).

[2] *H. G. Viehe, R. Fuks*, and *M. Reinstein*, Angew. Chem. *76*, 571 (1964); Angew. Chem. internat. Edit. *3*, 581 (1964); *H. Ficini* and *C. Barabara*, Bull. Soc. chim. France *1964*, 871; *1965*, 2787; see also *M. Franck-Neumann*, Tetrahedron Letters *1966*, 341.

[3] *R. Huisgen*, Angew. Chem. *75*, 604 (1963), Angew. Chem. internat. Edit. *2*, 565 (1963).

[4] Stoichiometric amounts of this condensing agent were necessary in similar addition reactions: *H. J. T. Bos* and *J. F. Arens*, Recueil Trav. chim. Pays-Bas *82*, 845 (1963).

## Chlorination of Cyclooctatetraene

By Prof. Dr. R. Huisgen, Dr. G. Boche, Dipl.-Chem. W. Hechtl, and H. Huber

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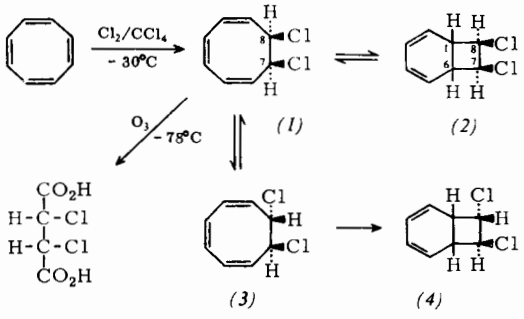
*W. Reppe et al.* [1] obtained the bicyclic *cis*-dichloride *(2)* from cyclooctatetraene and chlorine or sulfuryl chloride [2]. Studies on Diels-Alder adducts by *C. D. Nenitzescu et al.* [3] strongly suggest the *trans*-structure *(4)* for a dichloride formed from *(2)* under the influence of heat or acid catalysis.

This chlorination was found to follow a similar course as bromination [4]. Four isomeric dichlorides can be isolated in pure, crystalline form. Rapid stereospecific *cis*-addition of chlorine, yielding the isomer *(1)*, is observed in both polar (acetonitrile) and nonpolar solvents (hexane).



According to the NMR spectrum, *cis*-7,8-dichloro-1,3,5-cyclooctatriene *(1)* arises quantitatively as primary product on low-temperature chlorination and can be isolated by crystallization at 0 °C (m.p. 34 °C; 91 % yield). Ozonolysis in ethyl acetate gives 67 % of *meso*-dichlorosuccinic acid. The $^1$H-NMR spectrum of *(1)* in $CCl_4$ includes bands at 4.09 (s)

(vinyl-H) and 4.88 τ (s) (tert-H) with relative intensities of 3:1. When the solution is cooled to −54 °C the signal from H-7 and H-8 is split reversibly into a doublet plus a singlet, the areas of which indicate a 54:46 equilibrium of *endo-cis*- and *exo-cis*-dichlorides (boat form), the coalescence temperature being −30 °C.

*cis*-7,8-Dichlorobicyclo[4.2.0]octadiene *(2)*: The valence tautomerism *(1)* ⇄ *(2)* is mobile above 50 °C; at 70 °C there is 20 % of *(1)* and 80 % of *(2)* in the equilibrium mixture. Compound *(2)* (m.p. −7 °C) crystallizes from ether at −75 °C; its $^1$H-NMR spectrum shows 4 vinyl-H at 4.19 (s), H-7 and H-8 at 5.35 τ (d) with fine structure, and H-1 and H-6 at 6.67 τ (not resolved).

*trans*-7,8-Dichloro-1,3,5-cycloctatriene *(3)* can be obtained from *(1)* by stirring the $CCl_4$ solution with alumina at −30 °C; it is obtained pure, m.p. 24–25 °C, by crystallization from ether at −70 °C. The equilibrium, which can be attained from either side, corresponds to 66 % of *(3)* and 34 % of *(2)* at −30 °C. The $^1$H-NMR spectrum of isomer *(3)* (in $CCl_4$) shows vinyl-H and tert-H with relative intensities 3:1, and H-7 and H-8 at 5.37 τ (s). Ozonolysis in ethyl acetate at −78 °C gives racemic dichlorosuccinic acid.

*trans*-7,8-Dichlorobicyclo[4.2.0]octadiene *(4)* arises on tautomerization of *(3)* in $CCl_4$ at temperatures ≥ 0 °C. Compound *(3)* was not detectable in equilibrium with *(4)*. Compound *(4)* is formed also from *(1)* or *(2)* at 140 °C in $CCl_4$, at 75 °C in nitrobenzene, or at 70 °C in dioxane/HCl. It has m.p. −12 °C (from diethyl ether), and its $^1$H-NMR spectrum shows signals for 4 vinyl-H at *ca.* 4.2 τ (m), H-7 and H-8 at 5.36 (t) and 5.58 τ (t), and H-1 and H-6 at 6.2 to 7.3 (t).

Compounds *(2)* and *(4)* react with dienophiles, giving crystalline adducts. Reaction of *(1)* with maleic anhydride can be followed dilatometrically as described previously for 1,3,5-cyclooctatriene[5]. The rates and the activation energy of the tautomerization *(1)* → *(2)* can thus be measured.

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[1] *W. Reppe, O. Schlichting, K. Klager*, and *T. Töpel*, Liebigs Ann. Chem. *560*, 1 (1948).

[2] For the configuration see *V. Georgian* and *L. Georgian*, Tetrahedron *19*, 1219 (1963).

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## Addition of Trialkyl Methanetricarboxylates to 1-Alkenes Initiated by Peroxides

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Peroxide-initiated addition of trialkyl methanetricarboxylates to 1-alkenes affords high yields of the corresponding trialkyl 1,1,1-alkanetricarboxylates.

Of 625 mmoles of triethyl methanetricarboxylate (TEM) a quarter to a third is placed in a flask fitted with stirrer, reflux condenser, thermometer, and dropping funnel, saturated with argon in the cold, and warmed to 130–150 °C (thermostat containing silicone oil). 125 mmoles of 1-alkene and 12.5 mmoles of a peroxide[*] are dissolved in the remainder of the TEM and dropped into the flask with vigorous stirring during 2–5 hr. The excess of TEM is then distilled off through a column 1 m long with a mirrored vacuum jacket (internal diameter 25 mm; packed with glass spirals 5 mm long and 2 mm in diameter) (b.p. 76–78 °C/0.1 mm). The residue contains the addition product and is rectified through a 15-cm vacuum jacketed column (internal diameter 20 mm; filling as above). For the products see the Table.

The trialkyl 1,1,1-alkanetricarboxylates are converted by alkaline hydrolysis and subsequent acidification with concentrated HCl into the corresponding 1,1-alkanedicarboxylic acids, whence thermal decarboxylation affords monocarboxylic acids whose chains are by two carbon atoms longer than those of the 1-alkene.

Small amounts of 2:1 telomers are formed alongside the 1:1 adducts. Thus addition of TEM to 1-octene gave triethyl 3-hexyl-1,1,1-undecanetricarboxylate, b.p. 165–182 °C/0.15 mm Hg (yield 5–15 %), hydrolysis, decarboxylation, and re-esterification of which gave methyl 4-hexyldodecanoate, b.p. 115–116 °C/0.05 mm, $n_D^{20} = 1.4454$.

Attempted addition of TEM to open-chain alkenes with non-terminal double bonds always failed, but was successful with cyclic olefins in exceptional cases, *e.g.* bicyclo[2.2.1]-hept-2-ene (more than 60 % yield).

| Alkene | 1:1 Adduct | Yield [a] (%) |
|---|---|---|
| 1-Octene | $CH_3(CH_2)_7-C(CO_2C_2H_5)_3$ | 73 |
| 1-Dodecene | $CH_3(CH_2)_{11}-C(CO_2C_2H_5)_3$ | 70 |
| Methyl 1-undecenoate | $CH_3OOC(CH_2)_{10}-C(CO_2C_2H_5)_3$ | 51 |
| Vinyl acetate | $CH_3COO(CH_2)_2-C(CO_2C_2H_5)_3$ | 60 |
| β-Pinene | Triethyl 7,7-dimethyl-bicyclo-[3.1.1]heptan-2-yl-1,1,1-ethanetricarboxylate | 51 |

[a] Initiator: di-t-butyl peroxide (10 mole-%, based on alkene); 150 °C; reaction time 5 hr; molar ratio TEM: alkene = 5:1.

Allyl alcohol, allyl bromide, 4-vinylcyclohexene, and phenylacetylene do not undergo addition to TEM under the conditions described. Numerous attempts at radical-initiated addition of methanetri- and disulfonic esters to 1-alkenes were unsuccessful.

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[*] The most favorable molar ratios are TEM: alkene = 5:1 to 10:1, peroxide 10 mole-% of alkene used. The peroxide used was di-t-butyl peroxide.

## Reaction of Aryl Azides with Alkali Metals

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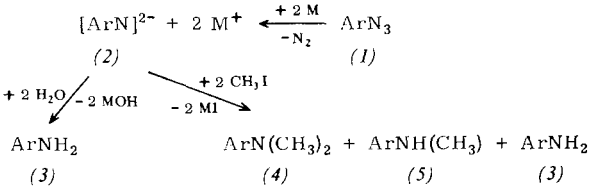
In a new type of reaction, aryl azides *(1)* react with sodium or potassium in liquid ammonia mainly (to the extent of *ca.* 96 %) according to Scheme I, whereby one mole of aryl azide consumes two gram-atoms of alkali metal with formation of the dianions *(2)* and evolution of one mole of $N_2$.




Ar = $C_6H_5$, o-$CH_3$-$C_6H_4$, p-$CH_3$-$C_6H_4$; M = Na, K

Scheme I

The nitrogen was determined by gas chromatography and volumetrically. The dianions *(2)* were identified indirectly,

in that the deep red solution in liquid ammonia gave arylamines *(3)* when treated with an excess of water, and dimethylarylamines *(4)*, methylarylamines *(5)*, and unsubstituted arylamines *(3)*, in a total yield of 90 % calculated on *(1)*, when treated with methyl iodide. The products *(3)* and *(5)* can have arisen only by protolysis of the ions *(2)* by ammonium iodide, the ammonolysis product of methyl iodide.

To a minor extent [*ca.* 4 % of *(1)* brought into reaction] there is also reductive cleavage of the N–C linkage of *(1)*, which leads to azide *(6)* and aryl anions *(7)* (see Scheme II).

$$\underset{(1)}{ArN_3} \xrightarrow{+\,2M} 2\,M^+ + \underset{(6)}{N_3^-} + \underset{(7)}{Ar^-} \xrightarrow{+\,NH_3} \underset{(8)}{ArH} + \underset{(9)}{MNH_2}$$

Scheme II

The intermediate formation of the aryl anions *(7)* is assumed because of the occurrence of alkali-metal amides *(9)* and of aromatic hydrocarbons *(8)*, which can arise only by ammonolysis of *(7)*. These anions are derived from the weak acids HAr and thus react readily with ammonia.

The reactions shown in Schemes I and II proved to be independent of the temperature (from −80 to −33 °C), of concentrations ($c_{ArN_3}$ from 0.01 to 0.5 moles/l; $c_M$ from 0.01 to 0.1 mole/l), and of the manner of mixing of the reactants.

*Experimental*: Ethereal solutions of phenyl or *o*- or *p*-tolyl azide were added from a dropping funnel, with stirring and equalization of pressure, to a solution of the alkali metal in liquid ammonia (0.05 M) at −80, −60, −48, or −33 °C [0.025 mole of *(1)* in 1 hr to 250 ml of solution; Hg seal; Hg-filled gas buret]. When the blue color of the metal solution had changed to red (dianion) the $NH_3$ was distilled off and the hydrocarbon was extracted with diethyl ether. The residue was cautiously dissolved in water at 0 °C. Extraction of the alkaline solutions with ether gave the arylamine $ArNH_2$; the aqueous phase was tested for alkali-metal azide.

For conversion of the dianions $ArN^{2-}$ into the *N*-methyl compounds the reaction mixture was treated with an excess of methyl iodide. The amines *(3)*, *(4)*, and *(5)* were extracted with ether after evaporation of the ammonia and separated by gas chromatography.

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## The Rearrangement of Amino[1,2,3]thiadiazolo-[5,4-d]pyrimidines to Mercapto-8-azapurines, and its Retrogression

By Prof. A. Albert and K. Tratt

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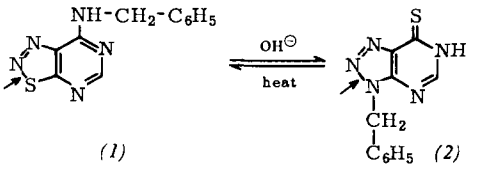
9-Benzyl-6-hydroxy-8-azapurine[1], when heated with phosphorus pentasulphide in boiling pyridine for 1.5 hr gave the alkali-insoluble 7-benzylamino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine *(1)* in 70 % yield, m.p. 140 °C, $\lambda_{max}$ = 325 mμ (log ε = 3.86 in $H_2O$), $\nu_{max}$ = 3310, 1615, 1530, 1330, and 1305 $cm^{-1}$, with absence of thiocarbonyl stretching frequency in the 1100–1200 $cm^{-1}$ region[1a]. The structure was confirmed by obtaining the same product (in 75 % yield) by refluxing 7-methoxy[1,2,3]thiadiazolo[5,4-*d*]pyrimidine[2] with benzylamine (1 hr in ethanol).

When *(1)* was refluxed with 1 N sodium hydroxide for 30 minutes, it was converted (90 % yield) to the alkali-soluble 6-mercapto-9-benzyl-8-azapurine *(2)*, m.p. 150 °C, $\lambda_{max}$ = 332 mμ (log ε = 4.26 in $H_2O$), $\nu_{max}$ (all strong) at 3030, 1590, 1345, and 1195 (C=S) $cm^{-1}$. This substance is re-isomerized to *(1)* when refluxed with alcohol for 3 hours (80 % yield).




*(1)* *(2)*

Rings open and close at arrow.

We prepared the mercapto-compound *(2)* also by refluxing 9-benzyl-6-chloro-8-azapurine[3] with thiourea in methanol for 15 min (90 % yield).

No record could be found of 6-mercaptopurine (which differs from *(2)* by having a CH group in position 8) rearranging to 7-aminothiazolo[5,4-*d*]pyrimidine, but the latter is known to be converted to the former by alkali[4].

Although earlier workers[5] claimed to have obtained 6-mercapto-8-azapurine (in 10 % yield) by the action of phosphorus pentasulphide on 6-hydroxy-8-azapurine[6] in boiling pyridine, the ultraviolet spectrum of their product resembled that of 7-amino[1,2,3]thiadiazolo[5,4-*d*]pyrimidine. In our hands, repetition of this work gave the alkali-insoluble thiadiazolopyrimidine in 60 % yield, but no 6-mercapto-8-azapurine. However, we obtained the latter (70 % yield) by refluxing the thiadiazolo-isomer in 1 N sodium hydroxide for 20 minutes; it begins to turn brown at 250 °C but is unmelted at 300 °, $\lambda_{max}$ = 330 mμ (log ε = 4.25 in $H_2O$ at pH 2.0), $\nu_{max}$ (all strong) at 3185, 1590, 1565, and 1180 (C=S) $cm^{-1}$, $pK_a$ 4.6 (*i.e.* about the same strength as acetic acid.) Re-isomerization of this substance to the thiadiazolopyrimidine was very slow in boiling water (10 % in 5 hours), and the mercapto-compound was rapidly destroyed by boiling 0.1 N hydrochloric acid.

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## Triphenylcyclotriphosphinedipotassium, $K_2[P(C_6H_5)_3]$ [*]

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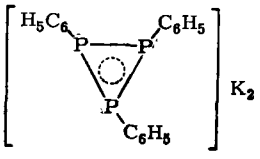
Depending on the relative quantities of the reactants, "phosphobenzene" $(C_6H_5P)_n$ and potassium in tetrahydrofuran afford not merely compounds KRP–PR–PR–PRK and KRP–PRK (R = $C_6H_5$)[1], whose analogues with aliphatic

groups R have long been known[2], but also the compound $K_2[P(C_6H_5)]_3$ *(1)*.

*Experimental*: 8 g of $(C_6H_5P)_n$ (m.p. 154–156 °C) and 1.9 g of potassium in 150 ml of THF are refluxed for 1 hr. A red solution is formed in an exothermic reaction, and after concentration and addition of light petroleum (b.p. 30–50 °C) the product *(1)* crystallizes. It is filtered off, washed with benzene, and vacuum dried; the yield is 12 g (90 %). Compound *(1)* crystallizes with 2 molecules of THF as an orange-red material. It is readily soluble in THF and dioxane, sparingly soluble in benzene and ether, and sensitive to air and hydrolysis.

The $^{31}P$-resonance spectrum of compound *(1)* in THF shows a single sharp line at $\delta = 49.8 \pm 0.5$ ppm, indicating chemical equivalence of the P atoms and thus a cyclic structure.

A $2\pi$-electron system is to be assumed for the anion of *(1)*, which is to some extent an analogue of the triphenylcyclopropenylium cation. Whereas in the cyclopropenylium cation[3] the $\pi$-electron system is composed of three $p_z$-orbitals, the two $\pi$-electrons in the $[PC_6H_5]_3^{2-}$ ion probably



*(1)*

occupy a molecular orbital composed of $d_z$-atomic orbitals. This $\pi$-electron system should have a stability similar to that of the cyclopropenylium cation[4].

Cleavage experiments with $[C_2H_5P]_n$ (n = 4 or 5) and potassium[5], and with "phosphobenzene" $(C_6H_5P)_n$ and lithium, as well as treatment of *(1)* with LiBr or water, show that not only the phenyl groups but also the potassium (which is more electropositive than lithium)are a prerequisite for stabilization of the cyclic anion of *(1)*. Thus, according to the NMR spectra, compound *(1)* and LiBr in THF give numerous phosphines $LiRP-(PR)_n-PRLi$ of different chain lengths as primary products, these phosphines being the same compounds that were found after treatment of $(C_6H_5P)_n$ with lithium (cf. Table, right-hand part). This exothermal reaction is signalled by a change in color of the solution from red-brown to yellow. If *(1)* is treated with two moles of LiBr, the principal product is 1,4-dilithio-1,2,3,4-tetraphenyltetraphosphine, which has sharp $^{31}P$–NMR lines at 3.4, 12.5, 80.0, and 88.9 ppm (Table, left-hand part; spectrum measured

Relative intensities $I_{rel}$ and positions of $^{31}P$–NMR signals (in THF; 22 °C) [*] on ring scission of:

| *(1)* with LiBr (molar ratio 1:2) | | | | $(C_6H_5P)_n$ with Li (molar ratio 3:8) | | | |
|---|---|---|---|---|---|---|---|
| δ (ppm) | $I_{rel}$ | δ (ppm) | $I_{rel}$ | δ (ppm) | $I_{rel}$ | δ (ppm) | $I_{rel}$ |
| 3.7 | 10 | 57.5 | 2 | 3.7 | 10 | 57.6 | 5 |
| 12.7 | 12 | – | – | 12.6 | 12 | 65.4 | 1 |
| 21.3 | 1 | 69.7 | 4 | 21.2 | 1 | 70.3 | 2 |
| – | – | 79.6 | 12 | 30.3 | 1 | 80.0 | 12 |
| – | – | 88.5 | 10 | 37.7 | 1 | 88.9 | 10 |
| – | – | 96.0 | 2 | 44.1 | 1 | – | – |
| – | – | 110.5 | 1 | 51.6 | 2 | – | – |

[*] Accuracy: ± 1.0 ppm; $I_{rel}$ is estimated.

several days after preparation. Dilithio-1,2,3-triphenyltriphosphine[1] is not found, probably owing to dismutation with formation of more stable lithium phosphides.

Hydrolysis of compound *(1)* in benzene with an excess of water at 20 °C leads to immediate decoloration of the solution and – analogously to the behavior of acyclic phosphines $HRP-(PR)_n-PRH$ (n = 0, 1, or 2) – to dismutation to "phosphobenzene" (m.p. 152 °C) and phenylphosphine $C_6H_5PH_2$, each arising in about 90 % yield.

Compound *(1)* behaves as an electron donor towards metal carbonyls. Thus ultraviolet irradiation of its mixture with $Ni(CO)_4$ and $Fe(CO)_5$ in THF leads to replacement of CO and formation of compounds *(2)* (decomp. from 95 °C) and

$$(1) + M(CO)_n \xrightarrow{-CO} K_2[M(CO)_{n-1}(PC_6H_5)_3]\cdot THF$$

*(2)*, M = Ni; *(3)*, M = Fe

*(3)* (decomp. from 195 °C), whose compositions are confirmed by elemental analyses. On concentration of the solutions, *(2)* and *(3)* are obtained as orange-red and brown crystals, respectively, in yields of about 90 %. They dissolve readily in THF and dioxane, are insoluble in light petroleum or n-hexane, and decompose in ethanol or water.

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## Derivatives of Phospha-2,5-cyclohexadien-4-one and 4,4'-Diphosphabi-(2,5-cyclohexadienylidene)

By Priv.-Doz. Dr. G. Märkl and H. Olbrich

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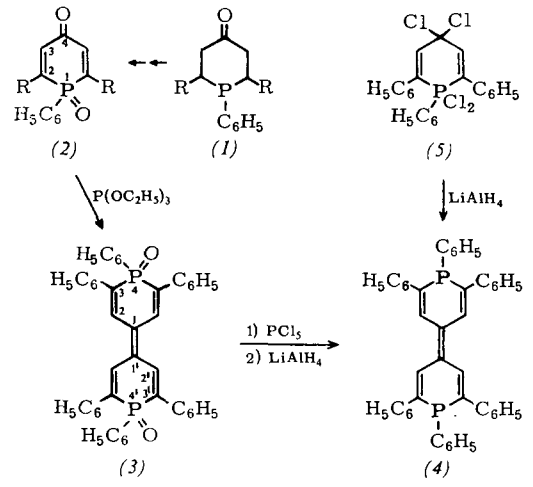
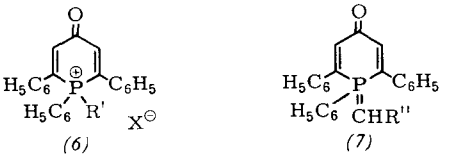
1-Phenylphosphacyclohexan-4-ones *(1)*, R = $C_6H_5$, m.p. 178 °C[1]; R = H, m.p. 44 °C[2], are dehydrogenated by treatment with $SeO_2$ for 36 hr in boiling ethanol by way of the *P*-oxides of their didehydro compounds (R = $C_6H_5$, m.p. 218–220 °C, $\tilde{\nu}_{CO}$ = 1662 $cm^{-1}$) to the 1-phenylphospha-2,5-cyclohexadien-4-one *P*-oxides *(2)* [R = $C_6H_5$, m.p. 162 °C, $\tilde{\nu}_{CO}$ = 1627 $cm^{-1}$, $\lambda_{max}$ = 323 and 342 mμ, 2 vinyl protons at τ = 3.28 (s), 67–80 % yield; R = H, m.p. 130–131 °C, $\tilde{\nu}_{CO}$ = 1650 $cm^{-1}$, 10 % yield).

The same products *(2)* are obtained by dehydrogenation of the 1-oxides or 1-sulfides of *(1)* with $SeO_2$. Neither silanes[3] nor strongly nucleophilic phosphines or phosphites reduce *(2)* to the phosphacyclo-2,5-cyclohexadien-4-ones although the latter correspond to γ-pyridones. Reduction of *(2)*, R = $C_6H_5$, in triethyl phosphite at 80–100 °C affords a quantitative yield of 3,3',4,4',5,5'-hexaphenyl-4,4'-diphosphabi-(2,5-cyclohexadienylidene)-4,4'-dioxide *(3)*, m.p. 425 to 428 °C, $\lambda_{max}$ = 324.5 and 437 mμ. The deep red *P,P,P',P'*-tetrachloro compound obtained from *(3)* and $PCl_5$ can be reduced smoothly by $LiAlH_4$ to 3,3',4,4',5,5'-hexaphenyl-4,4'-diphosphabi-(2,5-cyclohexadienylidene) *(4)* in 90 % yield. This product forms brownish-red crystals, m.p. 335–337 °C, $\lambda_{max}$ = 337 and 467 mμ, mol. wt. (mass spectrum) 648, is not autoxidizable in the solid state or in solution, and does not give phosphonium salts when treated even with strong alkylating agents (trialkyloxonium fluoroborates).

Sulfur reacts with *(4)* in boiling chloroform giving the bis-*P*-sulfide (m.p. 403–405 °C) corresponding to the oxide *(3)*; this product is also obtained by treating 1,1,4,4-tetrachloro-1,2,6-triphenylphospha-2,5-cyclohexadiene *(5)* with $H_2S$ or thioacetic acid in benzene at 25 °C. The latter reactions proceed by way of the dithio analogue of *(2)*, which is however not isolable. On reduction of *(5)* with $LiAlH_4$ direct dimerization to *(4)* intervenes.



The phosphonium salts *(1)*·R′X obtainable from *(1)*, R = $C_6H_5$, are dehydrogenated by $SeO_2$ in boiling ethanol within 24 h to phosphoniocyclohexadienones *(6)* [R′ = $CH_2C_6H_5$, X = $ClO_4^{\ominus}$, m.p. 218–220 °C, $\lambda_{max}$ = 317 and 342 mμ, $\tilde{\nu}_{CO}$ = 1650 $cm^{-1}$; R′ = $C_2H_5$, X = $ClO_4^{\ominus}$, m.p. 173–175 °C, $\tilde{\nu}_{CO}$ = 1648 $cm^{-1}$]. The salts *(6)* may also be prepared by brominating the salts *(1)*·R′X with $C_5H_5N$·HBr in acetic acid; the intermediate α,α′-dibromides need not be isolated. When R′ = $CH_2C_6H_5$, bromination leads immediately to *(6)*, R′ = $CHBrC_6H_5$; X = $ClO_4^{\ominus}$, m.p. 213 to 215 °C, $\tilde{\nu}_{CO}$ = 1659 $cm^{-1}$.



1,2,6-Triphenylphospha-2,5-cyclohexadien-4-one is formed as an intermediate on pyrolysis of *(6)* at 250–300 °C but under the reaction conditions is converted into the dioxide *(3)* and a small amount of the monoxide *(2)* by intra- or intermolecular transfer of the carbonyl oxygen to phosphine phosphorus. The alkylidenephosphoranes *(7)* formed from *(6)*, *e.g.* by "transylidation", are only very weakly basic.

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## 4-Methylenephospha-2,5-cyclohexadienes

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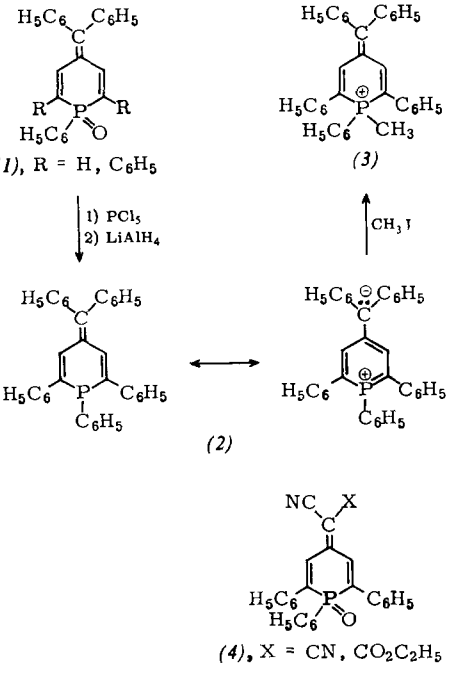
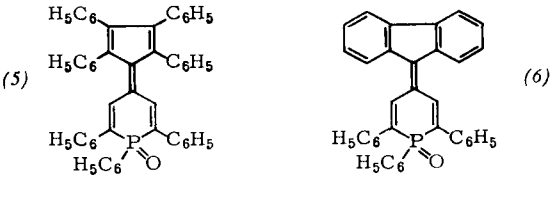
1-Phenylphospha-2,5-cyclohexadien-4-one *P*-oxides[1] react smoothly with the quinoline adduct of diphenylketene at 170 °C affording 4-(diphenylmethylene)-1-phenylphospha-2,5-cyclohexadiene *P*-oxides *(1)* [R = $C_6H_5$, lemon-yellow crystals, m.p. 319–321 °C, $\lambda_{max}$= 365.5 mμ, $^1$H-NMR band complex at 2.3–3.0 τ in $CDCl_3$, 80 % yield; R = H, m.p. 136–138 °C]. The phosphine dichloride obtained from *(1)* with $PCl_5$ can be converted by $LiAlH_4$ into 4-(diphenylmethylene)-1-phenylphospha-2,5-cyclohexadiene *(2)* (R = $C_6H_5$, m.p. 238–240 °C, yellow, non-autoxidizable crystals, $\lambda_{max}$ = 372 mμ, 76 %]. The dipolar limiting structure of *(2)* contains a phosphabenzene system comparable with aromatic pyrylium salts, but *C*-alkylation at the diphenylmethylene side-chain could not be observed alongside (kinetically controlled?) *P*-alkylation. Methyl iodide converts *(2)* smoothly into the quaternary salt *(3)* {m.p. 257–258 °C, orange-yellow needles, $\lambda_{max}$ = 376 mμ, 84 % yield, NMR: $CH_3$ signal in $CD_3NO_2$ at 7.42 τ (d), J = 13 cps $[(C_6H_5)_3\overset{\oplus}{P}-CH_3Br^{\ominus}$ (in $CDCl_3$) $CH_3$ doublet at 6,75 τ, J = 13 cps]}.

Under the conditions of the Knoevenagel condensation 1-phenylphospha-2,5-cyclohexadien-4-one *P*-oxides react with ethyl cyanoacetate or malononitrile in benzene or $CHCl_3$ in the presence of catalytic amounts of *N*-ethyldicyclohexylamine to the cyano derivatives *(4)* [R = $C_6H_5$, X = $COOC_2H_5$, m.p. 205–206 °C, $\lambda_{max}$ = 277 and 374 mμ, 54 % yield; X = CN, m.p. 259–260 °C, $\lambda_{max}$ = 285 and 388 mμ, 31 % yield]. Use of malononitrile leads in addition to a 40–60 % yield of the phosphorus analogue of a quinodimethane (deep red leaflets with a green metallic sheen, m.p. 185–187 °C, $\lambda_{max}$ = 361 and 533.5 mμ) by replacement of the P=O by a P=C(CN)$_2$ group in *(4)*, X = CN.



The 4,4-dichloro derivative (m.p. 128–131 °C) readily preparable in 70 % yield from 1,2,6-triphenylphospha-2,5-cyclohexadien-4-one *P*-oxide and $PCl_5$ can be condensed with cyclopentadienes, *e.g.* 1,2,3,4-tetraphenylcyclopentadiene or fluorene in a melt at 170–180 °C, leading directly to the fulvenoid 4-cyclopentadienylidene-1-phenylphospha-2,5-cyclohexadiene *P*-oxides *(5)* [m.p. 261–263 °C, $\lambda_{max}$ = 321 and 443.5 mμ, yellowish olive-green needles, 76 % yield] and *(6)* [m.p. 264–266 °C, $\lambda_{max}$ = 316 and 432 mμ, orange-red leaflets, 40 % yield)]; 3,3′,4,4′,5,5′-hexaphenyl-4,4′-diphosphabi-(2,5-cyclohexadienylidene)[1] is always formed as by-product.

Compound *(6)* can be reduced, after conversion into the *P*,*P*-dichloride, with $LiAlH_4$ to 4-(9-fluorenylidene)phospha-2,5-cyclohexadiene [m.p. 223–225 °C, $\lambda_{max}$ = 322 and 458 mμ].



Work is in progress to determine whether greater importance should be attached to the dipolar phosphabenzene limiting

structure – which is supported by the tendency of the cyclopentadienylidene residue to aromatize – in fulvenoid phosphacyclohexadienes than is indicated in structure *(2)*.

Received: April 19th, 1966 [Z 205b IE]
German version: Angew. Chem. *78*, 598 (1966)

[1] *G. Märkl*, Angew. Chem. *78*, 598 (1966); Angew. Chem. internat. Edit. *5*, 588 (1966).

## A New Synthesis of the Bullvalene System

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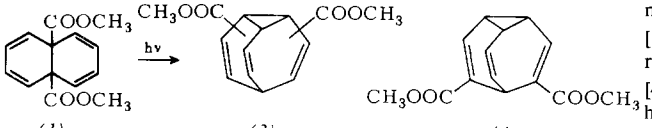
Thermolysis at 80–90 °C of dimethyl *cis*-9,10-dihydronaphthalene-9,10-dicarboxylate *(1)* [1] produces a complex mixture of isomeric 9,10-dihydronaphthalenedicarboxylic esters, but so far there has been no reliable indication for the occurrence of a cyclodecapentaene intermediate during this reaction. We have now examined the photochemical behavior of *(1)* and of *cis*-9,10-dihydronaphthalene-9,10-dicarboxylic anhydride *(2)* [1].

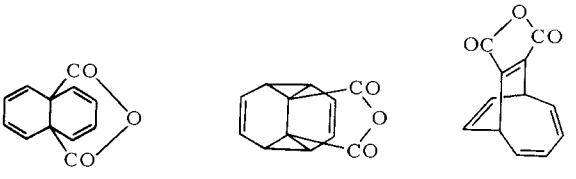
Irradiation of a solution of *(1)* in methanol with a low-pressure mercury vapor lamp [2] produced, in addition to dimethyl 2,6-naphthalenedicarboxylate and a few other products which could not be isolated in pure form, an isomer of m.p. 135–136 °C in 10 % yield. The ultraviolet spectrum of this compound contains only end absorptions with shoulders at 222 ($\varepsilon$ = 8800) and 245 m$\mu$ (6300) in $CH_3OH$. The NMR spectrum varies with temperature, indicating that the molecule has a fluctuating structure.




*(1)* *(3)* *(4)*

At 30 °C the NMR spectrum contains only a sharp singlet at $\tau$ = 6.3 and two very broad bands at $\tau$ = 4.3 and 6.4 (half-width about 100 cps each) in relative intensities of 6:4:4. For maximum resolution, cooling to −50 °C was necessary. Here, instead of the broad bands, a symmetrical signal at $\tau$ = 2.75 (two olefinic protons), a broadened doublet centered at $\tau$ = 4.08 (two more olefinic protons), a broadened doublet at $\tau$ = 5.78 (approx. 0.8 protons), a multiplet centered at $\tau$ = 6.60 (approx. 0.7 protons), and an only partially resolved signal centered at $\tau$ = 7.35 (approx. 2.5 protons) are observed. In addition, the sharp signal at $\tau$ = 6.20, which can be assigned to the six methyl protons of the ester groups, remains almost unaltered by cooling to −50 °C. At higher temperatures all of the signals coalesce, with the exception of the singlet for the methyl protons, first to give the two broad bands observed at room temperature and then (above 55 °C) to a single signal at $\tau$ = 5.25. The half-width of this signal at 100 °C is 4.5 cps. This dependence of the spectrum on temperature indicates the bullvalene structure *(3)* for this isomer. The intensities of the signals in the low-temperature spectrum reveal that of the twelve possible positional isomers of dimethyl bullvalenedicarboxylate, only those (at the most four) with the substituents on the unsaturated carbon atoms can be present in our product. By analogy to the analysis of the spectra of methyl bullvalenecarboxylate [3] and of two disubstituted bullvalene derivatives [4], it can be deduced that the isomer *(4)* predominates in the equilibrium mixture (minimum content 75 %).

On irradiation in ether with a low-pressure Hg lamp, *cis*-9,10-dihydronaphthalenedicarboxylic anhydride is transformed mainly into two isomeric anhydrides (A and B). Compound A has so far been isolated only in about 90 % purity. Its very simple NMR spectrum – a single signal at $\tau$ = 5.38 at 30 °C – proves it to be bullvalenedicarboxylic anhydride. This structure is also supported by the fact that reaction of A with methanolic hydrochloric acid and afterwards with diazomethane produces dimethyl bullvalenedicarboxylate *(3)*. The isomer B of m.p. 182–183 °C [ultraviolet spectrum with $\lambda_{max}$ at 255 m$\mu$ ($\varepsilon$ = 9100) and a shoulder at 310 m$\mu$ ($\varepsilon$ = 1400) in $CH_3OH$] gives an NMR spectrum with a doublet at $\tau$ = 2.47 (2 protons), a symmetrical multiplet centered at $\tau$ = 4.22 (4 protons), and a complex multiplet at $\tau$ = 6.35 (2 protons). Since the three absorptions can be ascribed to four sets of two equivalent protons, the molecular skeleton of B must be symmetrical. Judging from the multiplicity of the signals, B probably has the bicyclo-[4.2.2]decatetraene structure *(5)*; final proof of the constitution is yet to be obtained.




*(2)* *(6)* *(5)*

Compound *(5)* may be formed by a photochemically induced isomerization (4+4 cycloaddition [5]) of *(2)* to the tetracyclic system *(6)* followed by a retro-diene rearrangement of the latter [6].

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German version: Angew. Chem. *78*, 599 (1966)

[1] *E. Vogel, W. Meckel*, and *W. Grimme*, Angew. Chem. *76*, 786 (1964); Angew. Chem. internat. Edit. *3*, 634 (1964).

[2] Model NK 3/12 from Messrs. Quarzlampen-Gesellschaft mbH., Hanau (Germany).

[3] *G. Schröder, J. F. M. Oth*, and *R. Merényi*, unpublished results.

[4] *J. F. M. Oth, R. Merényi, G. Engel*, and *G. Schröder*, Tetrahedron Letters, in press.

[5] Cf. the selection rule for synchronous cycloadditions derived quantum-mechanically by *R. Hoffmann* and *R. B. Woodward*, J. Amer. chem. Soc. *87*, 1046 (1965).

[6] After completion of this work we were informed that *W. von E. Doering* and co-workers have photo-isomerized *cis*-9,10-dihydronaphthalene to bullvalene.

## Structure of an Odd Nucleoside from Serine-Specific Transfer Ribonucleic Acid [1]

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The odd nucleoside iPA [2] has been found immediately adjacent to the probable anticodon of the serine-specific tRNA, the nucleotide sequence of which has been elucidated recently [3]. In five solvent systems iPA has Rf = 0.8 to 0.9; it has an adenosine-like ultraviolet spectrum ($\lambda_{max}$ = 265 and 269 m$\mu$ at pH 2 and pH 7–12, respectively [4]. By treatment of iPA with acid (1 N HCl, 30 min, 100 °C) two compounds, A and B, are formed (Rf = 0.57 and 0.73, respectively, in n-butanol/$H_2O$/conc. $NH_4OH$, 86:14:5). In

the following, experiments are described which prove iPA to be *N*(6)-(γ,γ-dimethylallyl)adenosine *(1)*.

The high-resolution mass spectrum of iPA[5] showed its elemental composition to be $C_{15}H_{21}N_5O_4$. The abundance of ions containing five nitrogen atoms and no oxygen, particularly $C_5H_5N_5$ and $C_{10}H_{13}N_5$, indicated the presence of a substituted adenine pentoside. Nitrogen-free ions containing four oxygen atoms, particularly $C_5H_9O_4$, show that all of the oxygen atoms are in the sugar moiety. It follows that iPA is an adenosine derivative substituted by five carbon atoms. The presence of ions of the type $C_nH_mN$ up to $(C_5H_9NH)^+$ indicates an *N*(6)-$C_5$-alkenyl or cyclopentyl adenine derivative, which can eliminate all 5 carbon atoms on electron impact. A distinction between the two could be made by consideration of the fragments formed from the $C_{10}H_{13}N_5$ ion, which represents the free adenine derivative formed[6] on electron impact.

The low abundance of a $C_8H_{8\text{ or }9}N_5$ ion as contrasted to that of $N_5$-ions containing 6,7, or 9 carbon atoms implies that loss of two carbon atoms (as $C_2H_5$ or $C_2H_4$) from the side chain is much more difficult than the loss of one, three, or more carbon atoms. This behavior excludes a cyclopentyl substituent and suggests an isopentenyl group. The position of the double bond was clarified by NMR spectroscopy[7].

The spectrum shows the signals of the two aromatic adenosine hydrogens unchanged at 8.1 and 8.3 ppm (each of relative intensity 1). The signal at 8.1 ppm is superposed by the resonance of *one* amidine hydrogen, which exchanges slowly with deuterium (relative intensity 1). It therefore may be concluded that this nitrogen (at the 6-position) carries an additional substituent, *i.e.* the isopentenyl group. The signals of the 1′- and 5′-hydrogens of the ribose moiety appear at 5.94 ppm (intensity 1) and 3.84 ppm (intensity 2), respectively, as they do in adenosine. The region between 4.1 and 5.6 ppm cannot be analysed because of strong absorption by the solvent. A sharp signal at 1.73 ppm (intensity 6) proves the presence of a 2,2-dimethylvinyl group in the isopentenyl side chain.

The acid conversion product A has the composition $C_{10}H_{13}N_5$ according to mass spectrometry. The difference in abundance of the $C,H,N_5$ ions in this spectrum as compared to that of iPA, particularly the lower abundance of $(C_5H_5N_5)^+$ in the former, suggests the absence of an open-chain substituent attached to N(6) only. Acid-catalysed cyclization with the adenine ring would account for this product. The product B has an elemental composition $C_{10}H_{15}N_5O$ and thus contains one molecule of water more than the base of the iPA. The high abundance of a $C_3H_7O^-$ ion requires hydration of the double bond to produce a $C(OH)(CH_3)_2$ grouping; this is also corroborated by ions ($C_9H_{12}N_5O$ and $C_7H_8N_5$) representing the loss of a methyl- or dimethylcarbinol group.

Simultaneously with this work, iPA was isolated from unfractionated tRNA, elucidated, and synthesized[8].

It is interesting to note that the plant growth hormone zeatin is an *N*(6)-(γ-methyl-γ-hydroxymethylallyl)adenine[9] and that *N*(6)-(γ,γ-dimethylallyl)adenine also shows growth promoting activity[10].

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German version: Angew. Chem. *78*, 600 (1966)

[1] Communication X on Serine-specific Transfer Ribonucleic Acids. – Communication IX: *G. H. Zachau, D. Dütting*, and *H. Feldmann* in: Structure and Function of Genetic Elements. Symposium of the Federation of European Biochemical Societies, Warsaw 1966. Academic Press, in press.

[2] Abbreviations: tRNA, transfer ribonucleic acid; iPA, *N*(6)-isopentenyladenosine or *N*(6)-(γ,γ-dimethylallyl)adenosine.

[3] *H. G. Zachau, D. Dütting*, and *H. Feldmann*, Angew. Chem. *78*, 392 (1966); Angew. Chem. internat. Edit. *5*, 422 (1966).

[4] Further details on iPA: *H. Feldmann, D. Dütting*, and *H. G. Zachau*, to be published.

[5] The spectrum was obtained by vaporizing part of the eluate from a paper electropherogram containing about 10–20 μg iPA directly into the ion source of a CEC 21–110 double-focusing mass spectrometer; *K. Biemann, P. Bommer*, and *D. Desiderio*, Tetrahedron Letters *1964*, 1725.

[6] *K. Biemann* and *J. A. McCloskey*, J. Amer. chem. Soc. *84*, 2005 (1962).

[7] The spectrum was obtained from 300 μg iPA in $D_2O$ with an A-60 Varian-Spectrometer connected to a C-1024 Time Averaging Computer.

[8] *R. H. Hall, M. J. Robins, L. Stasiuk*, and *R. Thedford*, J. Amer. chem. Soc., in press.

[9] *D. S. Letham, J. S. Shannon*, and *I. R. McDonald*, Proc. chem. Soc. (London) *1964*, 230.

[10] *H. Q. Hamzi* and *F. Skoog*, Proc. nat. Acad. Sci. U.S.A. *51*, *76* (1964).

## On the Secondary Structure of Soluble Ribonucleic Acids

By Dipl.-Chem. H. Doepner, Dr. H. Seidel, and Prof. Dr. F. Cramer

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*N*-Oxidation of adenosine units in polynucleotides with monoperoxyphthalic acid at pH 7.0 is inhibited by base pairing, a fact that can be used[1] to obtain information on the secondary structure of s-RNA[2]. We have applied this method to RNA from various sources isolated by different methods. s-RNA from brewer's yeast (AMP 19.8 %, UMP, 24.5 %, GMP 28.2 %, CMP 27.5 %, and terminal A 47 % of the theoretical value) and s-RNA from *Escherichia coli* B (AMP 20.5 %, UMP 18.2 %, GMP 30.2 %, CMP 31.1 %, and terminal A 34.0 % of the theoretical value) were examined in the native state and after heat denaturation and cooling. The results were interpreted as described previously[1]. The quotient $\varepsilon_{232\ m\mu}/\varepsilon_{259\ m\mu}$ served as a measure for the degree of oxidation. The average content of oxidized AMP units per molecule was determined from this quotient by means of a

| | s-RNA from brewer's yeast | | *E. coli* B | |
|---|---|---|---|---|
| | native | heated and cooled | native | heated and cooled |
| Final degree of oxidation ($\varepsilon_{232}/\varepsilon_{259}$) | 0.825 | 1.080 | 0.910 | 1.025 |
| Av. no. of AMP units oxidized per molecule | 2.68 | 4.93 | 3.41 | 4.44 |
| Av. no. of nucleotide units per molecule in single-strand regions | 13.54 (18 %) | 24.93 (32 %) | 16.64 (23 %) | 21.67 (30 %) |
| Av. no. of nucleotides per molecule | 77 | 77 | 73 | 73 |
| Av. no. of base pairs per molecule | 73–17<br>2<br>31.5 | 77–25<br>2<br>26 | 73–22<br>2<br>28 | 77–14<br>2<br>25.5 |
| Hyperchromicity of the untreated s-RNA (0.4 M phosphate; 0.01 M $Mg^{2+}$) | 35 % | 19 % | 25 % | 19 % |

calibration curve. By addition of the remainder of the bases in the ratios determined by analysis, the average total number of nucleotides present per molecule in single-strand regions was then derived.

The low oxidizability of s-RNA from brewer's yeast compared to that of the s-RNA from *E. coli* B is probably due to its higher content of UMP and is in accordance with its stronger hyperchromicity [2]. If s-RNA is heated for a prolonged period above its "melting temperature" $T_m$ [2] and then gradually cooled, the oxidizability of both preparations is significantly higher; the hyperchromicity also decreases with this treatment.

Subtraction of the average number of nucleotide units present per molecule in the single-strand regions from the average total number of nucleotides per molecule [3] gives the number of nucleotides occurring in double-strand regions (and hence the number of paired bases), which when plotted against the values for the hyperchromicity gives an almost linear dependence between about 15 and 40 % hyperchromicity.

Data for the *N*-oxidizability and hyperchromicity of s-RNA from baker's yeast obtained previously under different conditions [1] exhibit this same dependence within the limits of error. Thus, a direct relationship between the hyperchromicity of s-RNA and the degree of base pairing is established. The latter can be determined by means of *N*-oxidation.

s-RNA has presumably a variable secondary structure which depends strongly upon the $Mg^{2+}$ concentration and perhaps on other factors as well. A means is now available for determining the extent of base pairing even with minute amounts of substance by measurements of hyperchromicity.

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German version: Angew. Chem. *78*, 601 (1966)

[1] *H. Seidel* and *F. Cramer*, Biochim. Biophysica Acta *108*, 367 (1965).

[2] Abbreviations: A = adenosine. – s-RNA = soluble ribonucleic acid. – AMP = adenosine monophosphate. – UMP = uridine monophosphate. – CMP = cytidine monophosphate. – GMP = guanosine monophosphate. – $T_m$ = the temperature at half the total extinction increment. – Hyperchromicity is the increase in extinction on thermal breakdown of ordered macromolecular structures.

[3] *G. L. Brown* and *G. Zubay*, J. molec. Biol. *2*, 287 (1960); *J. E. M. Midgley*, Biochim. biophysica Acta *108*, 340 (1965); *T. Lindahl, B. B. Henley*, and *J. R. Fresco*, J. Amer. chem. Soc. *87*, 4961 (1965).

## Protein Synthesis in Rat Liver Chromatin and Chromatin Fractions [1]

By Doz. C. E. Sekeris, W. Schmid, Dr. D. Gallwitz, and Dr. I. Lukacs

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In addition to "classical" protein biosynthesis on messenger RNA and ribosomes, which also occurs in cell nuclei [2], another type of protein synthesis seems to take place in cell nuclei. We have found that chromatin isolated from rat liver cell nuclei can incorporate [$^{14}$C]leucine into protein. The new protein-synthesizing system has the following characteristics (cf. Table):

1. The incorporation of radioactively labelled amino acid into the protein is resistant to attack by ribonuclease.

2. The protein synthesis is independent of the addition of amino-acid activating enzymes.

3. The protein synthesis is not stimulated by messenger RNA.

4. The system loses some of its activity on incubation with deoxyribonuclease.

The chromatin was isolated from rat liver cell nuclei according to *Weiss* [4]. The preparation (aggregate enzyme [4]) incorporates ribonucleoside triphosphates into RNA; it consists of DNA, RNA, and protein in weight ratios of 1:2:10–15. The preparation could be freed from the major fraction (about 90 %) of its protein by treatment with 0.2 % sodium deoxycholate in 0.065 M tris buffer at pH 7.9. The sediment obtained after low-speed centrifugation contained the whole activity and had DNA:RNA:protein ratios of 1:0.4:1.5. It was suspended in 0.065 M tris buffer at pH 7.9 and shaken for 30 min at 37 °C with 100 µg/ml of deoxyribonuclease and 2 µM magnesium chloride. During this treatment, the clear glassy fibrous structure of the preparation disappears and a white powder is obtained. Centrifugation then separates the suspension into a white precipitate and a cloudy supernatant. The precipitate contains all of the activity; the supernatant, which contains liberated deoxynucleotide, RNA, and protein, inhibits protein synthesis, but the nature of the inhibitor is not yet known. It is thermally stable and has a molecular weight of 3000 to 15000. Treatment of the precipitate with ribonuclease (100 µg/ml) for 20 min at 37 °C removes proteins and RNA without loss of activity. The DNA:RNA:protein ratio after this treatment is 2:1.5:6.5. Partial digestion with trypsin solubilizes part of the enzyme in an active state; it occurs in the supernatant after centrifugation.

| | Incorporation of [$^{14}$C]leucine [counts/min × mg of protein] |
|---|---|
| Chromatin alone [a] | 1840 |
| Chromatin + ribonuclease (50 γ/ml) | 1945 |
| Chromatin + 105000 g supernatant (2 mg of protein) | 1795 |
| Chromatin + 50 γ of messenger RNA from rat liver | 1825 |
| Chromatin + deoxyribonuclease (100 γ/ml) | 525 |

[a] Chromatin (1 mg of protein, preparation obtained after treatment with deoxycholate, see below), 7.5 µmoles of KCl, 3 µmoles of $MgCl_2$, 80 µmoles of tris-(2-amino-2-hydroxymethyl-1,3-propanediol), 0.15 µmole of ATP, 150 µmoles of GTP, 0.5 µmole of creatine phosphate, 10 γ of creatine phosphokinase, 0.025 µmole each of 20 amino acids, and 0.1 µCi of [$^{14}$C]leucine with a specific activity of 150 mCi/mmole. Volume: 0.5 ml. Incubation time: 60 min at 37 °C. The degree of incorporation was measured as described in [3].

The protein synthesis is inhibited by histones from rat liver cell nuclei (up to 90 % inhibition with 1 mg/ml), by protamine sulfate (up to 98 % inhibition with 1 mg/ml), and by antibiotics such as chloromycetin (98 % with 1 mg/ml) and puromycin (80 % with 0.4 mg/ml). It was shown by the fingerprint method that leucine is incorporated into peptides. Between 10 and 15 % of the incorporated radioactivity is soluble in 0.2 N hydrochloric acid. The newly synthesized protein is not liberated from the enzyme complex. Only a small amount of the radioactive protein that is not extractable with HCl dissolves in 8 M urea.

The biological significance of this RNA-independent protein synthesis is still unknown. Part of the protein formed is probably structural protein of the chromatin, but the possibility of a regulatory function must also be considered. The fact that the protein synthesis on chromatin is influenced by hormonally active steroids and that it is promoted by partial hepatectomy support the latter suggestion.

Received: April 29th, 1966 [Z 224 IE]
German version: Angew. Chem. *78*, 601 (1966)

[1] Protein Synthesis in Cell Nuclei, Part 2. – Part 1: *C. E. Sekeris, W. Schmid, D. Gallwitz*, and *S. Lucas*, Life Sciences *5*, 969 (1966).

[2] *J. H. Frenster, V. G. Allrey*, and *A. E. Mirsky*, Proc. nat. Acad. Sci. U.S.A. *46*, 432 (1960); *T. Wang*, Biochim. biophysica Acta *49*, 108 (1961).

[3] *N. Lang* and *C. E. Sekeris*, Hoppe-Seylers Z. physiol. Chem. *339*, 238 (1965).

[4] *S. B. Weiss*, Proc. nat. Acad. Sci. U.S.A. *46*, 1020 (1960).

## Peptide and Azapeptide Syntheses with α-N-[1-(1,2,4-Triazolyl)carbonyl]amino Esters

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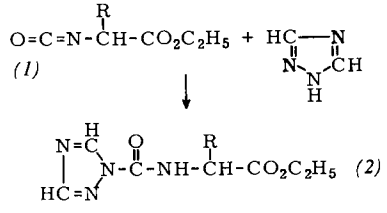
der Freien Universität Berlin (Germany)

Equimolar amounts of 1,2,4-triazole and ethyl α-isocyanato esters *(1)*[1] react exothermally to give the previously unknown ethyl α-*N*-[1-(1,2,4-triazolyl)carbonyl]amino esters *(2)*. The reaction is induced with the less reactive isocyanates *(1c)* and *(1d)* by heating to 90 °C.

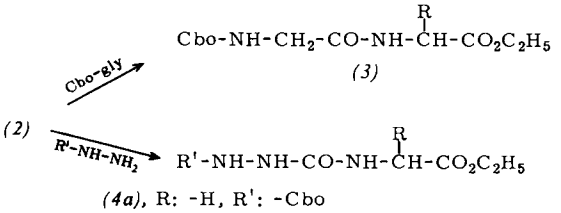


*(1)* *(2)*

| | R | Yield [%] | M.p. [°C] | $[\alpha]_D^{25}$ (in ethyl acetate) |
|---|---|---|---|---|
| *(2a)* | H | 84 | 109–111 | |
| *(2b)*, DL-form | $CH_3$ | 79 | 62 | |
| *(2c)*, L-form | $CH_2-C_6H_5$ | 95 | 103 | −15.0 ° (c = 1) |
| *(2d)*, L-form | $CH_2-CH(CH_3)_2$ | 75 | 65–67 | −6.1 ° (c = 1) |

Compounds *(2a)–(2d)* are colorless and crystallize well from dry ethyl acetate/petroleum ether or from dry ether/petroleum ether. The point of substitution in the triazole ring follows from the NMR spectra (measured in $CCl_4$) of *(2b)* and *(2d)*: in agreement with investigations of *Staab* with *N*-acetyl 1,2,4-triazole[2], the observation of two proton signals of equal intensities – at 2.13 and 1.17 τ for *(2b)* and at 2.15 and 1.20 τ for *(2d)* – established the unsymmetrical structure *(2)* with non-equivalent triazole protons.

Like the corresponding imidazole derivatives[3], *(2a)–(2d)* can be used for peptide syntheses. On heating them with equimolar amounts of carbobenzoxy(Cbo-)glycine for 9–12 h at 90–110 °C, carbon dioxide is evolved and triazole is liberated, producing the Cbo-dipeptide esters *(3a)–(3d)*, which can be purified by precipitation from ethanol/water.



*(3)*

*(4a)*, R: -H, R': -Cbo

*(4b)*, R: $-CH_2-CH(CH_3)_2$, R': Cbo-NH-$CH_2$-CO-

| | R | Yield [%] | M.p. [°C] |
|---|---|---|---|
| *(3a)* | H | 72 | 80–81 |
| *(3b)*, DL-form | $CH_3$ | 59 | 56–58 |
| *(3c)*, L-form | $CH_2-C_6H_5$ | 87 | oil |
| *(3d)*, L-form | $CH_2-CH(CH_3)_2$ | 76 | oil |

The triazole derivatives can also be used to prepare azapeptides[4] by their reaction with hydrazides. For example, when *(2a)* is refluxed for 3 hr with Cbo-hydrazine in anhydrous ethyl acetate and when *(2d)* is heated with Cbo-glycine hydrazide to 110 °C without solvent, each in equimolar amounts, aminolytic elimination of triazole occurs leading to the peptide analogues *(4a)*, m.p. 139–141 °C, and *(4b)*, m.p. 79–82 °C, in yields of 15 and 55 %, respectively.

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[*] Thanks are expressed to the Deutsche Forschungsgemeinschaft for support of this work, and to Dr. *Ch. Arndt* (Institut für Organische Chemie, Technische Universität Berlin) for measuring the NMR spectra.

[1] *W. Siefken*, Liebigs Ann. Chem. *562*, 105 (1949); *St. Goldschmidt* and *M. Wick*, *ibid. 575*, 217 (1952).

[2] *H. A. Staab*, Angew. Chem. *76*, 407 (1962); Angew. Chem. internat. Edit. *1*, 351 (1962).

[3] *J. Gante*, Angew. Chem. *78*, 334 (1966); Angew. Chem. internat. Edit. *5*, 315 (1966).

[4] On the concept of "azapeptides", see *J. Gante*, Chem. Ber. *98*, 540 (1965).

## Conformational Enantiomerism of a Derivative of Cyclotriveratrylene [1]

By Prof. Dr. A. Lüttringhaus and cand. chem. K. C. Peters

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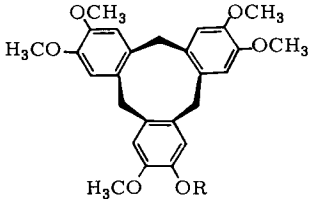
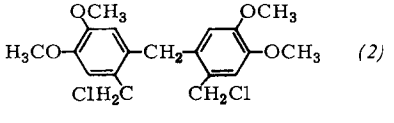
der Universität Freiburg (Germany)

The major product formed by acid-catalysed condensation of veratrole with formaldehyde was found by *Lindsey*[2] to be the nine-membered cyclic compound "cyclotriveratrylene" *(1)*. He also isolated the bischloromethyl derivative *(2)* as an intermediate of the condensation in hydrochloric acid. We have confirmed all of *Lindsey*'s results and also the findings of *Miller* and *Gesner*[3] on the constitution and conformation of *(1)*.

Replacement of one of the methoxy groups in *(1)* by a different substituent is expected to give a molecule, *e.g. (3)*, exhibiting conformational enantiomerism. We condensed *(2)* with *O*-benzylguaiacol in glacial acetic acid for 8 h at 120 °C and obtained *(3)* in 45 % yield.



*(1)*, R: $-CH_3$
*(3)*, R: $-CH_2-C_6H_5$



*(2)*

Compound *(3)*, purified by column chromatography on silica with a 1:1 mixture of benzene and ether, was homogeneous in thin-layer chromatography. 2-Benzyloxy-3,7,8,12,13-pentamethoxytribenzo[*a,d,g*]cyclo-1,4,7-nonatriene *(3)* crystallizes from benzene/petroleum ether (3:1 v/v) in clusters, m.p. 160–162 °C. Its ultraviolet absorption maxima lie at 232 (log ε = 4.51) and 291 mμ (4.01). Its NMR spectrum (0.3 M in $CDCl_3$; Varian A 60 instrument) shows aromatic proton signals at τ = 2.55 (m,5) and 3.02–3.14 (m,6), a benzyloxy methylene proton signal at 4.82 (s,2), methoxy proton signals at τ = 6.12 (s,12), and 6.26 (s,3); the methylene protons give rise to an AB quadruplet with doublets at τ = 5.26 and 6.48 of coupling constants J = 14 cps each. It has been possible partially to resolve *(3)* in benzene on "cellulose-$2^1/_2$-acetate"[4] into *stable* optical antipodes. A single passage through a column 120 cm long and 2 cm in

diameter afforded two fractions with specific optical rotations $[\alpha]_{405}^{22} = +4.3°$ and $-2.5°$. After a second passage the rotations were $[\alpha]_{405}^{22} = +7.5°$ and $-5°$ (1 % in $CHCl_3$).

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German version: Angew. Chem. 78, 603 (1966)

[1] Conformational Enantiomerism, Part 2. – Part 1: *A. Lüttringhaus, U. Hess,* and *H.-J. Rosenbaum,* Z. Naturforsch., in press.

[2] *A. S. Lindsey,* J. chem. Soc. (London) *1965*, 1685.

[3] *B. Miller* and *B. D. Gesner,* Tetrahedron Letters *1965*, 3351.

[4] *A. Lüttringhaus* and *G. Eyring,* unpublished results; *G. Eyring,* Dissertation, Universität Freiburg, 1961.

## Synthesis of $\Delta^{3a,5a}$-Bicyclo[3.2.0]heptene and $\Delta^{4a,6a}$-Bicyclo[4.2.0]octene

By Prof. Dr. W. Kirmse and Dipl.-Chem. K. H. Pook

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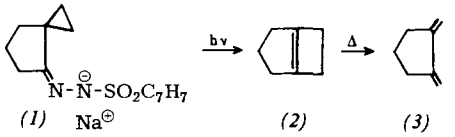
We have applied the rearrangement of cyclopropylcarbenes – a reaction that has already been extensively examined[1] – to compounds with spiran structures.

The *p*-toluenesulfonylhydrazone (m.p. 159–160 °C) of spiro[2.4]heptan-4-one[2] was prepared. Photolysis[*] of the sodium salt *(1)* of the tosylhydrazone in diethylene glycol dimethyl ether (diglyme) produced in 70 % yield a hydrocarbon $C_7H_{10}$, b.p. 118–119 °C, $n_D^{21.5} = 1.4775$, which was ascribed the structure of $\Delta^{3a,5}{}_a$-bicyclo[3.2.0]heptene *(2)*. Thermolysis of *(1)* by addition to diglyme at 160 °C afforded an approximately equimolar mixture of *(2)* and 1,2-dimethylenecyclopentane *(3)*[3] in a total yield of 65 %. Control experiments showed that *(2)* is transformed into *(3)* under the conditions of the thermolysis.

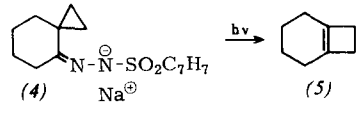



*(1)* *(2)* *(3)*

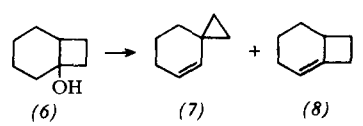
Compound *(2)* has no C=C absorption in the infrared; however, it does exhibit a Raman band at 1677 $cm^{-1}$[4] (1,2-dimethylcyclobutene: 1689 $cm^{-1}$). Its NMR spectrum contains multiplets at 7.48 τ (4 H) and 7.7–8.1 τ (6 H) [for comparison, cyclobutene $CH_2$: 7.46 τ; cyclopentene $CH_2$: 7.72 and 8.10 τ].

Treatment of *(2)* with NOCl in acetone produces a blue unstable nitrosochloride. Hydrogenation of *(2)* with Adams catalyst leads to bicyclo[3.2.0]heptane. Ozonolysis of *(2)* affords cycloheptane-1,4-dione.

$\Delta^{4a,6a}$-Bicyclo[4.2.0]octene *(5)* was obtained analogously in 65 % yield from spiro[2.5]octan-4-one[5] *via* the sodium salt *(4)* of its tosylhydrazone, m.p. 173–174 °C.




*(4)* *(5)*




*(6)* *(7)* *(8)*

The hydrocarbon *(5)* cannot be made from bicyclo[4.2.0]-octan-4a-ol *(6)*: pyrolysis of the acetate of *(6)* produces mainly spiro[2.5]hept-4-ene *(7)* together with a little $\Delta^{4,4a}$-bicyclo[4.2.0]octene *(8)* [5a].

The absence of spiro[2.4]hept-4-ene and spiro[2.5]oct-4-ene *(7)* respectively from the products of thermolysis of *(1)* and *(4)*[6] shows that the cyclopropylcarbene rearrangement is preferred to an intramolecular hydrogen shift[7]. The main products obtained from spiro[m.n]alkanone tosylhydrazones with m,n ≥ 3 were spiroalkenes[8].

Received: April 18th, 1966 [Z 215 IE]
German version: Angew. Chem. 78, 603 (1966)

[1] *L. Friedmann* and *H. Shechter,* J. Amer. chem. Soc. *82*, 1002 (1960); *J. A. Smith, H. Shechter, J. Bayless,* and *L. Friedman, ibid. 87*, 659 (1965); *P. K. Freeman* and *D. G. Kuper,* J. org. Chemistry *30*, 1047 (1965); *J. W. Wilt, J. M. Kosturik,* and *R. C. Orlowski, ibid. 30*, 1052 (1965); *W. Kirmse* and *K. H. Pook,* Chem. Ber. *98*, 4022 (1965).

[2] *R. Mayer* and *H. J. Schubert,* Chem. Ber. *91*, 768 (1958); *D. E. Applequist* and *J. A. Landgrebe,* J. Amer. chem. Soc. *86*, 1543 (1964).

[*] Lamp: Q 81 (Hanau); time: 4 hours.

[3] *A. T. Blomquist, J. Wolinsky, Y. C. Meinwald,* and *D. T. Longone,* J. Amer. chem. Soc. *78*, 6057 (1956).

[4] We thank Dr. *B. Schrader,* Dortmund (Germany), for measuring the Raman spectrum.

[5] *M. Hanack* and *H. J. Schneider,* LiebigsAnn.Chem. *686*, 8 (1965).

[5a] *M. Hanack,* Angew. Chem. 77, 624 (1965); Angew. Chem. internat. Edit. *4*, 603 (1965); and personal communication.

[6] It could be shown by comparisons with authentic samples that no spiro[2.4]heptane or spiro[2.5]octane was produced from the reaction products by catalytic hydrogenation.

[7] Intramolecular hydrogen shift to form olefins is one of the main stabilization reactions of alkyl- and dialkylcarbenes; cf. *W. Kirmse*: Carbene Chemistry. Academic Press, New York 1964, Chapter 3.

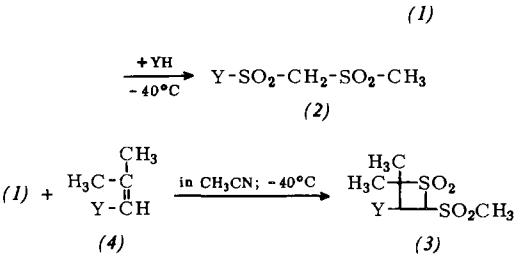
[8] *A. P. Krapcho* u. *R. Donn,* J. org. Chemistry *30*, 641 (1965).

## A Sulfene Stable at −40 °C

By Prof. Dr. G. Opitz, Dr. M. Kleeman, cand.-chem. D. Bücher, Dipl.-Chem. G. Walz, and cand.-chem. K. Rieth

Chemisches Institut der Universität Tübingen (Germany)

If a solution of 0.15 mole of triethylamine in 150 ml of acetonitrile is treated with 0.10 mole of methanesulfonyl chloride at −40 °C within 30 min, pure triethylammonium chloride is precipitated (99 % after 60 min). If dimethylamine, pyrrolidine, aniline, or *p*-nitrophenol is added to the colorless filtrate, the corresponding methanesulfonylmethanesulfonic acid derivative *(2)* is obtained. The NMR spectrum of product *(2d)* in perdeuterioacetone shows 2 H (*ortho* to $NO_2$) as a doublet (J = 4.5 cps) at 1.6 τ, 2 H (*meta* to $NO_2$) as a doublet (J = 4.5 cps) at 2.3 τ, 2 H ($CH_2$) as a singlet at 4.5 τ, and 3 H ($CH_3$) as a singlet at 6.7 τ. Use of YH = *p*-$O_2N$-$C_6H_4$-OD leads to *p*-$O_2N$-$C_6H_4$-O-$SO_2$-CHD-$SO_2CH_3$ which undergoes rapid D/H exchange with $H_2O$. Thus a disulfene structure with two methylene groups, analogous to diketene, is excluded for the elimination product *(1)*.




| | Y | M.p. [°C] | Yield [%] |
|---|---|---|---|
| *(2a)* | $(CH_3)_2N$ | 113–114 | 60 |
| *(2b)* | $(CH_2)_4N$ | 176 | 62 |
| *(2c)* | $C_6H_5NH$ | 155–156 | 63 |
| *(2d)* | *p*-$O_2N$–$C_6H_4$–O | 123–124 | 61 |
| *(3a)* | $(CH_3)_2N$ | 114–116 | 61 |
| *(3b)* | $(CH_2)_4N$ | 138–139 | 63 [a] |

[a] 35 % yield on use of methanesulfonic anhydride instead of methanesulfonyl chloride.

In favor of the presence of the methanesulfonylsulfone *(1)* are the smooth 1,2-1′,2′-cycloadditions to enamines *(4)*, yielding compounds *(3)*, and the fact that products *(2)* and *(3)* are formed also on treatment of methanesulfonylmethanesulfonyl chloride[1]/triethylamine with YH or an enamine in tetrahydrofuran at 20 °C.

The H-NMR signal of compound *(3a)* in $CHCl_3$ shows signals at 4.6 τ (d, J = 8 cps, $SO_2CHSO_2$), 6.6 (d, J = 8 cps, NCH), 6.7 (s, $SO_2CH_3$), 7.6 [s, $N(CH_3)_2$], and 8.35 τ [s, $C(CH_3)_2$] in the ratio 1:1:3:6:6. The doublets for the ring protons in compound *(3b)* appear in acetone at 4.3 and 6.6 τ, but in pyridine the former signal is shifted to 3.3 τ; we have observed similar shifts to lower field for other 1,3-disulfones. Quaternization of *(3a)* with methyl iodide and heating of the salt with aqueous-alcoholic sodium hydroxide gives isopropyl methanesulfonylmethyl sulfone (m.p. 101–102 °C).

Capture experiments with *N*-isobutenylpyrrolidine show that compound *(1)* is stable for several days in acetonitrile at −40 °C [after 90 hr at −38 °C it gives *(3b)* in 52 % yield], but when warmed it decomposes above about −30 °C with formation of a reddish-brown color. On freeze-drying there remains a colorless powder composed of an adduct of triethylamine and *(1)*, elucidation of whose structure is in progress.

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German version: Angew. Chem. *78*, 604 (1966)

[1] *G. Opitz* and *G. Walz*, unpublished work.

## Preparation of trans,trans- and cis,cis-1,6-Cyclodecadiene from cis,trans-1,5-Cyclodecadiene

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1,3-Cyclooctadiene is formed when 1,5-cyclooctadiene is heated with $Fe(CO)_5$ for 7 hr at 115 °C[1]. Under similar conditions *cis,trans*-1,5-cyclodecadiene *(1)*[2] yields almost exclusively *cis*-1,2-divinylcyclohexane *(2)*. This valence isomerization[3] is appreciably faster than isomerization of the double bonds in compound *(1)*. On ultraviolet irradiation $Fe(CO)_5$ is active as isomerization catalyst even at 20-50 °C[4]. We have therefore irradiated a solution of 3 ml of $Fe(CO)_5$ in 400 g of *(1)* at about 60 °C with a low-pressure Hg lamp (Messrs. Gräntzel, Karlsruhe). The products were *cis,cis-(3)* and *trans,trans*-1,6-cyclodecadiene *(4)*.

| Reaction time [hr] | Conversion [a] of *(1)* [%] | Yield [%] [a] *(3)* | *(4)* | other olefins |
|---|---|---|---|---|
| 0.5 | 21.4 | 84 | 16 | — |
| 1 | 36.3 | 84 | 16 | — |
| 4 | 65.7 | 85.9 | 13.8 | 0.3 |
| 21 | 86.5 | 90.3 | 9.4 | 0.3 [b] |
| 48 | 90.4 | 92.0 | 7.5 | 0.4 [b] |

[a] Conversions and yields determined by gas chromatography (50 m $V_2A$ capillary column, silicone oil DC 200, 120 °C, 1 atm of argon, retention time for *(3)* 12.3 min, for *(4)* 13.4 min).
[b] Two compounds in equimolar amounts.

*(3)*: B.p. 67 °C/11 mm, m.p. 28–28.5 °C (from ethanol) (lit.: 21–22 °C[5], 22 °C[6]), $n_D^{30} = 1.4964$ (lit.: $n_D^{25} = 1.4972$[5]); infrared bands of the *cis*-double bonds at 707 $cm^{-1}$ (s) and 1655 $cm^{-1}$ (m).

*(4)*: B.p. 65 °C/11 mm; $n_D^{30} = 1.4917$; infrared bands of the *trans*-double bonds at 952 and 977 $cm^{-1}$ (s) and 1667 $cm^{-1}$ (m).

The 1,6-position of the double bonds in compounds *(3)* and *(4)* was proved by ozonolysis and oxidation of the ozonide to glutaric acid. The ratio *(3)*:*(4)* was 5:1 after reaction for 1 hour and 12:1 after 48 hours, *i.e.* isomerization of *(4)* to *(3)* accompanies the shift of the double bond. Any *cis,trans*-1,6-cyclodecadiene – as intermediate in the conversion of *(4)* into *(3)* – can occur in the reaction mixture with a concentration of only *ca.* 0.3 %, if at all. This result does not agree with the report by *Dale et al.* that 8.0 % of *cis,trans*-1,6-cyclodecadiene was identified in the *cis,trans*-equilibrium mixture of 1,6-cyclodecadienes (7-hr irradiation of the *cis,cis*-isomer in the presence of diphenyl sulfide at 75 °C).

The isomerization *(1)* → *(3)* can also be effected by reduction of 1 g of an acetylacetonate of a group VIIIb metal in 10 g of diene *(1)* with $Al(C_2H_5)_3$ (1 mole per equivalent of metal acetylacetonate) and heating for 24 hr at about 60 °C.

| Acetylacetonate | Conversion of *(1)* [%] | Yield of *(3)* [%] |
|---|---|---|
| $Ni(C_5H_7O_2)_2$ | 61 | 98 |
| $Pd(C_5H_7O_2)_2$ | 90 | 98 |
| $Co(C_5H_7O_2)_2$ | 84 | 79 |
| $Fe(C_5H_7O_2)_2$ | 73 | 76 |

Isomerization of *(1)* to *(3)* was further observed on partial hydrogenation of *(1)* to cyclodecene (maximally 3 % of *trans*-cyclodecene was formed alongside *cis*-cyclodecene). When 1 mole of hydrogen had been absorbed in presence of Pd/$BaSO_4$ as catalyst, 65 % of cyclodecene, 19 % of cyclodecane, and 16 % of *(3)* (which is difficult to hydrogenate) were identified. Attempts to isomerize *(1)* with various hydrogenation catalysts in the presence of catalytic amounts of hydrogen did not give reproducible results.

Received: April 21st, 1966 [Z 210 IE]
German version: Angew. Chem. *78*, 604 (1966)

[1] *J. E. Arnet* and *R. Pettit*, J. Amer. chem. Soc. *83*, 2954 (1961).
[2] *G. Wilke* and *P. Heimbach*, Angew. Chem. *75*, 10 (1963); Angew. Chem. internat. Edit. *2*, 113 (1963).
[3] *P. Heimbach*, Angew. Chem. *76*, 859 (1964); Angew. Chem. internat. Edit. *3*, 702 (1964).
[4] *F. Asinger*, *B. Fell*, and *K. Schrage*, Chem. Ber. *98*, 372 (1965).
[5] *D. J. Cram* and *N. L. Allinger*, J. Amer. chem. Soc. *78*, 2518 (1956).
[6] *J. Dale* and *C. Moussebois*, J. chem. Soc. (London) *1966*, C 264, obtained *(3)* from *(1)* in 95 % yield by the method of *W. O. Haag* and *H. Pines*, J. Amer. chem. Soc. *82*, 387 (1960).

## Hammett Constants of Substituents Containing Phosphorus [1]

By Dr. G. P. Schiemenz

Institut für Organische Chemie
der Universität Kiel (Germany)

Previously σ′-constants[2] for the groups $(C_6H_5)_2P-$, $(C_6H_5)_2P(O)-$, $(C_6H_5)_2P(S)-$, and $(C_6H_5)_2(CH_3)P^{\oplus}-$ were calculated from the half-neutralization potentials (HNP) of *p*-P-substituted dimethylanilines[3,4]. However, owing to lack of a reliable equation only approximate σ-values were obtained from the $pK'_a$ values of the corresponding *p*-P-substituted benzoic acids[5].

Equation (a) was obtained from the $pK'_a$ values of eight reference substances (see table), determined under the same conditions (67 % aq. $CH_3OH$; 0.02 N NaOH), together with the known substituent constants[2], by the method of least squares. With the parameters r = 0.996, s = 0.058, and ρ = 1.278, this is an "excellent"[2] Hammett equation. From it were obtained the σ-values of phosphorus-containing groups assembled in the table.

$$pK'_a = -1.278\,\sigma + 5.27 \quad (a)$$

$$\tilde{\nu} = 18.385\,\sigma + 1621.12 \quad (b)$$

A further method of determining σ is based on the fact that the frequency of the amide I infrared bands of *p*-substituted *N,N*-dimethylbenzamides depends linearly on the Hammett constants of the *para*-substituents. Wave numbers measured for seven reference substances in KBr lead to the "satis-

factory"[2] equation (b) (r = 0.965); of the three σ-values (see table) determined for phosphorus-containing substituents with this equation, those of the *p*-diphenylphosphino and diphenylphosphinyl groups agree well with the constants derived from the $pK'_a$ values of the acids.

Phosphorus behaves throughout as an electron acceptor, the order being phosphonium- > phosphinyl- ≈ thiophosphinyl- > phosphine-phosphorus. $(C_6H_5)_2P(O)$ has $\sigma_{para}$ only slightly greater than $\sigma_{meta}$ = +0.485 determined by alkaline cleavage of 3-(diphenylphosphinyl)benzyltrimethylsilane[6]; thus in this case 3d-orbital participation appears not to be significant. However, the fact that $\sigma_{(C_6H_5)_2P} < \sigma_{(C_6H_5)_2P(O)}$ – as in the phosphine $p$-$(C_6H_5)_2P$–$C_6H_4$-$N(CH_3)_2$[3] – indicates a certain amount of 3p-orbital participation by the phosphine-phosphorus.

| X | *p*-X–$C_6H_4$–COOH | | *p*-X–$C_6H_4$–$CON(CH_3)_2$ | |
|---|---|---|---|---|
| | $pK'_a$ | σ [a] | ν̃ (amide I) [$cm^{-1}$] | σ [a] |
| $NH_2$ | 6.09 | −0.660 | – | −0.660 |
| $N(CH_3)_2$ | – | −0.600 | *ca.* 1610 | −0.600 |
| OH | 5.74 | −0.357 | – | −0.357 |
| $CH_3$ | 5.50 | −0.170 | 1618 | −0.170 |
| H | 5.34 | 0.0 | 1624 | 0.0 |
| Cl | 4.97 | +0.227 | 1626 | +0.227 |
| Br | 4.94 | +0.232 | 1621 | +0.232 |
| CN | 4.38 | +0.628 | 1632 | +0.628 |
| $NO_2$ | 4.35 | +0.778 | 1637 | +0.778 |
| $(C_6H_5)_2P$ | 5.03 | +0.19 | 1625 | +0.21 |
| $(C_6H_5)_2P(S)$ | 4.64 | +0.49 | 1637 | +0.86 |
| $(C_6H_5)_2P(O)$ | 4.63 | +0.50 | 1632 | +0.59 |
| $(C_6H_5)_2(CH_3)P^{\oplus}$ | 3.98 | +1.01 | – | – |
| $(C_6H_5)_2(p\text{-}O_2N\text{–}C_6H_4CH_2)P^{\oplus}$ | 3.86 | +1.10 | – | – |
| O=P [b] | 4.66 | +0.48 | – | – |

[a] σ-Values of phosphorus-free substituents are taken from the literature [2]. [b] In $(p\text{-}HOOC\text{–}C_6H_4)_3PO$.

Received: April 21st, 1966 [Z 207 IE]
German version: Angew. Chem. *78*, 605 (1966)

[1] Aromatic Phosphines with Electron-Attracting Substituents, Part IV; Part III: *G. P. Schiemenz* and *J. Tobe*, Chem. Ber., in press.

[2] *H. H. Jaffé*, Chem. Reviews *53*, 191 (1953).

[3] *G. P. Schiemenz*, Angew. Chem. *78*, 145 (1966), Angew. Chem. internat. Edit. *5*, 129 (1966).

[4] On inclusion of further reference points [$p$-X-$C_6H_4$-$N(CH_3)_2$, X = H: HNP = −608 mV, σ = 0; X = NO: HNP = −595 mV, σ = +0.123; X = $SO_2N(CH_3)_2$: HNP = −481 mV, σ = +0.965 (*R. W. Bott, C. Eaborn*, and *B. M. Rushton*, J. organomet. Chemistry *3*, 448 (1965)] the best equation (r = 0.971, "satisfactory") for calculation of σ′ from the previously given HNP values becomes: $\sigma' = 6.571 \times 10^{-3}$ HNP + 4.095

[5] Calculated with the reaction constant ρ ≡ 1.000 (which is too small for an alcoholic medium [2]) and the measured value $pK'_a(C_6H_5COOH)$ = 5.34 as $-\log K_0$.

[6] *R. W. Bott, B. F. Dowden*, and *C. Eaborn*, J. chem. Soc. (London) *1965*, 4994.

## An Optically Active Carbodiimide

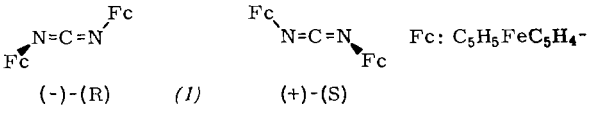
By Prof. K. Schlögl and H. Mechtler[1]

Organisch-Chemisches Institut, Universität Wien (Austria)

Carbodiimides (R–N=C=N–R) have as their sole element of symmetry a $C_2$ axis and therefore possess axial chirality; by analogy to allenes, they should therefore be resolvable into optical antipodes[2].

We have found that *N,N′*-diferrocenylcarbodiimide *(1)* is stable and is therefore suited to attempting racemate resolutions of compounds of this class. We have thus obtained the first sample of an optically active carbodiimide.

The racemic form of *(1)* was prepared from Fc–N=C=O[3] by the method of *Cambell et al.*[4] in 85 % yield in the form of crystals, m.p. 140–145 °C (decomp.). Elemental analyses, a sharp infrared band at 2120 $cm^{-1}$, and the mass spectrum are all in agreement with structure *(1)*. Addition of water to the compound gives *N,N′*-diferrocenylurea, Fc–NHCONH–Fc, m.p. 250 °C (decomp.)[3]; reaction with ethoxide in ethanol produces the isourea derivative Fc–NH–$C(OC_2H_5)$=N–Fc, m.p. 147–150 °C.




(−)-(R) *(1)* (+)-(S)

Partial resolution of the racemate *(1)* was effected by chromatography in benzene on a column (4 m long × 3 cm diam.) of partially acetylated cellulose[5]: 250 mg of *(1)* was passed through the column and seven fractions of approx. 50 ml each were collected. Subsequent purification by thin-layer chromatography on silica gel with benzene gave chemically unchanged (infrared spectrum) dextrorotatory *(1)*, which was enriched in the seventh (last) fraction: $[\alpha]_D^{20} = +4.1 \pm 0.2°$ (c = 0.4 in dry benzene). All the other fractions showed practically no optical activity.

Partial reaction of *(1)* with (+)-(*R*) or (−)-(*S*)-6,6′-dinitrodiphenic acid in anhydrous benzene at 25 °C to form the corresponding acylurea effected kinetic resolution of the racemate. The chemically unchanged carbodiimide *(1)* recovered by preparative thin-layer chromatography after the reactions was optically active: $[\alpha]_D^{20} = -4.8 \pm 0.2°$ (c = 0.3) and $+1.6 \pm 0.1°$ (c = 0.4 in benzene).

It follows from stereochemical considerations of the preferred transition state (stereoselective addition of the carboxyl group from the diphenic acid onto the –N=C= structure) that (+)-*(1)* should have the (*S*)-configuration. Application of a rule derived for allenes[6] leads to the same conclusion.

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[1] This work was supported by the U.S. Government under Contract 61(052)–383.

[2] *L. J. Roll* and *R. Adams*, J. Amer. chem. Soc. *54*, 2494 (1932); *W. C. Schneider, ibid. 72*, 761 (1950).

[3] *K. Schlögl* and *H. Seiler*, Naturwissenschaften *45*, 337 (1958).

[4] *T. W. Campbell, J. J. Monagle*, and *V. S. Foldi*, J. Amer. chem. Soc. *84*, 3673, 4288 (1962).

[5] Average degree of acetylation about 2.5 per glucose unit. We thank Messrs. Deutsche Rhodiaceta AG., Freiburg (Germany) for the sample.

[6] *G. Lowe*, Chem. Commun. *1965*, 411.

## Reaction of Substituted Vinylsulfonium Salts with CH-Acidic Compounds. – A New Route to Polysubstituted Cyclopropanes

By Priv.-Doz. Dr. J. Gosselck, Dipl.-Chem. L. Béress, and Dipl.-Chem. H. Schenk

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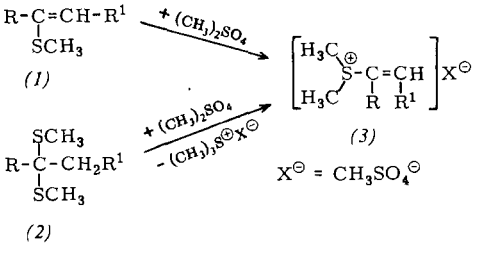
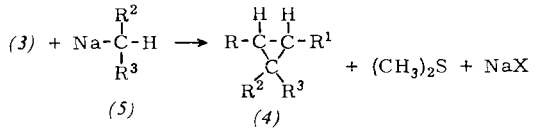
der Universität Gießen (Germany)

Dimethylvinylsulfonium salts *(3)* with a mono- or disubstituted vinyl group were obtained either by methylation of the corresponding methyl vinyl sulfides *(1)* with one equivalent of dimethyl sulfate or by heating dimethyl mercaptals *(2)* with excess of dimethyl sulfate[1].



If ethanolic solutions of *(3)* are added to the sodium salts of CH-acidic compounds *(5)* in ethanol, elimination of dimethyl sulfide occurs already at 0 °C to yield polysubstituted cyclopropanes *(4)*.



*(3)* + Na-C(R²)(R³)-H → R-C(H)(R²)-C(H)(R³)-R¹ + $(CH_3)_2S$ + NaX

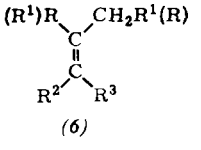
*(5)* *(4)*

The products *(4)* are isolated by pouring the reaction mixture into ice/dilute sulfuric acid and extracting with ether; they are purified by fractional distillation or crystallization.

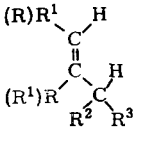
| *(4)* [a] | R | $R^1$ | $R^2$ | $R^3$ | B.p. [°C/mm Hg] m.p. [°C] | Yield [%] |
|---|---|---|---|---|---|---|
| *(a)* | H | $C_6H_5$ | —C≡N | —C≡N | 61 | 30 |
| *(b)* | H | $C_6H_5$ | —C≡N | $COOC_2H_5$ | 122–123/0.005 | 60 |
| *(c)* | H | $C_6H_5$ | $COOC_2H_5$ | $COOC_2H_5$ | 103/0.01 | 60 |
| *(d)* | H | $C_6H_5$ | $C_6H_5$ | —C≡N | 141–143/0.005 | 40 |
| *(e)* | H | $C_6H_5$ | 4-$O_2N$—$C_6H_4$ | —C≡N | 176–177 | 30 |
| *(f)* | $C_6H_5$ | $C_6H_5$ | —C≡N | —C≡N | 133 | 30 |
| *(g)* | $C_6H_5$ | $C_6H_5$ | —C≡N | $COOC_2H_5$ | 66–67 | 40 |
| *(h)* | $C_6H_5$ | $COOC_2H_5$ | —C≡N | —C≡N | 68–69 | 25 |
| *(i)* | *p*-Cl—$C_6H_4$ | $COOC_2H_5$ | —C≡N | —C≡N | 101–102 | 20 |
| *(j)* | *p*-Cl—$C_6H_4$ | $COOC_2H_5$ | —C≡N | $COOC_2H_5$ | 168–170/0.001 | 44 |
| *(k)* | H | $COOC_2H_5$ | —C≡N | $COOC_2H_5$ | 101–102/0.005 | 33 |
| *(l)* | H | $COOC_2H_5$ | $COOC_2H_5$ | $COOC_2H_5$ | 100–101/0.4 | 30 |
| *(m)* | $C_3H_7$ | $COOC_2H_5$ | —C≡N | $COOC_2H_5$ | 118–120/0.01 | 50 |
| *(n)* | $C_3H_7$ | $COOC_2H_5$ | $COOC_2H_5$ | $COOC_2H_5$ | 112/0.005 | 45 |
| *(o)* | H | $C_6H_5$—$CH_2$ | $COOC_2H_5$ | $COOC_2H_5$ | 141/0.02 | 45 |

[a] The intermediate *(3)* was obtained from a compound of type *(1)* for products *(4a)*–*(4e)* and from a compound of type *(2)* for products *(4f)*–*(4o)*.

It was shown by NMR spectroscopy and by degradation of the cyclopropane derivatives to known compounds that the products had the structure *(4)* and not the isomeric ones *(6)* or *(7)* [2].



*(6)*



*(7)*

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[1] Cf. *J. Gosselck, L. Béress, H. Schenk*, and *G. Schmidt*, Angew. Chem. *77*, 1140 (1965); Angew. Chem. internat. Edit. *4*, 1080 (1965).

[2] Thanks are extended to Prof. *F. Wessely*, Vienna for supplying a substance for comparison and to Dr. *E. Hoffmann*, Mülheim/Ruhr (Germany) for measuring the NMR spectra.

## A New Method for Preparing 1,3,4-Trithiadiborolanes and 1,3,5-Trithiatriboranes

By Prof. Dr. Max Schmidt and Dr. W. Siebert

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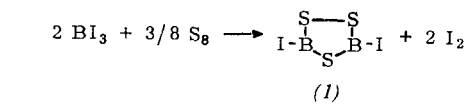
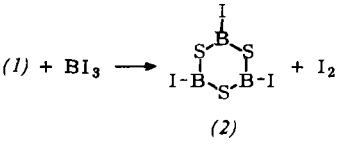
Thiol groups are oxidized by iodine to disulfide groups in an aqueous medium. In an anhydrous medium this reaction is quantitatively reversible [1]. We have now found that boron triiodide and substituted boron iodides can cleave sulfur-sulfur bonds. Thus treatment of sulfur with boron triiodide in $CS_2$ (20 hr at 21 °C) leads to 2,5-diiodo-1,3,4-trithiadiborolane *(1)* [2] (colorless needles, m.p. 27 °C) in *ca.* 80 % yield.



$2\ BI_3 + 3/8\ S_8 \longrightarrow$ *(1)* $+ 2\ I_2$

Heating of the borolane *(1)* with $BI_3$ to *ca.* 90 °C (there is no reaction at room temperature) leads to formal introduction of "borene" IB: into the S–S linkage, with ring



*(1)* + $BI_3$ → *(2)* + $I_2$

expansion, leading to the known [3] 2,4,6-triiodo-1,3,5-trithiatriborane (m.p. 145 °C, lit. [3] 122 °C).

The B–I group can also cleave S–S bonds, as is shown by the formation of 2,5-bis(methylthio)- and 2,5-bis(phenylthio)-1,3,5-trithiadiborolane from compound *(1)* and R–S–S–R (R = $CH_3$, b.p. 74 °C/2 mm; R = $C_6H_5$, b.p. 207 °C/2 mm). Use of $BI_3$ in place of *(1)* affords smoothly the trithioboric esters $B(SR)_3$. $BI_3$ and diphenyl sulfide give, as expected, only a 1:1 adduct, m.p. 150 °C.

Since it is less electrophilic than $BI_3$, $BBr_3$ does not react with sulfur [2], although it does react with sulfanes [4, 5]. The stronger Lewis acid $C_6H_5BBr_2$ is reported to react with sulfur to yield the six-membered cyclic compound $(C_6H_5)_2B_2S_4$ [6]; we found this reaction to be exothermal and obtained, besides violet, polymeric B–S compounds, $BBr_3$ and a crystalline substance of m.p. 50 °C, as well as 2,5-dibromo-1,3,4-trithiadiborolane, which has already been prepared by another route [4]. Our product may have arisen from the primary product 2,5-diphenyl-1,3,4-trithiadiborolane by further reaction with bromine formed simulataneously (from $C_6H_5BBr_2$).

Received: April 4th, 1966 [Z 195/30 IE]
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[4] *M. Schmidt* and *W. Siebert*, Angew. Chem. *76*, 687 (1964); Angew. Chem. internat. Edit. *3*, 637 (1964).

[5] *M. Schmidt* and *W. Siebert*, Z. anorg. allg. Chem., in press.

[6] *R. H. Cragg* and *M. F. Lappert*, Organometal. Chem. Rev. *1*, 43 (1966).

## Equilibria between Mono- and Di-bromoamines. Violet Bromoamine

By Prof. J. Jander and Dr. Chr. Lafrenz

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Technische Hochschule München (Germany)

If the amount of methylamine required by Equation (1) is condensed into an ethereal bromine solution at −60 °C, a precipitate of $[CH_3NH_3]Br$ is at once formed and the resulting yellow solution has oxidizing properties. According

$$2\ CH_3NH_2 + Br_2 \rightarrow CH_3NHBr + [CH_3NH_3]Br \quad (1)$$

to analysis (N:Br = 1:1) it should contain $CH_3NHBr$[1]; free bromine cannot be detected. This solution shows three ultraviolet bands at 20 °C, namely, $\lambda_{max}$ = 370, 305, and 245 mμ. Of these, the second only is to be attributed to the $CH_3NHBr$, since solutions richer in $CH_3NH_2$ give only this band ($\varepsilon_{max}$ = 465) and the comparable $(CH_3)_2NBr$[2] in pentane gives a band at $\lambda_{max}$ = 318 mμ ($\varepsilon_{max}$ = 575). The first and the third band relate to $CH_3NBr_2$[3], which is obtained from $CH_3NH_2$ and bromine (molar ratio 3:4) in ether or pentane ($\varepsilon_{max}$ = 350 and 3380, respectively). The band of longer wavelength has not been previously recorded[4].

The equilibrium (2) is indicated by three isosbestic points at 340, 280, and 210 mμ. The spectra do not vary with time.

$$2\ CH_3NHBr \rightleftarrows CH_3NBr_2 + CH_3NH_2 \quad (2)$$

Analogously, the product from $NH_3$ and bromine (molar ratio 1:1) in dimethyl or diethyl ether at −78 °C (N:Br = 1:1 after removal of $NH_4Br$) is in equilibrium with $NHBr_2$ and $NH_3$ although it was previously held to be $NH_2Br$[5,6]. At −110 °C it gives shoulders at 350 and 288 mμ; the first of these is to be ascribed to $NHBr_2$, since solutions richer in $NH_3$ and solutions in liquid $NH_3$ give only a maximum at 288 mμ ($\varepsilon_{max}$ = 600). A corresponding equilibrium exists in aqueous solution[9].

The deviation from the N:Br ratio 1:1[6] observed on isolation of $NH_2Br$ by removal of the ether is thus explained, neglecting decomposition, by removal also of $NH_3$ from the equilibrium mixture, so that the material isolated contains $NHBr_2$.

The solvent-dependence of the UV spectrum of $NH_2Br$ ($\lambda_{max}$ in $H_2O$: 277[4]–278[7], in liquid $NH_3$: 280, in ether: 284[7] to 288 mμ) indicates varying degrees of solvation. If bromine is treated with $NH_3$ (molar ratio 1:1) in the non-solvating pentane at −120 °C, a dark-violet $NH_2Br$ is precipitated together with $NH_4Br$. If a yellow ethereal solution of "$NH_2Br$" (N:Br = 1:1) is poured into an approximately twenty-fold excess of pentane at −120 °C, dark-violet $NH_2Br$ (N:Br = 1:1) is again precepitated. Ethereal yellow "$NH_2Br$" solutions (N:Br = 1:1) reversibly assume a reddish-violet color when frozen[8]; in this case, however, it is not yet known whether the reddish-violet material is suspended in the solid ether or whether there is a true solid solution.

Addition of the strongly electron-donating $(CH_3)_3N$ to ethereal solutions of "$NH_2Br$" ($\lambda_{max}$ is then at 332 mμ) completely prevents precipitation of the violet material on pouring into pentane, as well as the violet coloration on freezing. Ethereal solutions of "$NHBr_2$" (N:Br = 1.9:1) and solutions of the methylbromoamines give neither precipitates nor violet colors whether or not this addition is made.

Thus it appears, contrary to previous interpretations[9], that the dark-violet color is due to association of the unsolvated $NH_2Br$. Reddish-violet colors can either be interpreted as before (as being due to $NH_2Br \cdot xNH_3$, not to $NBr_3 \cdot 6NH_3$[9]) or as a smaller degree of association of $NH_2Br$, owing to cleavage of the associates by solvent molecules. In favor of the latter possibility is that $\lambda_{max}$ varies from 520 to above 600 mμ, according to the "$NH_2Br$" concentration, for frozen reddish-violet etheral solutions; the dark-violet suspensions in pentane absorb at still longer wavelengths.

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[2] *R. Willstätter* and *V. Hottenroth,* Ber. dtsch. chem. Ges. *37,* 1783 (1904).

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[5] *J. K. Johannesson,* J. chem. Soc. (London) *1959,* 2998; *W. Moldenhauer* and *M. Burger,* Ber. dtsch. chem. Ges. *62,* 1615 (1929); *G. H. Coleman, H. Soroos,* and *C. H. Yager,* J. Amer. chem. Soc. *55,* 2075 (1933).

[6] *J. Jander* and *E. Karzbach,* Z. anorg. allg. Chem. *296,* 117 (1958).

[7] *H.Galal-Gorchev* and *J.C.Morris,* Inorg.Chem. *4,* 899 (1965).

[8] Solutions of $NH_2Br$ in liquid $NH_3$ show the same phenomenon on freezing; cf. *E. Kurzbach,* Dissertation, Universität Freiburg 1962.

[9] *L. Birckenbach* and *M. Linhard,* Ber. dtsch. chem. Ges. *62,* 2265 (1929); *M. Schmeisser,* Z. anorg. allg. Chem. *246,* 281 (1941); Lecture in Freiburg, January 1959; *J. Jander* and *E. Kurzbach* in: Recent Aspects of the Inorganic Chemistry of Nitrogen. Special Publication No. 10, The Chemical Society, London 1957; see also 8.

## Theoretically and Experimentally Determined Properties of the Fundamental Indigo Chromophore [1]

By Prof. Dr. W. Lüttke, Dipl.-Chem. H. Hermann, and Dr. M. Klessinger

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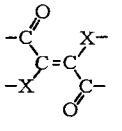
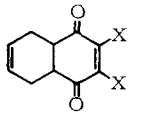
der Universität Göttingen (Germany)

According to Hückel molecular-orbital calculations, the structure *(1)* is to be regarded as the basic chromophore of indigo dyes[2]. Calculations by the Pople-Pariser-Parr method confirm these results and show that the spectroscopic properties of the grouping *(1)* depend on its configuration and conformation[1,2]. Our theoretically derived views were confirmed experimentally on compounds of type *(1)* with X = S, which we have now prepared[3].

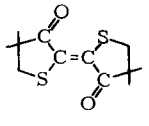


*(1)*
X = NH, S, Se, O

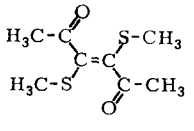
In Table 1 the experimental results for *trans- (3a)* and *cis*-$\Delta^{2,2'}$-bi-(4,4-dimethylthiolan-3-one) *(3b)*, *trans- (4a)* and *cis*-3,4-bis(methylthio)-3-hexene-2,5-dione *(4b)*, and 2,3-dianilino-4a,5,8,8a-tetrahydro- *(2a)*, 4a,5,8,8a-tetrahydro-2,3-bis(phenylthio)- *(2b)*, and 4a,5,8,8a-tetrahydro-2,3-bis(methylthio)-1,4-naphthoquinone *(2c)*[4] are compared with the



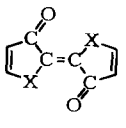
*(2a)*: X = NH-$C_6H_5$
*(2b)*: X = S-$C_6H_5$
*(2c)*: X = S-$CH_3$



*(3a)*



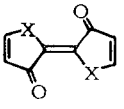
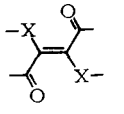
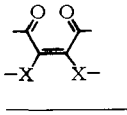
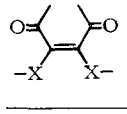
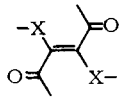
*(4a)*



*(5)*, X = S, NH

results of Pople-Pariser-Parr calculations on the structural isomers of *(1)*. Calculated values refer to systems with X = NH, but it was shown[5] that for indigoids the spectroscopic properties of the isolated molecule with X = NH agree very well with those of the corresponding molecule with X = S in the condensed phase.

Table 1. Comparison of the wavelengths $\lambda_{max}$ and intensities log ε of the longest-wavelength ultraviolet absorption maximum of compounds of type *(1)* (measured in cyclohexane), and of their stretching frequencies $\tilde{\nu}C{=}O$ (measured in KBr) with the wavelengths $\lambda_{max}$ and oscillator strengths f of the longest-wavelength $\pi\rightarrow\pi^*$ transition and the bond index $p_{C=O}$ of the C=O bond, determined by the Pople-Pariser-Parr method.

| Chromophore X = NH | Calculated | | | Observed | | | | |
|---|---|---|---|---|---|---|---|---|
| | $\lambda_{max}$ (mμ) | f | $p_{CO}$ | Compound | $\lambda_{max}$ (mμ) | log ε | $\nu C{=}O$ ($cm^{-1}$) | $\tilde{\nu}C{=}C$ ($cm^{-1}$) |
|  | 486 | 0.42 | 0.74 | *(5)*, X = S | 502 | — | 1639 | — |
|  | 453 | 0.34 | 0.81 | *(3b)* | 450 | 4.13 | 1674 | — |
| | | | | *(4a)* | 315 | 3.95 | 1654<br>1709 | 1484 |
|  | 398 | 0.27 | 0.85 | *(3b)* | 394 | 4.05 | 1692<br>1719 | 1520 |
| | | | | *(4b)* | 318 | 3.94 | 1668<br>1698 | 1485 |
|  | 415 | 0.55 | 0.83 | *(2a)* | 434 | 4.02 | 1642 | — |
| | | | | *(2b)* | 374 | 3.72 | 1677 | 1488 |
| | | | | *(2c)* | 386 | 3.83 | 1660<br>1693 | 1470 |
|  | 424 | 0.56 | 0.82 | | | | | |

If the calculated results for bispyrroleindigo *(5)* (X = NH) in Table 1 are compared with those for group *(1)* in the *trans-s-cis-s-cis*-orientation, or if the experimental values for the bisthiopheneindigo *(5)* (X = S) are compared with those for compound *(3a)*, then it is clear that *(3a)* — and thus *(1)* — can be regarded as the basic chromophore of the indigo dyes.

(a) Compound *(3a)* shows the unusually long-wavelength absorption predicted by the theory (in comparison with thioindigo the longest-wavelength absorption band is shifted by only 88 mμ to shorter wavelengths in spite of a reduction of the conjugated system from 22 to 10 π-electrons).

(b) Compound *(3a)* can be reduced reversibly to the leuco-form.

(c) Compound *(3a)* can, like thioindigo[6], be reversibly converted by irradiation to the *cis*-form; the hypsochromic shift $\Delta\lambda = -56$ mμ is in excellent agreement with the values for thioindigo ($\Delta\lambda = -53$ mμ) and the calculated values ($\Delta\lambda = -55$ mμ). Also the shift of the CO frequency from $\tilde{\nu}_{C=O} = 1674$ for *(3a)* to 1719 $cm^{-1}$ for *(3b)* is in agreement with the change in the CO bond index from $p_{CO} = 0.81$ to 0.85.

Thus the concepts developed by *Dähne*[7] to account for the color of indigo are experimentally disproved.

According to the calculations (Table 1) it is expected that compounds *(2b)* and *(2c)* absorb at a wavelength 17 mμ higher, and more intensely, than *(3b)*. However, only very broad bands of rather low intensity at 386 and 374 mμ, respectively, are observed; these undergo only a small hypsochromic shift in ethanol instead of the expected bathochromic shift [found for *(2c)*: $\Delta\lambda = -4$ mμ; *(2b)*: $\Delta\lambda = 3$ mμ; but *(2a)*: $\Delta\lambda = +13$ mμ]. Steric reasons are responsible for these discrepancies between predicted and observed results: The carbonyl groups on the six-membered ring and the SR groups cannot all be coplanar with the C=C double bond. For *(4a)*, which should have the same spectroscopic properties as *(3a)*, the deviation from coplanarity due to steric interaction of the CO—$CH_3$ with the S—$CH_3$ groups is so great that the indigoid character is completely lost; compounds *(4a)* and *(4b)* have similar infrared and ultraviolet spectra to α,β-unsaturated ketones having an alkylthio group at the β-position[8]. Since, owing to the distortion, compound *(4a)* has no symmetry center, both the $\tilde{\nu}_{C=O}$ and the $\tilde{\nu}_{C=C}$ vibrations are infrared-active.

Even the simplest Hückel molecular-orbital calculations (carbon approximation[2]) give the correct trend in spectroscopic properties in the series thioindigo, bisthiopheneindigo, *trans*-$\Delta^{2,2'}$-bi-(4,4-dimethylthiolan-3-one), as shown in Table 2. Hence it is concluded that important properties of the indigo dyes are determined by the topology of the grouping *(1)*.

Table 2. Comparison of Hückel molecular-orbital results (carbon approximation [2]) with spectroscopic data.

| | Calculated | | Observed (in $CHCl_3$) | |
|---|---|---|---|---|
| | ΔE | $p_{CO}$ | $\lambda_{max}$ ($cm^{-1}$) | $\tilde{\nu}CO$ ($cm^{-1}$) |
| Thioindigo (= *trans*) | 0.224 | 0.725 | 18300 | 1650 |
| Bisthiopheneindigo | 0.242 | 0.690 | 19800 | 1641 |
| *trans*-$\Delta^{2,2'}$-Bi-(4,4-dimethylthiolan-3-one) | 0.261 | 0.798 | 21800 | 1674 |

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German version: Angew. Chem. *78*, 638 (1966)

[1] Part VI of Theoretical and Spectroscopic Studies on Indigo Dyes; Part V: *M. Klessinger*, Tetrahedron 1966, in press.

[2] *M. Klessinger* and *W. Lüttke*, Tetrahedron *19*, Suppl. *2*, 315 (1963).

[3] *H. Hermann*, Dissertation, Universität Göttingen, 1966.

[4] Synthesis of *(2a)* to *(4b)*: *W. Lüttke* and *H. Hermann*, unpublished work.

[5] *M. Klessinger* and *W. Lüttke*, Chem. Ber. (1966), in press.

[6] *G. M. Wyman* and *W. R. Brode*, J. Amer. chem. Soc. *73*, 1487 (1951).

[7] *D. Leupold* and *S. Dähne*, Theoret. chim. Acta *3*, 1 (1965).

[8] *K. Bowden*, *E. A. Braude*, and *E. R. H. Jones*, J. chem. Soc. (London) *1946*, 948; *L. Bateman* and *F. W. Shipley*, *ibid. 1955*, 1997.

## Nature of the Bonding in Aminoquinones

By Dr. S. Kulpe, Dr. D. Leupold, and Dr. S. Dähne

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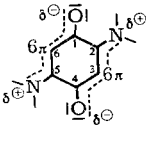
The physicochemical behavior of aminoquinones, *e.g.* of 2,5-diamino-1,4-benzoquinones *(1)*, is determined, in our opinion[1,2], by coupling of dipolar structural elements of merocyanine type. The compounds are, therefore, described as quadrupolar merocyanines. Crystal-structure analysis of 2,5-diamino-3,6-dichloro-1,4-benzoquinone (Fig. 1) con-



*(1)*

firms, in general, the bond lengths predicted [2] by a simple quantum-mechanical approximation on the basis of this concept. Interpretation of the properties of diaminoquinones on the basis of a quinone structure [3,4] is thus to be considered incorrect.

The coupling bonds $C^1-C^2$ and $C^4-C^5$ are much longer than an aromatic bond ($1.39_5$ Å). The polymethine chain shows clearly an averaging of the bond lengths. In comparison with the quinone structure [5,6] this amounts to lengthening of the $C^2-C^3$ and $C^5-C^6$ bonds and shortening of the $C^3-C^4$ and $C^6-C^1$ bonds. The C–N separation is appreciably less than the C–N single-bond distance (1.48 Å).

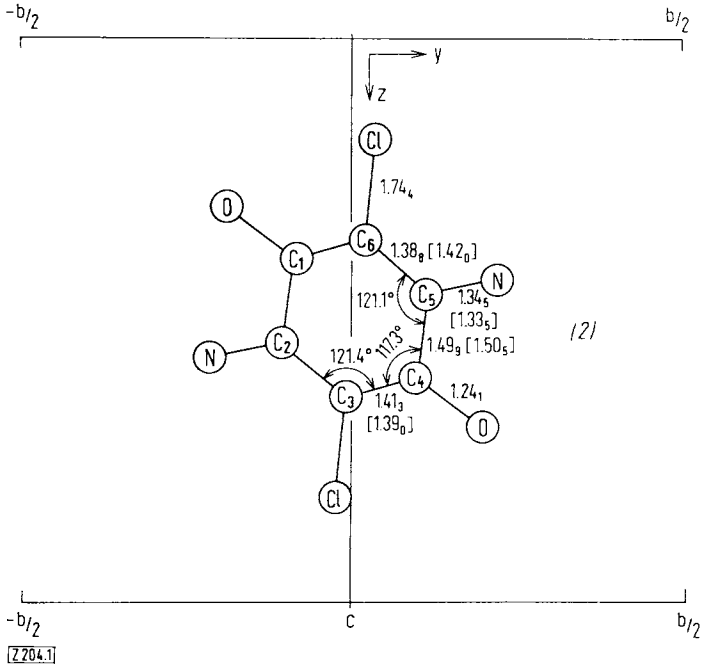



Fig. 1. A molecule of 2,5-diamino-3,6-dichloro-1,4-benzoquinone in (y,z)-projection about the center (x = 0, y = 0, z = 1/2). Distances in Å. Angles in degrees. Predicted values [2] in brackets.

The X-ray structure analysis was carried out on reddish-brown needle-shaped crystals of 2,5-diamino-3,6-dichloro-1,4-benzoquinone [X-ray density, 1.825 g/cm³; two molecules per unit cell; space group, $P2_1/c$ ($P2_1/n$ was used in the calculations); lattice constants, a = 3.787 ± 1 Å, b = 10.771 ± 3 Å, c = 9.305 ± 2 Å, β = 97.2 ± 1 °].

About 730 intensities, determined photometrically or estis mated, were used in the calculation. Patterson synthese-[$P_0$(u,w) and $P_0$ (v,w)] and $M_4$-minimum functions obtained therefrom gave first approximations for the x-, y-, and z-coordinates of the centers of gravity of the Cl, O, N, and C-atoms. Fourier and Fourier difference syntheses in two and three dimensions, as well as use of systems of linear structure factor equarions [6], led to refinement of the coordinates. The H atoms could be located approximately. The R factor for the space data (including $F_0 \approx 0$) is at present less than 14%. The mean error of the atomic distances given is estimated as 0.015 Å. The positions of the coordinates are being further refined.

Received: April 25th, 1966 [Z 204 IE]
German version: Angew. Chem. 78, 639 (1966)

[1] *S. Dähne* and *H. Paul*, Chem. Ber. *97*, 1625 (1964); *S. Dähne, J. Ranft*, and *H. Paul*, Tetrahedron Letters *1964*, 3355.

[2] *D. Leupold* and *S. Dähne*, Theoret. chim. Acta *3*, 1 (1965).

[3] *K. Wallenfels* and *W. Draber*, Tetrahedron *20*, 1889 (1964).

[4] *M. Klessinger*, Eighth European Congress on Molecular Spectroscopy, Copenhagen, August 1965; Theor. chim. acta, in press.

[5] *J. Trotter*, Acta crystallogr. *13*, 86 (1960).

[6] *L. Kutschabsky*, Mber. dtsch. Akad. Wiss. Berlin *7*, 511 (1965).

## Synthesis of 3,3,3-Trifluoroalanine and of 3,3,3-Trifluoroalanyl Peptides [1]

By Prof. F. Weygand, Doz. W. Steglich, W. Oettmeier, A. Maierhofer, and R. S. Loy

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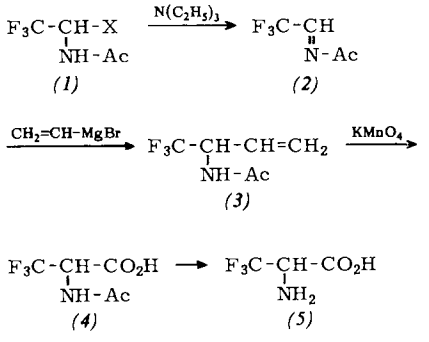
The reaction of *N*-acyl-1-ethanesulfonyl-2,2,2-trifluoroethylamines *(1)*, X = $SO_2C_2H_5$ [2], or of *N*-acyl-1-halogeno-2,2,2-trifluoroethylamines *(1)*, X = Cl or Br [1], with triethylamine gives rise to *N*-acyl-2,2,2-trifluoroiminoethanes *(2)* [1], which react with vinylmagnesium bromide to give *N*-acyl-1-trifluoromethylprop-2-enylamines *(3)*. Oxidation of the latter with potassium permanganate in acetone/water (1:3) + 3 $NH_2SO_4$ (4.5 vol-%) affords high yields of *N*-acyl-3,3,3-trifluoroalanines *(4)* [Ac = $C_6H_5CO-$, 92%, m.p. 152 °C [2]; Ac = $C_6H_5-CH_2O-CO-$, 75%, m.p. 112 °C].

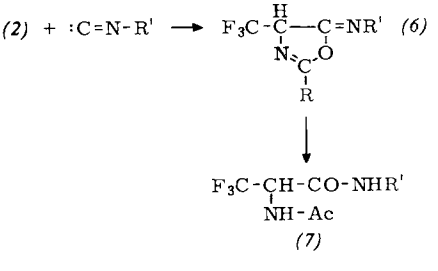



The *N*-benzoyl compound *(4)*, Ac = $C_6H_5CO-$, is transformed by heating with concentrated hydrochloric acid into 3,3,3-trifluoroalanine hydrochloride, which can be dissolved in chloroform by addition of triethylamine. Addition of acetic acid liberates trifluoroalanine *(5)* in 75% yield, which sublimes above 210 °C. Compound *(5)* is markedly acidic ($pK_1^* = 2.32$, $pK_2^* = 5.61$ [3]). In contrast to unsubstituted α-monoamino monocarboxylic acids it forms a crystalline dicyclohexylammonium salt (m.p. 152 °C) and dissolves on treatment with diazomethane in ether.

*N*-Benzyloxycarbonyl-3,3,3-trifluoroalanine can be used in the normal fashion to produce *N*-benzyloxycarbonyltrifluoroalanyl peptide esters, *e.g.* the methyl ester of benzyloxycarbonyl-3,3,3-trifluoroalanyl-L-phenylalanine, m.p. 158 °C, is obtained in 74% yield using *N*-ethynylmethyldiethylamine as condensing agent [4].

The method described can be adapted to prepare any α-amino acid with a perfluoroalkyl side-chain. *N*-Benzoyl-3,3,3-trichloroalanine, m.p. 163 °C, was made analogously.

Another synthesis of broad scope for the preparation of derivatives of 3,3,3-trifluoroalanine involves treatment of *(2)* with isonitriles. The adducts *(6)* initially formed [5] need not be isolated but are transformed by treatment with dilute acid into *N*-acyl-3,3,3-trifluoroalanine amides *(7)*; *e.g.* the cyclohexylamide of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanine obtained in 80% yield is identical with that prepared from *N*-benzyloxycarbonyltrifluoroalanine itself.



This method can therefore be used to prepare trifluoroalanyl peptides directly, for the isonitriles are readily obtainable from *N*-formylamino esters[6]. For example, the methyl ester of *N*-benzyloxycarbonyl-3,3,3-trifluoroalanyl-L-leucine, m.p. 165 °C, was obtained in 64 % yield in this way. It was shown by conversion of the product into the *N*-trifluoroacetyl dipeptide methyl ester and separation of the diastereoisomers by gas chromatography[7] that an asymmetric induction takes place during the synthesis; the ratio of the diastereomers was 72:28.

The scope of these reactions is extended by using *N*-(*N* benzyloxycarbonylaminoacyl)-1-chloro-2,2,2-trifluoroethylamines *(1)*, X = Cl, Ac = $C_6H_5$–$CH_2O$–CO–NH–CHR–CO, which are obtained by reaction of *N*-benzyloxycarbonylamino acid amides with trifluoroacetaldehyde and subsequent treatment with phosphorus pentachloride. The reaction sequence described above then leads to *N*-benzyloxycarbonyl tripeptide esters with trifluoroalanine in the center; for example, the methyl ester of *N*-benzyloxycarbonylglycyl-3,3,3-trifluoroalanyl-L-leucine was obtained in the form of an oil, and the amino-acid sequence was confirmed by mass spectrometry[8] after conversion of the product into the *N*-trifluoroacetyl compound.

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German version: Angew. Chem. *78*, 640 (1966)

[1] *N*-Acyliminotrihalogenoethanes as Reactive Intermediates in Elimination-Addition Reactions, Part IV. – Part III: *F. Weygand, W. Steglich, I. Lengyel, F. Fraunberger, A. Maierhofer*, and *W. Oettmeier*, Chem. Ber., in the press. – We wish to thank the Deutsche Forschungsgemeinschaft for material support of this work, Dr. *O. Scherer*, Farbwerke Hoechst AG., Frankfurt (Germany) for supplying trifluoroacetaldehyde, and Dr. *A. Prox* for measuring the mass spectra.

[2] *F. Weygand* and *W. Steglich*, Chem. Ber. *98*, 487 (1965).

[3] *E. J. Cohn* and *J.T. Edsall*: Proteins, Amino Acids and Peptides. Reinhold, New York 1943, p. 83, give $pK_1^* = 2.34$ and $pK_2^* = 9.69$ for alanine at 25 °C.

[4] *R. Buyle* and *H. G. Viehe*, Angew. Chem. *76*, 572 (1964); Angew. Chem. internat. Edit. *3*, 582 (1964).

[5] The formation of oxazoline derivatives from 2-(*N*-benzoylimino)propane and isonitriles is described by *N. P. Gambaryan et al.*, Habilitation Thesis, Moscow 1965. – Hydrolysis: cf. *E. M. Rochlin*, 3rd Internat. Fluorine Symposium, Munich 1965.

[6] *I. Ugi, W. Betz, U. Fetzer*, and *K. Offermann*, Chem. Ber. *94*, 2814 (1961); *F. Sakiyama* and *B. Witkop*, J. org. Chemistry *30*, 1905 (1965).

[7] *F. Weygand, A. Prox, L. Schmidhammer*, and *W. König*, Angew.Chem.*75*,282(1963); Angew.Chem.internat.Edit.*2*,183(1963).

[8] *F. Weygand, A. Prox, H. H. Fessel*, and *K. K. Sun*, Z. Naturforsch. *20b*, 1169 (1965).

## Oligonucleotide Synthesis with a Soluble Polymer as Carrier

By Prof. Dr. F. Cramer, Dipl.-Chem. R. Helbig, Dr. H. Hettler, Dr. K. H. Scheit, and Dipl.-Chem. H. Seliger

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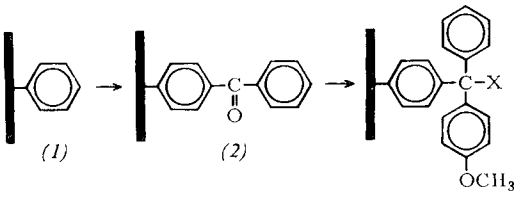
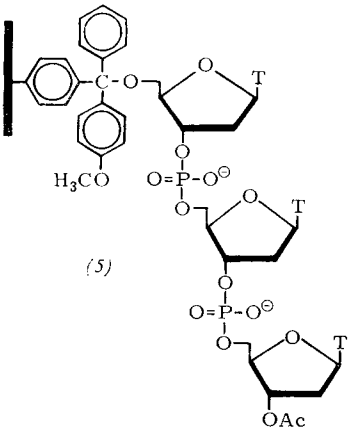
Stepwise synthesis of oligonucleotides requires column separations in aqueous systems after each step with consequent loss of time and material. By analogy with *Merrifield*'s method[1], we have tried to build oligonucleotides on a polymeric carrier[2], where use of a polystyrene derivative soluble in pyridine[3] proved expedient. In order to be able to link all four nucleotides to the polymers, we used a polystyrene containing *p*-methoxyphenylphenylmethyl chloride functional groups. Polystyrene *(1)* (mol. wt. 170000) was converted by benzoyl chloride/$AlCl_3$ into the polymeric ketone *(2)*, which was treated with *p*-methoxyphenylmagnesium bromide to give the tertiary alcohol *(3)*. This was converted into the chloride *(4)* with acetyl chloride. About 20 % of the phenyl groups of the polystyrene were thus transformed into functional groups.




*(1)* *(2)*

*(3)*, X : -OH
*(4)*, X : -Cl

The polymer *(4)* was treated with 3′-*O*-acetylthymidine in pyridine, wherupon 40 % of the functional groups reacted. The acetyl groups were then removed with 0.01 M sodium methoxide or ammonia in dioxane, and the polymeric residue was brought into reaction with 3′-*O*-acetyl-5′-thymidylic acid. Repetition of the procedure gave a polymer *(5)* containing a trinucleotide. After each reaction step the polymer can be precipitated by an nonpolar solvent or by water and freed from reagents and unchanged starting material by washing or reprecipitation.




*(5)*

After the last reaction the nucleotide mixture was split off by 1 ml of 50 % trifluoroacetic acid in 100 ml of dioxane (1 hr at room temperature), and the products were separated chromatographically and analysed. In this way thymidine and the nucleotides pT, TpT, and TpTpT were obtained in molar proportions of 28:7:25:40. The yield of TpTpT was 11 % calculated on thymidine.

Linear aminopolystyrenes can be loaded with nucleotides by formation of the (acid-labile) phosphoric amide linkage. The polymer used is one containing on an average one aromatic amino group on every fourth styrene unit. 9 % of the amino groups react with 5′-thymidylic acid (condensing agent: dicyclohexylcarbodiimide). Fission from the polymeric carrier is effected with 80 % acetic acid at 80 °C (24 hr).

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[1] *R. B. Merrifield*, J. Amer. chem. Soc. *85*, 2149 (1963); *86*, 304 (1964).

[2] Cf. *R. L. Letsinger* and *V. Mahadevan*, J. Amer. chem. Soc. *87*, 3526 (1965).

[3] *M. M. Shemyakin, Yu. A. Ovchinnikov, A. A. Kiryushkin*, and *I. V. Kozhevnikova*, Tetrahedron Letters *1965*, 2323.

## A Model for the Action of Chymotrypsin

By Prof. Dr. F. Cramer and Dipl.-Chem. G. Mackensen

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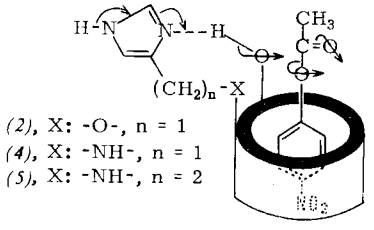
Chymotrypsin catalysis consists in an acid-base catalysis by imidazole, in which a histidine imidazole group of the enzyme increases the nucleophilicity of a serine hydroxyl group of the protein to such an extent that at pH 7 to 9 ester transfer with subsequent splitting of the enzyme-product complex occurs[1]. In the first step of this reaction the substrate must be bound to the enzyme by a very specific, non-covalent bond

and must be presented to the catalytically active groups in the correct orientation; the "bonding" in inclusion compounds [2] resembles this lock and key relation of enzyme and substrate in many respects [3].

Cyclodextrins catalyse the fission of substituted pyrophosphates [4] and substituted phenyl acetates [5]; in both cases an acyl-catalyst intermediate complex is formed. The catalytically active groups are the hydroxyl groups of the cyclodextrin. We have now attached an imidazole residue to β-cyclodextrin *(1)* as additional catalytically active group. *(1)* was converted with 4-(or 5)-(chloromethyl)imidazole in the presence of base into the hydroxymethylimidazole ether *(2)*, whereby products with an average of two imidazole substituents per molecule of *(1)* were formed. A further possibility is treatment of hepta(6-*O*-tosyl)-β-cyclodextrin *(3)* with 4-(or 5)-(aminomethyl)imidazole or histamine, giving *(4)* and *(5)*, respectively. Finally, *(3)* was treated with imidazole to give derivatives *(6)* in which the imidazole nitrogen is linked to a C-6 atom of *(1)*.



*(2)*, X: -O-, n = 1
*(4)*, X: -NH-, n = 1
*(5)*, X: -NH-, n = 2

We determined the catalytic activity of substituted cyclodextrins from the rate of hydrolysis of *p*-nitrophenyl acetate ($0.3\times10^{-4}$ M) spectrophotometrically at 400 mμ, starting with the addition of the catalyst. Reaction conditions: 23 °C; $0.3\times10^{-2}$ M *(1)* or $0.3\times10^{-2}$ M free or bound imidazole in a mixture of 0.02 M tris buffer (pH 7.5) and dioxane (98:2 v/v). Our results are shown in the table.

| Catalyst | Imidazole groups per molecule of *(1)* | $10^4$k ($sec^{-1}$) |
|---|---|---|
| None (pH 7.5) | | 0.21 |
| α-Dextrin | | 0.32 |
| β-Dextrin (1) | | 0.59 |
| Imidazole | | 15 |
| *(1)* + Imidazole | | 17 |
| 4-(Hydroxymethyl)imidazole | | 3.3 |
| *(2)* | 2 | 41 |
| 4-(Aminomethyl)imidazole | | 2.1 |
| *(4)* | 3 | 3.6 |
| Histamine | | 4.0 |
| *(5)* | 3 | 6.1 |
| *(5)* | 4 | 13.0 |
| 1-Methylimidazole | | 8.8 |
| *(6)* | 2 | 12 |

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German version: Angew. Chem. *78*, 641 (1966)

[1] See, *e.g.*, *B. Hartley* in: Structure and Activity of Enzymes. Academic Press, New York 1964, p. 47.
[2] *F. Cramer*: Einschlußverbindungen. Springer, Heidelberg 1954.
[3] *F. Cramer* and *W. Kampe*, J. Amer. chem. Soc. *87*, 1115 (1965).
[4] *N. Hennrich* and *F. Cramer*, J. Amer. chem. Soc. *87*, 1121 (1965).
[5] *W. Kampe*, Dissertation, Universität Heidelberg 1961; cf. *M. Bender et al.*, J. Amer. chem. Soc. *88*, 2318, 2319 (1966).

## Synthesis and Properties of 5,6-Dimethyl-1,2,3,4-tetraphenylcalicene

By Prof. Dr. H. Prinzbach [1] and Dipl.-Chem. U. Fischer

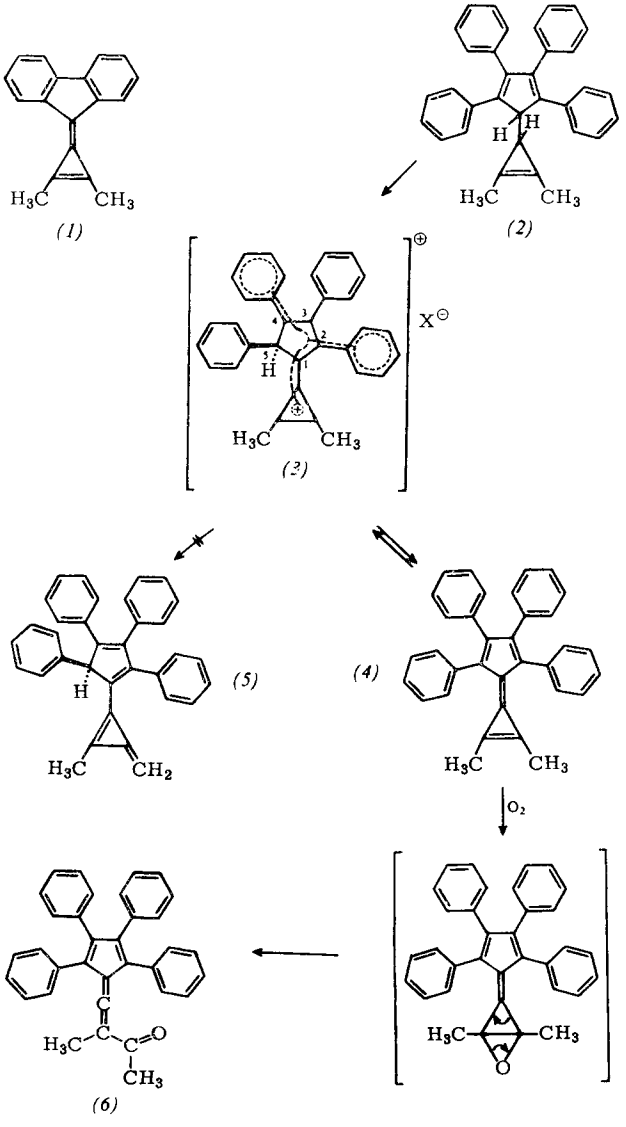
Chemisches Laboratorium
der Universität Freiburg (Germany)

We have prepared 5,6-dimethyl-1,2,3,4-tetraphenylcalicene *(4)* by way of the dihydro compound *(2)* in a synthesis analogous to that of 5,6-dimethyl-1,2;3,4-dibenzocalicene *(1)* [2]. Our product is a further stable derivative [3] of an evidently unstable parent that has not yet been isolated.

Tetraphenylcyclopentadienyl-lithium (32.4 mmole) and dimethylcyclopropenium fluoroborate (37.0 mmole) give the dihydro compound *(2)* in 40 % yield (in tetrahydrofuran at 0 °C under nitrogen).

The structure *(2)* is proved by, *inter alia*, the infrared spectrum ($\tilde{\nu}_{C=C}$ 1945 and 1876 $cm^{-1}$) and NMR spectrum ($CCl_4$) [2.5–3.1 τ (20H, m); 5.94 τ (1H, d; J = 5.5 cps); 8.5 τ (1H, d; J = 5.5 cps); 8.59 τ (6H, s)].

Removal of hydride from compound *(2)* by triphenylmethyl fluoroborate ($CHCl_3$, 20 °C, 15 min, 75–80 % yield) is accompanied by isomerization [5] to *(3)*. The salt *(3)* ($X^{\ominus}$ = $BF_4^{\ominus}$) forms lemon-yellow crystals, m.p. 202–206 °C, $\lambda_{max}$ (in $CF_3COOH$) = 418 mμ (ε = 17200) and 328 (7900), NMR spectrum (in $CF_3COOH$): 2.25–2.9 τ (20H, m), 4.31 τ (1H, s), and 7.76 τ (6H, s). In $CF_3COOD$, H-5 of the fluoroborate *(3)* is exchanged for D within a few minutes; there is no change in the relative intensity of the $CH_3$ signal when the substance is kept for several days in an 80 % (v/v) mixture of $CF_3COOD$ and $D_2O$. In agreement therewith, triethylamine in $CHCl_3$ or aqueous $NaHCO_3$ liberates the calicene *(4)* (65 % yield) selectively from the salt *(3)*. The isomeric triafulvene *(5)* is not formed in detectable amounts.



The calicene derivative *(4)* crystallizes from $O_2$-free benzene/cyclohexane as fine, yellow needles (m.p. 234.5–236 °C). In its infrared spectrum the bands of the endocyclic cyclopropene C=C linkage at 1852 $cm^{-1}$ are accompanied by further, very intense C=C bands at 1600, 1543, and 1499 $cm^{-1}$. Its NMR

spectrum ($CDCl_3$) shows a broad multiplet (2.45–2.8 τ) and a singlet (2.9 τ) for the 20 phenyl protons, and a singlet (8.29 τ) due to the two methyl groups. In $C_6D_6$ the $CH_3$ signal appears at appreciably higher field (8.84 τ), and the phenyl protons give two complex multiplets (2.3–2.6 τ; 2.6–3.0 τ; ratio of areas 8:12) which can be clearly differentiated. The diamagnetic shift of the $CH_3$ signal of *(4)*, which is remarkable in view of $\tau_{CH_3}$ for *(1)*, may perhaps indicate a considerable anisotropy effect for the phenyl substituents. The strongest peak in the mass spectrum[4] is that of the molecule ion at m/e = 434.

The ultraviolet spectrum of *(4)*, which shows only slight structure, is little influenced by the polarity of the solvent: $\lambda_{max}$ (acetonitrile) = 334 mμ (ε = 26500), 300 (26200), and 237 (15800); $\lambda_{max}$ (cyclohexane) = 336 mμ (ε = 23800), 298 (26000). As in the case of the vinylogous 7,8,9,10-tetraphenylsesquifulvalene[6] electrophilic attack in $CF_3COOH$ by the proton takes place exclusively at position 1, giving compound *(3)*, $X^{\ominus} = CF_3COO^{\ominus}$ (NMR analysis).

The calicene derivative *(4)* is thermally quite stable, but, like *(1)*[7], reacts rapidly with oxygen, giving the allene ketone *(6)* whose structure is proved by, *inter alia*, ultraviolet, infrared, NMR, and mass spectra: $\lambda_{max}$ ($CH_3CN$) = 420 mμ (ε = 2000), 308 (shoulder, 14200), 258 (shoulder, 34800), and 246 (37200); $\nu_{C=C}$ at 1927 $cm^{-1}$; $\nu_{C=C}$ at 1684 $cm^{-1}$; 2.6–2.1 τ (m), 7.84 τ (s), and 8.11 τ (s) ($CCl_4$; ratio of areas 20:3:3). The strongest peaks in the mass spectrum[4] a those of the molecule ion of *(6)* (m/e = 450), of *(6)*–tolan (272), and of tolan (178).

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[1] Laboratoire de Chimie organique de l'Université de Lausanne (Switzerland).

[2] *H. Prinzbach* and *U. Fischer*, Angew. Chem. *77*, 621 (1965); Angew. Chem. internat. Edit. *4*, 598 (1965).

[3] *A. S. Kende* and *P. T. Izzo*, J. Amer. chem. Soc. *87*, 4162 (1965); *W. M. Jones* and *R. S. Pyron*, *ibid.* *87*, 1608 (1965); *M. Ueno*, *I. Murata*, and *Y. Kitahara*, Tetrahedron Letters *1965*, 2967; *E. D. Bergmann* and *I. Agranat*, Chem. Commun. *21*, 512 (1965).

[4] We thank Dr. *H. Achenbach* (Universität Freiburg) for the mass-spectrometric measurements.

[5] *H. Prinzbach*, *D. Seip*, and *U. Fischer*, Angew. Chem. *77*, 258 (1965); Angew. Chem. internat. Edit. *4*, 242 (1965).

[6] *H. Prinzbach*, *D. Seip*, *L. Knothe*, and *W. Faisst*, Liebigs Ann. Chem., in press.

[7] *H. Prinzbach* and *U. Fischer*, Chimia *20*, 156 (1966).

## Attempted Synthesis of anti-1,6:8,13-Bismethano[14]annulene

By Prof. Dr. E. Vogel, Dr. M. Biskup, cand. chem. A. Vogel, cand. chem. U. Haberland, and Dipl.-Chem. J. Eimer

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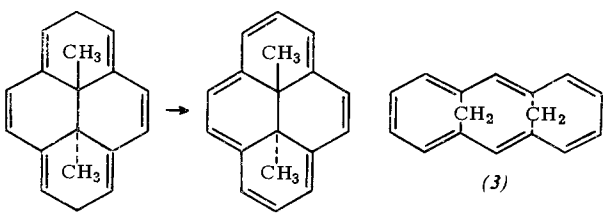
2,7,15,16-Tetrahydro-*trans*-15,16-dimethylpyrene *(1)* can be readily dehydrogenated to 15,16-dihydro-*trans*-15,16-dimethylpyrene *(2)*, a [14]annulene with aromatic properties[1]. Whereas *(2)* has an almost planar $C_{14}$ perimeter, planarity of the outer $C_{14}$ skeleton of the analogous *anti*-1,6:8,13-bismethano[14]annulene *(3)* could be achieved only at the cost of appreciable bond-angle deformation, mainly of the

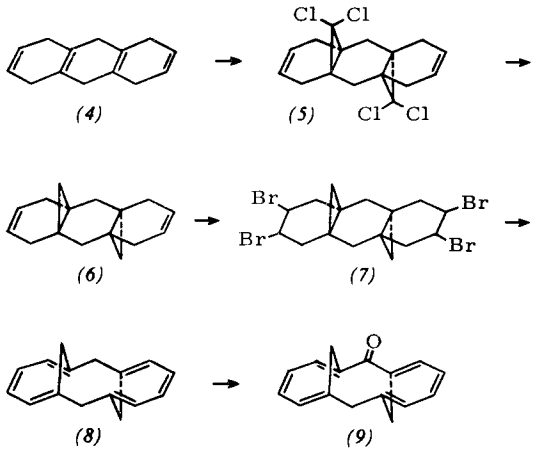



*(1)* *(2)* *(3)*

C–$CH_2$–C angles. Compound *(3)* might thus be an olefinic pendant to compound *(2)*.

We describe below the synthesis of 7,14-dihydro-*anti*-8,13-bismethano[14]annulene *(8)*, corresponding to *(1)*, and some of its reactions.

1,4,5,8,9,10-Hexahydroanthracene *(4)*[2] served as starting material. It was prepared by reduction of 9,10-dihydroanthracene with lithium in methylamine[3]. Addition of a



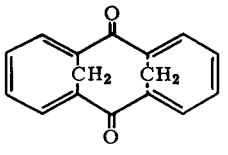

*(4)* *(5)* *(6)* *(7)* *(8)* *(9)*

cyclopropane ring to the skeleton of *(4)* by means of dichlorocarbene[4] (obtained by thermal decomposition of sodium trichloroacetate in 1,2-dimethoxyethane[5]) led, when the components were used in molar ratio 1:4, to the diadduct *(5)* (40 %), m.p. 262–263 °C, whose NMR spectrum showed a weakly split singlet at τ = 4.6, a multiplet at τ = 7.65, and a sharp singlet at τ = 7.75 (proton ratio 4:12). In favor of carbene addition in the *anti*-position is the finding that the resonances of the four middle $CH_2$ protons always appear as a singlet in the NMR spectra of compound *(5)* and the products *(6)* and *(8)* obtained therefrom (occurrence of a symmetry center)[6]. Compound *(5)* is converted by lithium and t-butyl alcohol in tetrahydrofuran[7] into the hydrocarbon *(6)* (90 %), m.p. 29 °C, which takes up two moles of bromine in methylene dichloride at −75 °C with formation of *(7)* (84 %), m.p. 129–130 °C (decomp.) (probably a mixture of isomers). When the tetrabromide is treated with methanolic KOH, the hexaene *(8)* (50–55 %), m.p. 147–148 °C, is formed directly with loss of four moles of HBr and opening of the three-membered ring. The structure of this hydrocarbon follows from its NMR spectrum: it consists of an AA'XX' system at $\tau_A \approx 3.6$ and $\tau_X \approx 4.0$, a broad singlet at τ = 6.6, and an AB system at $\tau_A = 7.27$ and $\tau_B = 8.54$ (J = 11.5 cps) (8:4:4). The ultraviolet spectrum contains maxima at λ = 221 mμ (ε = 41500) and 258 mμ (8400) in cyclohexane.

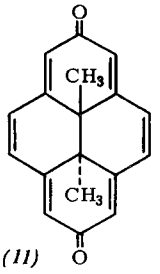
In remarkable contrast to the ready dehydrogenation of *(1)*, attempts to convert *(8)* into *(3)* by use of noble-metal dehydrogenation catalysts or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were unsuccessful. Selenium dioxide in dioxane / water oxidizes *(8)* at the allylic $CH_2$ groups of the peripheral ring, giving a mixture consisting in the main of a monohydroxy, a monooxo, and a hydroxyoxo compound. The colorless monoketone, m.p. 165–166 °C [ultraviolet spectrum: maxima at 213 (ε = 30500), 217 (31000), and 268 mμ (11900), with a shoulder at 315 mμ (4500), in cyclohexane], gives an NMR spectrum containing two complex groups of signals at τ = 3.2 and τ = 3.7, a broad singlet at τ = 6.4, and an AB system at $\tau_A = 7.26$ and $\tau_B = 8.55$ with J = 12.5 cps (6:2:2:4); it thus has structure *(9)*. This compound is a potential hydroxy derivative of the [14]annulene *(3)*; with potassium t-butoxide in dimethyl sulfoxide or tetrahydrofuran it gives intensely reddish-violet solutions, which are still under study.

Further oxidation, by chromium trioxide in pyridine, of the hydroxyketone obtained from *(8)* leads to a diketone, m.p.

299–300 °C [ultraviolet spectrum: $\lambda_{max}$ = 252 (ε = 25500) and 292 mμ (9200), in dioxane]; its NMR spectrum has only an AA'BB' system, centered at τ = 3.05, and an AB system at $\tau_A$ = 6.87 and $\tau_B$ = 8.43 (J = 13.5 cps) (8:4), so that structure *(10)* must be ascribed to it. Since this product is



*(10)*



*(11)*

colorless, and, as far as established, has no pronounced oxidizing capacity, it cannot be regarded as a quinone, in contrast to the yellow 15,16-dihydro-*trans*-15,16-dimethyl-2,7-pyrenedione *(11)* [8]. The main reason for this difference between *(11)* and *(10)* is doubtless to be sought in the steric hindrance to conjugation present in the latter.

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German version: Angew. Chem. 78, 642 (1966)

[1] *V. Boekelheide* and *J. B. Phillips*, Proc. nat. Acad. Sci. U.S.A. *51*, 550 (1964).

[2] *J. Runge*, Z. Chem. *2*, 374 (1962); *A. J. Birch*, *P. Fitton*, *D. C. C. Smith*, *D. E. Steere*, and *A. R. Stelfox*, J. chem. Soc. (London) *1963*, 2209.

[3] Reduction of 9,10-dihydroanthracene to *(4)* has meanwhile also been studied by Prof. *R. G. Harvey*, University of Chicago (personal communication).

[4] Reaction of *(4)* with methylene diiodide (molar ratio 1:3) and a zinc-copper couple in a Simmons-Smith reaction gives a complex mixture of cyclopropanation products, from which the monoadduct, 1,4,5,8,9,10-hexahydro-4a,9a-methanoanthracene (25 %), mp. 55–56 °C, can be isolated.

[5] *W. M. Wagner*, *H. Kloosterziel*, and *S. van der Ven*, Recueil Trav. chim. Pays-Bas *80*, 740 (1961).

[6] The dipole moment of *(5)* is less than 0.3 D.

[7] *P. Bruck*, *D. Thompson*, and *S. Winstein*, Chem. and Ind. *1960*, 405.

[8] *V. Boekelheide* and *J. B. Phillips*, J. Amer. chem. Soc. *85*, 1545 (1963); *F. Gerson*, *E. Heilbronner*, and *V. Boekelheide*, Helv. chim. Acta *47*, 1123 (1964).

## Tricyclo[4.3.1.0$^{1,6}$]deca-2,4,7-triene, an Acidic Alicyclic Hydrocarbon

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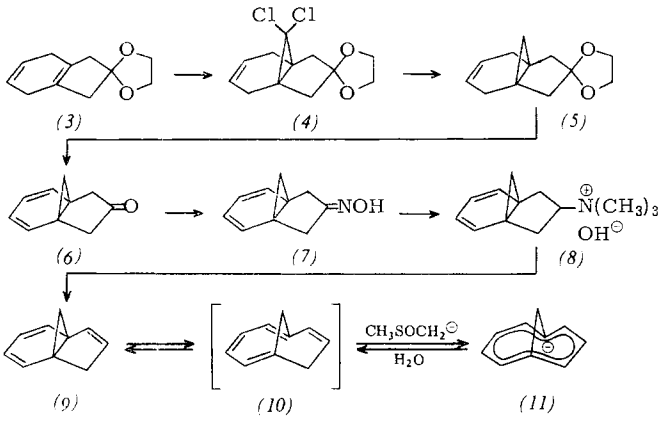
The existence and aromatic character of the neutral or positively charged 10π-electron systems 1,6-methanocyclodecapentaene *(1)* [1] and bicyclo[5.4.1]dodecapentaenylium cation *(2)* [2] suggested an attempt at synthesis of the bicyclo[4.3.1]decatrienyl anion *(11)* [3], the negatively charged analogue of compound *(1)* and cation *(2)*. If the anion is stable it should be produced by sufficiently strong bases from tricyclo[4.3.1.0$^{1,6}$]deca-2,4,7-triene *(9)*, which can be regarded as the stabilization product of 1,6-methano-1,3,5,7-cyclononatetraene *(10)*.

For the preparation of the hydrocarbon *(9)* we started from 4,7-dihydro-2-indanone ethylene ketal *(3)* [4]. This takes up dichlorocarbene (generated from chloroform and potassium t-butoxide) preferentially at the nucleophilic central double bond, whereby the product *(4)*, m.p. 97–98 °C, is formed (30 %). This can be nearly quantitatively reduced by sodium in liquid ammonia to compound *(5)*, b.p. 71–72 °C/0.4 mm, $n_D^{20}$ = 1.5085. Compound *(5)* is converted into the ketone *(6)* [56 %; m.p. 99–100 °C; NMR spectrum: $A_2B_2$ system




centered at τ = 4.0 (4); doublet at τ = 7.48 (4); and AB system at τ = 8.6 and 9.9 (2) with J = 5 cps], by reaction with bromine (0 °C, $CH_2Cl_2$), dehydrohalogenation of the dibromide with ethanolic $NaOC_2H_5$, and hydrolysis of the diene ketal produced by HCl in tetrahydrofuran, yields being increased if the intermediates are not isolated. The ketone is then converted into the oxime, m.p. 77–78 °C (80 %), which is reduced by $LiAlH_4$ to the corresponding amine (according to the NMR spectrum a mixture of the two stereoisomers) which is exhaustively methylated by methyl iodide and potassium carbonate in methanol; the yield of quaternary ammonium iodide calculated on *(7)* is 39 %. Hofmann degradation of the base *(8)* prepared from the iodide with silver oxide yields, finally, a 57 % yield of the norcaradiene hydrocarbon *(9)*, free from isomers, as a colorless liquid, b.p. 65–66 °C/14 mm, $n_D^{20}$ = 1.5470. The NMR spectrum of the hydrocarbon shows a multiplet at τ = 3.6–4.4 (5), a double triplet at τ = 4.8 (1), a quintuplet at τ = 7.4 (2), and an AB system at τ = 8.6 and 10.0 (2) with J = 3.0 cps. The ultraviolet-spectrum (in cyclohexane) has a double maximum at λ = 260 mμ (ε = 3100) and 270 mμ (ε = 3100), in excellent agreement with that of tricyclo[4.3.1.0$^{1,6}$] deca-2,4-diene [5]. Catalytic hydrogenation ($PtO_2$ in ethyl acetate) gives mainly tricyclo[4.3.1.0$^{1,6}$]decane [5]; the compound adds maleic anhydride even in the cold (m.p. of adduct 105–106 °C).

Compound *(9)* is not sufficiently acidic to exchange hydrogen for deuterium in $CH_3OD/CH_3ONa$ at room temperature. However, with sodium methylsulfinylmethylide ($CH_3SOCH_2^{\ominus}Na^{\oplus}$) [6] in [$D_6$]dimethyl sulfoxide a brownish-red solution is formed at once, in whose NMR spectrum the following signals appear: a double doublet at τ = 3.2 (2), a multiplet at τ = 4.0–4.6 (5), and an AB system at τ = 10.7 and 11.2 (2) with J = 7.5 cps. The changes from the spectrum of the hydrocarbon *(9)*, and in particular the shift of the signals for the bridgehead protons to higher field and the increase in the geminal coupling constant from 3.0 to 7.5 cps. indicate formation of the bridged cyclononatetraenyl anion *(11)* and the presence of a ring current in the $C_9$ perimeter. On addition of an excess of *(9)* to the solution of sodium methylsulfinylmethylide in [$D_6$]dimethyl sulfoxide the spectrum of the hydrocarbon appears together with that of the anion. It is thus shown that *(9)* is converted completely into *(11)* by the base, and that the NMR spectrum observed is not due to rapid proton exchange between *(9)* and *(11)*. Introduction of deuterium into *(11)* by [$D_6$]dimethyl sulfoxide at room temperature was not observed. If the solution of *(11)* in dimethyl sulfoxide is added to an excess of $D_2O$ a 45 % yield of compound *(9)*, which is 91 % deuterated at position 9, is obtained.

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[1] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964); *E. Vogel* and *W. A. Böll*, Angew. Chem. *76*, 784 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964).

[2] *W. Grimme*, *H. Hoffmann*, and *E. Vogel*, Angew. Chem. *77*, 348 (1965); Angew. Chem. internat. Edit. *4*, 354 (1965).

[3] Cf. the synthesis of cyclononatetraenyl anion: *T. J. Katz* and *P. J. Garratt*, J. Amer. chem. Soc. *86*, 5194 (1964); *E. A. LaLancette* and *R. E. Benson*, *ibid. 87*, 1941 (1965).

[4] *A. J. Birch*, *P. Fitton*, *D. C. C. Smith*, *D. E. Steere*, and *A. R. Stelfox*, J. chem. Soc. (London) *1963*, 2209.

[5] *E. Vogel*, *W. Wiedemann*, *H. Kiefer*, and *W. F. Harrison*, Tetrahedron Letters *1963*, 673.

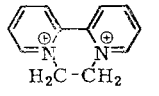
[6] *E. J. Corey* and *M. Chaykovsky*, J. Amer. chem. Soc. *87*, 1345 (1965).

## Synthesis of a Dipyridothiadiazepine Derivative

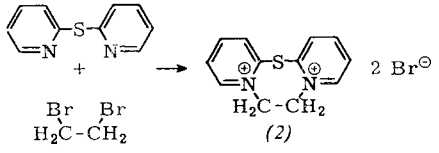
By Dr. L. A. Summers

University of Newcastle, New South Wales (Australia)

6,7-Dihydrodipyrido[1,2-*a*:2′,1′-*c*]pyrazinediium dibromide *(1)* is a herbicide[1]. We have now prepared the related, hitherto unknown 6,7-dihydrodipyrido[2,1-*b*:1′,2′-*f*][1,3,6]-thiadiazepinediium dibromide *(2)*.

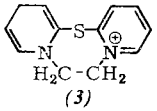


2 $Br^{\ominus}$ *(1)*



2 $Br^{\ominus}$

*(2)*



*(3)*

Treatment of 2,2′-dipyridyl sulfide (5g) with boiling ethylene dibromide (40 ml) for 1 hr gave a precipitate of *(2)*, which crystallized from aqueous ethanol as grey crystals of the monohydrate (65 % yield), m.p. 232 °C, $\lambda_{max}$ = 242 ($\varepsilon$ = 8600), 293 (12000), and 323 mμ (15000) in water. The structure was consistent with the elementary analyses (all bromine ionic) and with the NMR spectrum[2] in $D_2O$ with sodium 3-(trimethylsilyl)-1-propanesulfonate as internal reference. The NMR spectrum showed a singlet at $\delta$ = 5.7 ppm (four methylene protons) and a multiplet in the range $\delta$ = 8.1–9.2 (assigned to the eight aromatic protons) with an area ratio of 1:2.

An aqueous solution of compound *(2)* gave on treatment with zinc dust a yellow-green solution, the ESR spectrum[3] of which confirmed the presence of a comparatively stable radical, presumably the corresponding radical cation, one canonical form of which is represented by *(3)*. The complex ESR spectrum is difficult to interpret; it comprises 40 almost equally spaced lines with a total width of 33 gauss. No signal was obtained before treatment with zinc powder. Certain bipyridyl diquaternary salts, including *(1)*, are likewise readily reduced to the corresponding radical cations[4].

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[1] *R. C. Brian*, *R. F. Homer*, *J. Stubbs*, and *R. L. Jones*, Nature (London) *181*, 446 (1958); *W. R. Boon*, Chem. and Ind. *1965*, 782.

[2] The NMR spectrum was kindly taken by Mr. *V. A. Pickles* of the University of New South Wales.

[3] The ESR spectrum was kindly taken by Prof. *R. O. C. Norman* and Mr. *B. C. Gilbert* of the University of York (England) on a Varian V4502 instrument with 12″ magnet and 100 kc modulation. The concentration of the salt was $5\times10^{-3}$ M.

[4] *R. F. Homer* and *T. E. Tomlinson*, Nature (London) *184*, 2012 (1959); *R. F. Homer*, *G. C. Mees*, and *T. E. Tomlinson*, J. Sci. Food Agric. *11*, 309 (1960).

## Synthesis of Novel Heterocyclic Thiazolo Derivatives

By Doz. Dr. B. Stanovnik and Prof. Dr. M. Tišler

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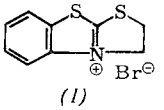
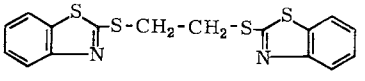
University of Ljubljana (Yugoslavia)

Reaction of heterocyclic compounds containing a thioamide grouping as part of the ring system[1] with 1,2-dibromoethane gives heterocyclic systems which to our knowledge have not been previously synthesized.

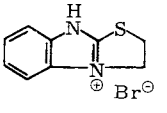
When equimolar amounts of benzothiazoline-2-thione, 1,2-dibromoethane, and potassium carbonate are left standing in dimethylformamide for 24 hr at room temperature, 2,3-dihydrothiazolo[2,3-*b*]benzothiazolium bromide *(1)*, m.p. 255–257 from dimethylformamide, is produced in 47 % yield. The yield of this product is not increased at higher temperatures (50 °C); instead 2,2′-ethylenedithiobis(benzothiazole) *(2)*, m.p. 150 °C from ethanol, is obtained in 42 % yield.



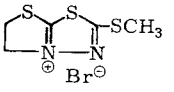
*(1)*



*(2)*



*(3)*



*(4)*

By applying the same method to benzimidazoline-2-thione, 2,3-dihydrothiazolo[2,3-*b*]benzimidazolium bromide *(3)*, m.p. 220–222 °C from ethanol, can be obtained in 43 % yield. Similarly, 2-methylthio-1,3,4-thiadiazoline-5-thione gives in 33 % yield 2-methylthio-5,6-dihydrothiazolo[2,3-*b*]-1,3,4-thiadiazol-4-ium bromide *(4)*, m.p. 225 °C (crystals separate from the melt which then melt at 280 °C).

The structures of compounds *(1)*, *(3)*, and *(4)* follow from their elemental compositions and infrared spectra. They are all soluble in water, their solutions forming a precipitate of AgBr immediately upon addition of silver nitrate; the iodoazide reaction[2] is negative.

Received: April 18th, 1966 [Z 213 IE]
German version: Angew. Chem. *78*, 645 (1966)

[1] *B. Stanovnik* and *M. Tišler*, Analytic. Biochem. *9*, 68 (1964); Arzneim.-Forsch. *14*, 1004 (1964); Croat. chem. Acta *36*, 81 (1964); *37*, 17 (1965); *A. Pollak* and *M. Tišler*, Mh. Chem. *96*, 642 (1965).

[2] *F. Feigl*: Spot Tests, Organic Applications. Elsevier, Amsterdam 1954, Vol. 2, p. 198.

## Inorganic Redox Ion Exchangers [1]

By Priv.-Doz. B. Sansoni[2], R. Winkler, and Prof. K. Starke

Institut für Kernchemie, Universität Marburg (Germany)

Redox ion exchangers can be made by loading commercial ion exchangers with redox ions. Previously only organic ion exchange resins had been used for this purpose. However, inorganic ion exchangers are more resistant to heat and radiation and are not irreversibly oxidized. We have therefore made and studied inorganic redox ion exchangers. The supports used were synthetic zirconium oxide hydrate and zirconium phosphate gels (BioRad HZO-1 and ZP-1, grains

of 50–100 mesh). Most silaceous ion exchangers are less suitable on account of their lower resistance to acids and bases.

Inorganic redox ion exchangers are obtained by loading either zirconium oxide hydrate gel with aqueous solutions of phosphite, dithionite, thiosulfate, sulfite, dichromate, permanganate, or oxalate, or zirconium phosphate gel with hydrazinium, hydroxylammonium, iron(II), iron(III), cerium(III), or cerium(IV) ions (see Table).

| Ion | Charging solution | | Capacity [a] | | |
|---|---|---|---|---|---|
| | | | | Time (min) | |
| | Concn. | pH | (meq/g) | half | totally charged |
| a) Zirconium oxide hydrate gel | | | | | |
| Dithionite | 1 N | 7.0 | 0.8 | 1.5 | 70 |
| Phosphite | 1 N | 6.2 | 1.2 | 2.5 | 90 |
| Sulfite | 1 N | 9.4 | 1.4 | 2.5 | 120 |
| Thiosulfate | 1 N | 6.2 | 0.75 | 0.5 | 35 |
| Dichromate | 0.1 N | 3.9 | 0.97 | 9 | 480 |
| | 0.8 N | 3.7 | 2.5 | — | — |
| Permanganate | 0.1 N | 6.3 | 0.36 | 1.0 | 12 |
| Oxalate | 1 N | 6.2 | 1.4 | 3 | 120 |
| b) Zirconium phosphate gel | | | | | |
| Hydrazinium | 1 N | 3.9 | 1.6 | 0.2 | 4 |
| Hydroxylammonium | 1 N | 2.8 | 1.1 | 0.2 | 4 |
| Iron(II) | 0.1 N | In 1N $H_2SO_4$ | 0.06 | 0.5 | 2 |
| | 1 N | In 1N $H_2SO_4$ | 0.13 | 0.5 | 2 |
| Iron(III) | 0.1 N | In 1N $H_2SO_4$ | 0.78 | 15 | 420 |
| | 1 N | In 1N $H_2SO_4$ | 2.1 | 60 | 600 |
| Cerium(III) | 0.1 N | In 1N $H_2SO_4$ | 0.06 | 0.5 | 2 |
| Cerium(IV) | 0.1 N | In 1N $H_2SO_4$ | 0.87 | 40 | 1800 |

[a] 0.5 g of support was shaken with 50 ml of charging solution until equilibrium was attained, and the bound ions were determined radiometrically or by redoxtitration.

The zirconium oxide hydrate gel is an amphoteric, the zirconium phosphate gel a weakly acidic, bifunctional ion exchanger. Sometimes the zirconium and phosphate ions in the support react irreversibly with ions in the charging solution. For this reason, the exchanger capacities found are much more dependent upon the experimental conditions than they are with organic ion exchangers. For example, zirconium oxide hydrate gel exhibits a strong pH dependence in its capacity for chromate and dichromate ions. At pH 1.0, the capacity is 1.4 meq/g but at pH 10.5 only 0.15 meq/g. Again, zirconium phosphate gel has a capacity of 7.5 meq/g for hydrazinium ions at pH 7.5 and a capacity of about 5 meq/g for hydroxylammonium ions at pH 5.5.

The high capacities, as well as the course of the loading reaction with time seem to indicate a precipitation of iron(III) on the zirconium phosphate matrix and complex formation of oxalate with the zirconium oxide hydrate support. Complex formation probably also occurs between hydrazinium and hydroxylammonium ions and zirconium phosphate supports.

Very strong oxidizing agents attack organic ion exchange resins. Consequently the cerium(IV)/zirconium phosphate and permanganate and dichromate/zirconium oxide hydrate systems are the first stable redox exchangers with extremely high redox potentials.

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German version: Angew. Chem. 78, 645 (1966)

[1] Redox ion exchangers, Part XIII. – Part XII: *B. Sansoni* and *O. Sigmund*, Angew. Chem. *74*, 695 (1962); Angew. Chem. internat. Edit. *1*, 554 (1962). The investigations were supported by the Bundesministerium für wissenschaftliche Forschung (St. Sch. 161).

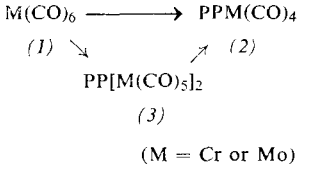
[2] Present address: Radiochemisch-analytische Abteilung, Institut für Strahlenschutz, Gesellschaft für Strahlenforschung mbH., 8042 Neuherberg bei München (Germany).

## Binuclear Complexes of Chromium and Molybdenum with Ethylenebis(diphenylphosphine) as Bridging Ligand [1]

By Dr. H. Werner, R. Prinz, E. Bundschuh, and K. Deckelmann

Anorganisch-Chemisches Laboratorium, Technische Hochschule München (Germany)

Chromium and molybdenum hexacarbonyls *(1)* react with ethylenebis(diphenylphosphine) (abbreviated PP) to give chelate complexes *(2)* in which the two phosphorus atoms of the diphosphine are coordinatively linked to the same metal atom [2]. Kinetic studies [3] show that these reactions occur by an $S_N1$ dissociation mechanism. If, however, a carbonyl *(1)* is treated with ethylenebis(diphenylphosphine) in a molar ratio 2:1 under mild conditions, binuclear complexes *(3)* are formed in which the diphosphine functions as bridging ligand and links two $M(CO)_5$ residues formed as primary dissociation products of *(1)*. After 20 hours in boiling dioxane, the yield of complex *(3)*, M = Cr, amounts to 55 %; for M = Mo it is 63 % after 4 hours' heating in a 1:1 mixture of dioxane and tetrahydrofuran. The complex *(3)* can be freed from the compounds *(2)* formed as by-product by chromatography on neutral alumina and recrystallization from toluene. Compound *(3)*, M = Cr forms pale yellow needles, m.p. 200–201 °C; compound *(3)*, M = Mo forms colorless crystals, m.p. 192–194 °C.



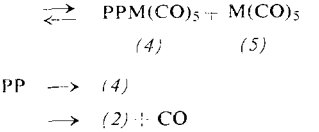

(M = Cr or Mo)

Proof of the structure of compounds *(3)* is based on elemental analyses, molecular-weight determinations (in $CHCl_3$ and $C_6H_6$), and infrared spectra. The $\nu_{CO}$ bands of *(3)* for M = Cr are at 2065, 1984, 1943, and 1933 $cm^{-1}$; those for M = Mo at 2073, 1990, 1952, and 1939 $cm^{-1}$ (in $CCl_4$).

The binuclear complexes *(3)* react with further ethylenebis(diphenylphosphine), giving the chelates *(2)*. The kinetics of these reactions can be followed by means of the infrared spectra. The results collected in the Table show that the reaction rate in toluene or dioxane is proportional to the concentration of *(3)* and independent of that of the diphosphine.

| | $PP[M(CO)_5]_2$:PP | $10^4 k_1$ (sec $^{-1}$) |
|---|---|---|
| M = Cr (in boiling toluene) | 1:2 | 1.08 |
| | 1:10 | 1.17 |
| | 1:20 | 1.05 |
| M = Mo (in boiling toluene) | 1:2 | 5.58 |
| | 1:10 | 5.42 |
| | 1:20 | 5.81 |
| M = Mo (in boiling dioxane) | 1:2 | 2.14 |
| | 1:20 | 2.23 |
| | 1:40 | 2.16 |

It follows that this substitution reaction is also governed by an $S_N1$ mechanism. The rate-determining step is probably the splitting of a metal-phosphorus bond. The coordinatively



unsaturated intermediate *(5)* reacts with the diphosphine in a second, rapid step, giving an intermediate *(4)* which forms the chelate with loss of CO.

Received: May 12th, 1966 [Z 230 IE]
German version: Angew. Chem. 78, 646 (1966)

[1] Kinetic Studies of Substitution Reactions of Metal Complexes, Part 4. – Part 3: *H. Werner* and *R. Prinz*, Chem. Ber., in press.

[2] *J. Chatt* and *H. R. Watson*, J. chem. Soc. (London) *1961*, 4980; *F. Zingales* and *F. Canziani*, Gazz. chim. ital. *92*, 343 (1962).

[3] *H. Werner* and *R. Prinz*, Angew. Chem. *77*, 1041 (1965); Angew. Chem. internat. Edit. *4*, 994 (1965); *H. Werner*, J. organomet. Chemistry *5*, 100 (1966).

## Free-Radical Initiated Addition of Bromotrichloromethane to Allyl Isocyanate

By Dr. W. J. Farrissey, Jr., F. P. Recchia, and Dr. A. A. R. Sayigh

The Upjohn Company, Carwin Research Laboratories, North Haven, Connecticut (U.S.A.)

The addition of radical species to allyl isocyanate has previously not been examined. We have now found that bromotrichloromethane undergoes rapid addition to the C=C double bond in the presence of azobisisobutyronitrile (AIBN) to form 2-bromo-4,4,4-trichlorobutyl isocyanate *(1)*.

A solution of allyl isocyanate (20 g) and AIBN (1 g) in bromotrichloromethane (200 g) is refluxed for 3 hr on a steam bath. Evaporation of the excess of $BrCCl_3$ gives crude product *(1)*, which is distilled at 92–94 °C/0.5 mm. Yield 80 %, colorless oil, $n_D^{22} = 1.5269$.

$$CH_2{=}CH{-}CH_2{-}NCO + BrCCl_3 \rightarrow Cl_3C{-}CH_2{-}CHBr{-}CH_2{\cdot}NCO$$

*(1)*

The NMR spectrum[1] of *(1)* comprises two doublets at 3.38 and 3.83 ppm (2 $CH_2$ groups) and a 5-peak multiplet at 4.45 ppm (CH group).

With methanol, *(1)* gives the urethane, m.p. 64–65.5 °C; with *p*-toluenesulfonamide in refluxing toluene it gives the urea derivative, m.p. 185–186 °C.

With stoichiometric quantities (or less) of $BrCCl_3$ in the synthesis of *(1)* the yield decreases and the amount of less volatile material increases. Presumably telomerization occurs, since the isocyanate function remains intact.

With $CCl_4$ in the presence of AIBN or benzoyl peroxide, allyl isocyanate reacts primarily at the isocyanate group.

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German version: Angew. Chem. 78, 646 (1966)

[1] Varian A-60 spectrometer; chloroform solution with tetramethylsilane as internal standard.

# CONFERENCE REPORTS

## Macromolecular Colloquium

This colloquium was held on March 3rd–5th, 1966, at the Institut für Makromolekulare Chemie der Universität Freiburg (Germany).

### Studies of the Thermal Dehydrochlorination of Poly(vinyl chloride)

*D. Braun* and *M. Thallmaier*, Darmstadt (Germany)

In spite of numerous studies of the thermal removal of hydrogen chloride from poly(vinyl chloride) (PVC), the positions in the macromolecule responsible for initiation of this reaction have hitherto remained obscure. To test the effect of irregularities in structure of the PVC chains on thermal decomposition, we have investigated the dehydrohalogenation of copolymers of vinyl chloride with small amounts of diethyl fumarate (DEF), isobutene (IBu), vinyl bromide (VBr), and 2-chloropropene (2-CP). The rate of thermal dehydrohalogenation of the copolymers with VBr and 2-CP between about 100 and 140 °C is proportional to the square of the mole fraction of these units in the copolymers; it can thence be shown that the rate is proportional to the mole fraction of those VBr or 2-CP units which are present in sequences of two or more units. It follows that under the experimental conditions used the liberation of a molecule of hydrogen halide from an isolated, thermally labile structural unit does not initiate further loss by a "zip" mechanism. Longer polyene sequences arise only if loss of a second molecule of hydrogen halide is possible owing to the neighboring presence of a second labile unit, or on use of higher temperatures. The significance of these results for the mechanism of thermal removal of HCl from poly(vinyl chloride) and for the mode of action of heat stabilizers was discussed.

The polyene sequences arising on thermal decomposition can be analysed by means of their electronic spectra. The regularities in polyene spectra permit approximate establishment of the distribution of polyene sequence lengths in PVC and poly(vinyl bromide) (PVBr), and in vinyl chloride-DEF and -IBu copolymers. In degraded PVC, the frequency of occurrence of sequences decreases continously with increasing number of conjugated double bonds; in degraded PVBr, polyene sequences with a mean of 12 to 13 double bonds are commonest. For PVC, the ratio of the total number of polyene sequences to the amount of HCl liberated decreases with increasing time of degradation, *i.e.* with increasing removal of HCl; the frequency distribution is shifted in favor of shorter sequences, a result attributed to preferential disappearance of the longer polyene sequences by secondary reactions.

### Solution Properties of Polyvinylpyrrolidone

*W. Burchard*, Freiburg (Germany)

Light-scattering measurements on polyvinylpyrrolidone(PVP) in several solvents and in mixtures of solvent and precipitant show that the radius of gyration is clearly dependent on the composition of the Θ-solvent (change of conformation). The change of one conformation into another is, however, initiated far above the Θ-point by a relatively small amount of precipitant. The conformational change is particularly marked for aqueous solutions to which acetone or dioxane has been added. Acetone causes expansion of the coil, dioxane a contraction; these effects are not due to intermolecular interactions. The conformational change is explained as being due to preferential solvation of certain groups in the macromolecule.

Measurements with alcohols containing alkyl groups of various lengths also disclose a change of the unperturbed radii of gyration with growing length of the alkyl chain. Direct proof of this is, however, difficult because the unperturbed radius of gyration can no longer be taken as equal to the radius of gyration at the Θ-point.

### Determination of the Units in Homo- and Co-polymers of Trioxane by Pyrolysis Gas Chromatography

*K. Burg*, Frankfurt/Main-Höchst (Germany)

If homo- or co-polymers of trioxane are pyrolysed on a platinum spiral and the products are immediately separated by gas chromatography, the majority of the fragments obtained at a pyrolysis temperature of 1000 °C are very hard to identify. Pyrolysis gas chromatograms of various copolymers of trioxane show characteristic differences, so that the method can be used for differentiation of polymers. It is, however, not possible to draw conclusions about the structure of the polymers from the nature of the fragments.

If small amounts of acidic reagents are mixed with the polymers and pyrolysis is then carried out at 500 °C with subsequent gas-chromatographic analysis, considerably simpler chromatograms are obtained. Only a few fragments result which can be readily identified and correlated with the structure of the polymers. The most important pyrolysis products from polytrioxane are formaldehyde, trioxane, and tetroxane, whereas the copolymer of trioxane and ethylene oxide yields mainly formaldehyde, 1,3-dioxolane, trioxane, 1,3,5-trioxepane, diethylene glycol formal, and tetroxane. Thus acetal linkages are catalytically cleaved on pyrolysis in the presence of an acidic reagent, the ether linkages remaining intact. By quantitative evaluation of the chromatograms the ethylene oxide content can be determined for copolymers of trioxane with ethylene oxide, as well as the ratios of mono-, di-, and tri-oxyethylene units in the polymers.

### Determination of Molecular Heterogeneity of Polymers by Gel-Permeation Chromatography

*M. J. R. Cantow, R. S. Porter*, and *J. F. Johnson*, Richmond, California (U.S.A.)

Gel-permeation chromatography (GPC) permits rapid determination of the distribution of molecular size in polymers. It consists of column-chromatography in which the stationary phase is a heteroporous swollen network whose permeability varies over several orders of magnitude. A liquid phase containing dissolved polymer is passed through the gel, whereby the polymer molecules diffuse into all parts of the network not closed to them by virtue of their size. As a result, the smaller molecules of the solute penetrate further than the larger ones and are retained longer on the column.

A commerical GPC instrument (Waters), with a styrene-divinylbenzene copolymer as stationary phase, was used for the investigation of polyisobutenes with wide and narrow ranges of molecular weight. The average molecular weights of the preparations lay between 2000 and $10^6$. A computer program is described for rapid evaluation of the experimental results. The information fed in was the elution volume (as measure of molecular size) and data from the registering refractometer (as measure of the amount of polymer). These data are integrated numerically and the elution volumes are converted into molecular weights by means of a calibration curve. Two methods are described for setting up calibration curves. The computer output consists of cumulative and differential distributions of molecular weight and values for $M_n$, $M_v$, $M_w$, $M_z$, and $M_{z+1}$. By using these mean values, the conventional heterogeneities, as defined by *G. V. Schulz*, are calculated and tabulated. Standard deviations of the differential frequency and mass distribution are also obtained. The advantages of these values for the characterization of molecular-weight distributions by only one parameter are discussed. By using the standard deviation, a good correlation was obtained between non-Newtonian viscosity and the width of the molecular-weight distribution.

### Elasto-Osmometry

*J. van Dam*, Delft (Holland)

In elasto-osmometry changes in tension in a stretched and swollen strip of cross-linked silicone rubber are measured at constant length. The changes in tension result from deswelling of the strip when pure solvent is replaced by polymer solution. Swelling equilibrium is established in 10–15 minutes. The resulting change in tension is a function of the chemical potential of the solvent and thus of the number-average molecular weight and the concentration of dissolved polymer:

$$\left(\frac{\partial f}{\partial c}\right)_{c=0} = BRT/M_n$$

B is a constant dependent on the rubber used and on the solvent.

The method gives good results for polystyrene and poly(vinyl acetate) in toluene and for cellulose triacetate in dioxane, provided the molecular weight is above 5000. The upper limit is a molecular weight of about 150000 with 10 % accuracy.

### Kinetics and Molecular-Weight Distributions in Anionic Polymerizations in Weakly Solvating Solvents

*R. V. Figini*, Mainz (Germany)

Previous studies of the kinetics and the corresponding molecular-weight distributions in anionic polymerizations were carried out with naphthalenesodium as initiator and in relatively strongly solvating solvents[1–3]. In order to analyse the molecular-weight distributions more accurately, we have selected cumylsodium as initiator, because this compound gives only a monoactively growing chain on addition of the monomer; cumyl methyl ether was used as solvent, so that the influence of its dissociative properties on the reactivity of the ionic group could be studied simultaneously. The difference between the dielectric constant (3.7) of this ether and those of tetrahydrofuran and tetrahydropyran (7.4 and 5.5, respectively, at 25 °C) would be expected to result in less solvation.

The kinetic analysis showed addition of monomer in a reaction of first order, as in systems studied earlier, and, as expected, a smaller propagation constant of *ca.* 1 l·mole$^{-1}$ sec$^{-1}$ at −20.5 °C, which is only slightly dependent on the concentration of initiator. The dependence disappears entirely on addition of an electrolyte (sodium tetraphenyloborate). The mean molecular weight increases during polymerization in proportion to the monomer conversion. The molecular-weight distributions of polymers prepared without electrolyte diverge strongly from a Poisson function; on addition of electrolyte, the spread of the distribution decreases to such an extent that the deviation from a Poisson function becomes very small.

The results are interpreted by means of a reaction mechanism involving two routes[1–3], in which free anions or ion pairs

[1] *H. Hostalka, R. V. Figini*, and *G. V. Schulz*, Makromolekulare Chem. *71*, 198 (1964); *R. V. Figini, H. Hostalka, K. Hurm, G. Löhr*, and *G. V. Schulz*, Z. physik. Chem. N.F. *45*, 269 (1965); *H. Hostalka* and *G. V. Schulz*, *ibid.* *45*, 286 (1965).

[2] *W. K. R. Barnikol* and *G. V. Schulz*, Makromolekulare Chem. *68*, 211 (1963); *86*, 298 (1965); Z. physik. Chem. N.F. *47*, 89 (1965).

[3] *D. N. Bhattacharyya, C. L. Lee, J. Smid*, and *M. Szwarc*, Polymer *5*, 54 (1964); J. physic. Chem. *69*, 612 (1965).

are considered to be propagators for the addition of monomer. On this hypothesis, molecular-weight distributions have been derived theoretically by the moment method[4]; they agree with the experimental results within the limits of error, providing independent evidence for the reaction scheme proposed.

## Characterization of Baker-Williams Fractions by Turbidimetric Titration

*G. Glöckner*, Dresden (Germany)

Analytical fractionation with a Baker-Williams column of 0.1–0.3 g of polymer gives many fractions containing only a few milligrams of material. The molecular weights of such small samples can be determined by turbidimetric titration. Plots of turbidity *vs.* volume fraction of precipitant are curves rising steeply from the abscissa. The corresponding curves of the samples used for calibration, which were obtained by fractional precipitation or "triangle" fractionation, rise only gradually and are S-shaped. It is therefore concluded that the Baker-Williams fractions are narrower than those used for calibration.

The effect of the rate of elution from the Baker-Williams column on the homogeneity of the fractions was studied. At a rate about four times that normally used, no broadening of the fractions could be detected turbidimetrically. S-shaped titration curves are obtained only at substantially higher rates of elution. This means that in the system studied [poly(butyl methacrylate) in acetone/methanol], and presumably in other systems as well, more rapid elution than previously thought permissible is possible.

## Investigation of Poly(vinyl dithioacetals) and their Use as Radiation-Protecting Substances

*K. Gollmer* and *H. Ringsdorf*, Marburg (Germany)

Vinyl dithioacetals (*S*-vinyl mercaptals, $CH_2=CH\text{-}S\text{-}CH_2\text{-}S\text{-}R$) have been prepared by dehydration of the corresponding 2-hydroxyethyl compounds and have been used for a kinetic study of their polymerization and for the synthesis of macromolecular compounds that might afford protection against ionizing radiation ($^{60}$Co-$\gamma$).

The over-all velocity ($V_p$, mole $l^{-1}$ $sec^{-1}$) of polymerization of the *S*-vinyl derivatives, initiated by radicals from azodiisobutyronitrile, is strongly dependent on the nature of the substituent R:

| R = | iso-$C_3H_7$ | $C_2H_5$ | $CH_3$ | $CH{=}CH_2$ | $C_6H_5$ | Styrene |
|---|---|---|---|---|---|---|
| $10^3$ $V_p$ = | 0.074 | 0.553 | 1.056 | 5.67 | 0.767 | 1.006 |

The assumption that there are overlapping inductive and steric effects is supported by the results of viscosity measurements and by the NMR spectra of the monomers.

Investigation of the protection of mice against irradiation[5] has shown that copolymers of the vinyl dithioacetals with vinylpyrrolidone are as effective as thiols of low molecular weight but remain active for longer periods. It is, moreover, characteristic of the polymers that they preferentially prevent damage to the intestinal tract and consequent disturbance of the electrolyte and water balance.

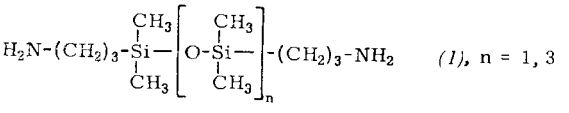
## Preparation and Polymerization of Difunctional Imide Derivatives

*G. Greber* and *R. Pense*, Freiburg (Germany)

The preparation of soluble and fusible macromolecules containing imide groups was attempted in two ways:

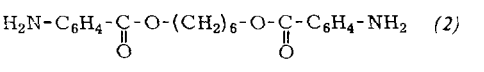
1. Pyromellitic dianhydride and trimellitic anhydride with *p*-aminophenol, ethanolamine, and *p*-aminobenzoic acid or its esters afford monomeric imides containing two reactive groups. These imides yield macromolecules by polycondensation with, or polyaddition to, suitable other reactants. Thus, for instance, reaction of *N,N'*-bis(2-hydroxyethyl)-pyromellitdiimide, the most soluble of these compounds, with adipic acid, phosgene, or hexamethylene diisocyanate leads to polyester-imides or polyurethane-imides, some of which are soluble and fusible.

2. Polyimide derivatives which also are soluble and fusible and which are stable up to more than 300 °C are obtained by polycondensation of pyromellitic dianhydride with $\omega,\omega'$-bis(3-aminopropyl)polysiloxanes *(1)*:



*(1)*, n = 1, 3

However, use of the ester diamine *(2)* as diamine component yields only insoluble and infusible products.



*(2)*

## Studies of Phase Equilibria as Basis for Fractionation of Polymers

*J. Klein*, München (Germany)

Fractionation of polymers is to be understood as a separation process, dependent on molecular weight, from a homogeneous system, with formation of a second phase. Analysis of the phases that are in equilibrium with each other – the dilute phase (sol phase) and the concentrated phase (gel phase) – with respect to polymer content, solvent, and precipitant shows that the phase equilibrium is univariant, as required by statistical thermodynamics.

Knowledge of the phase-equilibrium curve for the region of the dilute solution (sol phase) is important for a description of the fractionation, because this shows the maximum amount of soluble polymer that can be obtained under the respective conditions and, when the initial quantities in solution are known, permits the fraction of polymer precipitated in one fractionation step to be calculated.

The dependence of the equilibrium curve on concentration and molecular weight of the polymer, and on temperature, were determined for the system polystyrene/benzene/methanol, with the following results:

1. Concentration: The relation between content $\gamma^*$ of precipitant at the precipitation point (for constant M and T) and the logarithm of the polymer concentration c* gives a curve with a continuous curvature for measurements over a fairly large range of concentrations.

2. Molecular weight: The content $\gamma^*$ (for constant c and T) is a linear function of $1/M^\alpha$, where $\alpha < 0.5$, and varies with concentration.

3. Temperature: $\gamma^*$ is a linear function of the temperature T; the slope of the lines is independent of c and M.

Polydispersity must be considered as a fourth parameter. By using mixtures of samples of various molecular weights it was shown that species of low molecular weight (which change the number-average molecular weight) did not lead to higher solubility; the precipitation point is characteristic for the partial concentration of polymer which is responsible for the precipitation. Thence it can be concluded that the behavior of a polydisperse mixture can be described as the sum of the behaviors of the individual components in their respective partial concentrations. Thus the course of a fractionation can be predicted, and the most effective system chosen, from

[4] *R. V. Figini*, Makromolekulare Chem. *71*, 193 (1964); *R. V. Figini*, unpublished results.

[5] These investigations were carried out in collaboration with *W. Rüther* at the Institut für Strahlenbiologie und Isotopenforschung der Universität Marburg.

a knowledge of the analytically determined equilibrium curves.

The above argument assumes that equilibrium is in fact established in the fractionation process under consideration. Effects of coprecipitation (precipitation fractionation) or adsorption and transport phenomena (column fractionation) can have further influences and may distort the molecular-weight distribution predicted.

## Studies of Mucopolysaccharides of Normal and Sclerotic Human Aortas

*Almuth Klemer* and *D. Mempel*, Münster (Germany)

Normal and sclerotic human aortas, grouped according to degree of sclerosis and age, were degraded with papain. The contents of chondroitinsulfuric acid and heparitin sulfate were determined by preparative chromatography. Figure 1 shows the distribution pattern.

It is remarkable that aortas of patients with slight sclerosis show the highest content of chondroitinsulfuric acid.

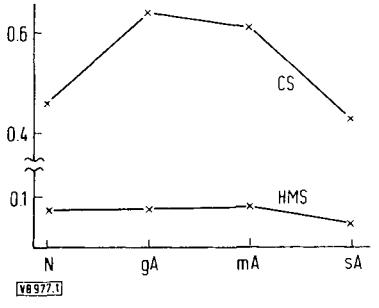



Fig. 1. Content of chondroitinsulfuric acid (CS) and heparitin sulfate (HMS) in human aortas.
Ordinate: % by weight of mucopolysaccharide.
Abscissae: Degree of sclerosis.
N = normal aortas (mean age of patients: 35 years).
gA = slight arteriosclerosis (52 years).
mA = medium arteriosclerosis (63 years).
sA = severe arteriosclerosis (66 years)

## Relation between Synthesis of Antibodies and Metabolism of Nucleic Acids

*H. Kröger*, Freiburg (Germany)

After a second immunization, spleen cells were removed from rabbits that had been immunized with alcohol dehydrogenase. These cells continued to form antibodies to the enzyme *in vitro*. Puromycin and actinomycin D suppress this synthesis. Therefrom it can be concluded that the antibody protein is formed *de novo*, with the aid of an RNA that must originate at the DNA. In order to investigate how the information necessary for antibody synthesis is built up during the first immunization, the metabolism of DNA in rat spleen during this period was studied. This metabolism was considerably increased, but synthesis of RNA was only slightly greater than in the controls.

Endoxan and 6-mercaptopurine disturb the synthesis of antibodies. Both inhibit the synthesis of nucleic acids. Attempts to discover a relation between the first immunization and the induction of enzymes led to the conclusion that these processes have different mechanisms.

## Synthesis of Nylon Oligomers by the Merrifield Method of Peptide Synthesis on Synthetic Resins

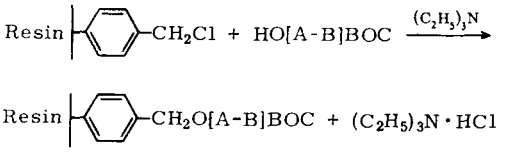
*P. Kusch*, Aachen (Germany) [*]

Stimulated by the work of *Merrifield*[1], we have prepared oligoamides of the type of Nylon 6 (H[Cap]$_n$OH, n = 2 to 4 and 8)[2], Nylon 11 (H[Und]$_n$OH, n = 2 to 5 and 10), and Nylon 6,6 (H[B–A]$_n$OH, n = 2 to 5 and 10).

[*] With collaboration by *G. Kalawrytinos*.

*Synthetic procedure*:

Step 1: The initial members of the above oligoamide series (n = 1) are converted into the readily soluble t-butoxycarbonyl derivatives and these are attached by ester bonds to chloromethylated polystyrene resin, *e.g.*:




Step 2: The amino group of the amino acid bound to the resin is unblocked and condensed with the corresponding BOC-amino acid by the DCC method[3] or by the mixed anhydride method[4], so that the chain is lengthened by one monomer unit.

Repetition of step 2 leads to further chain lengthening. At the end of the synthesis the ester bond between the resin and the oligomer is cleaved with HBr/glacial acetic acid. The oligomer set free is precipitated as oligoamide hydrobromide.

## Chemical Homogeneity of Binary Copolymers

*G. Markert*, Darmstadt (Germany)

The changes in chemical composition of mixtures of methyl methacrylate (MMA) and ethyl acrylate (EA) as a function of the conversion were calculated by an iteration method applied to the copolymerization equation. Extensive data obtained from eight initial mixtures permit integral and differential distribution curves to be drawn and regularities to be derived relating to the heterogeneity of the copolymers.

The distribution curves show that the chemical composition during polymerization changes the more the greater the difference between the chemical composition of the starting mixture and the polymer formed initially.

Some details can be deduced from the differential distribution curves, namely:

Starting mixtures with 15–70 % by weight of MMA give very heterogeneous polymers.

Of pairs mixed in reciprocal proportions the MMA-richer polymerizes more homogeneously.

Distribution curves have the highest symmetry when heterogeneity is large.

Units for characterization of the chemical heterogeneity proposed in the literature agree only partly with these results. In contrast, the frequency of the various over-all compositions provides a good measure of chemical homogeneity.

## Molecular Properties and Mode of Action of RNA Polymerase

*R. L. Millette*, *E. Fuchs*, and *W. Zillig*, München (Germany)

DNA-dependent RNA polymerase from *E. coli* has been prepared by a method that largely precludes changes in the

[1] *R. B. Merrifield*, Federat. Proc. *21*, 412 (1962).

[2] Abbreviations: [Cap] = $-NH(CH_2)_5CO-$, [Und] = $-NH(CH_2)_{10}CO-$; [B] = $-NH(CH_2)_6NH-$, [A]′ = $-OC(CH_2)_4CO-$, BOC = $(CH_3)_3C-O-CO-$.

[3] *J. C. Sheehan*, *G. P. Hess*, and *M. Goodman*, J. Amer. chem. Soc. *77*, 1067 (1955); *78*, 1367 (1956).

[4] *Th. Wieland* and *H. Bernhard*, Liebigs Ann. Chem. *572*, 190 (1951); *R. A. Boissonnas*, Helv. chim. Acta *34*, 874 (1951).

enzyme during isolation. It is based essentially on the high sedimentation coefficient of the enzyme. Together with differential centrifugation, chromatography on DEAE cellulose, precipitation with ammonium sulfate, and separation by zone electrophoresis in a sucrose gradient lead to a pure product that appears homogeneous in the analytical ultracentrifuge as well as on chromatography and electrophoresis. The physical and enzymatic properties of the purified enzyme are in accord with the properties established for the crude extract.

The Svedberg constant, $S_{20,w,c \to 0}$, is 24 S. The molecular weight is about 600000.

Electron micrographs (negative contrast) show the enzyme particles in two orientations. From these photographs a preliminary model can be derived in which six cylindrical subunits form the wall of a hollow cylinder whose internal "bore" has about the same cross-sectional area as a single subunit. The length of the enzyme particle is about 95 Å, the external diameter of the hollow cylinder is about 125 Å, and of the "bore" about 40 Å. Use of these dimensions and this model, and assuming a partial specific volume of 0.74, permit calculation of the molecular weight as about 600000 (cf. above).

When the ionic strength is increased, the enzyme particle dissociates reversibly into subunits of Svedberg constant $S_{20,w} = 12$ S and a molecular weight which is about one third of the molecular weight of the 24 S particle. These subunits no longer bind DNA and are thus enzymatically inactive. The enzymatic activity of the enzyme concerned with RNA synthesis is increased by raising the ionic strength. Enzyme particles that synthesize RNA are thus neither disintegrated nor separated from the DNA. Highly purified enzyme, when disintegrated in 6 M urea solution at pH 3.8, gives several bands on electrophoresis on starch gel, whence a complex composition involving various polypeptide chains appears probable.

The complex of DNA and polymerase can be recognized in the electron microscope. Analysis of such photographs provides information about the function of the enzyme.

In a cell-free DNA-dependent system from *E. coli*, synthesis of proteins commences already with nascent RNA. Synthesis of RNA and formation of protein thus proceed in the same direction.

## Phase Separation in Solutions of Polydisperse Polymers

*G. Rehage*, Aachen (Germany)

Isobaric phase-separation curves for binary systems are usually obtained from measurements of turbidity. The turbidity curve alone does not suffice for a description of phase separation in solutions of a polydisperse polymer. This was shown by diffusion measurements on the system polystyrene/cyclohexane, which shows a miscibility gap below 28 °C.

The phase-equilibrium curve varies with the initial concentration. The turbidity curve lies partly above and partly below the phase-equilibrium curve. Its maximum is shifted towards smaller polymer concentration and higher temperature with respect to the critical point. The position of the critical point can be determined directly from the course of the turbidity curve and the ratio of the phase volumes, and indirectly from the dependence of the chemical potential and the diffusion coefficient on concentration. The results are explained by means of a three-component system consisting of the solvent and two polymeric components of different molecular weights.

The effects observed are the stronger the higher the polydispersity of the macromolecular component. The difference between the point of maximum turbidity and the critical point is a sensitive criterion of polydispersity. This was demonstrated for polystyrenes prepared by anionic polymerization.

## Activity Changes of Ziegler-Natta Catalysts by Prepolymerization of Small Amounts of α-Olefins

*H. Schnecko, P. Freyberg, M. Reinmöller*, and *W. Kern*, Mainz (Germany)

Ageing of Ziegler-Natta catalysts, *i.e.* the action of the catalyst components on one another at the temperature of the subsequent polymerization, is usually carried out in absence of the monomer. This paper reports experiments in which ageing of the catalyst [mainly the system $Al(C_2H_5)_2Cl/TiCl_3$] was effected in the presence of small amounts of monomeric α-olefins (ethylene, propene, 1-butene, or 1s hexene). Partial polymerization of the olefins (prepolymerization) occurs during this time (usually 1 hour at 60 °C).

The rate of subsequent actual polymerization (main polymerization) of ethylene or propene with catalysts aged in this way is markedly different from the initial rate. It is lowered by preaddition of ethylene, but raised by preaddition of propene or higher α-olefins. The differences disappear with longer polymerization times. It is probable that copolymers are formed between the olefins used for prepolymerization and main polymerization.

The positive and negative changes in activity of the catalyst can in part be explained by the processes that occur in normal ageing. However, in addition, changes in solubility must be assumed to occur, caused by the products of the prepolymerization.

## The Formation of Oligomeric Amyloses by the Enzyme Amylomaltase

*G. V. Schulz, V. Häselbarth, H. E. Keller*, and *H. Schwinn*, Mainz (Germany)

The amylomaltase discovered by *Monod* in 1948 has been isolated in highly purified form. The enzyme has a sedimentation constant of 5.6 S and, on the basis of its elution volume from a Sephadex column, has a molecular weight of about 130000, in agreement with *Wiesmeyer* and *Cohn*'s results (M = 124000). The turnover number is about 10500 moles of maltose per mole of enzyme per minute, *i.e.* almost one order of magnitude higher than given by *Wiesmeyer* and *Cohn*.

Amylomaltase catalyses establishment of the equilibria

$$2\,G_2 \overset{K_1}{\rightleftharpoons} G_3 + G_1$$

$$G_3 + G_2 \overset{K_2}{\rightleftharpoons} G_4 + G_1$$

$$G_n + G_2 \overset{K_{n-1}}{\rightleftharpoons} G_{n+1} + G_1$$

($G_1$ = glucose, $G_2$ = maltose, *etc.*). The molar ratios of the oligomers were determined by thin-layer chromatography after the equilibria had been established, and the equilibrium constants were calculated therefrom. Since separations can be achieved up to maltopentaose, the constants $K_1$, $K_2$, and $K_3$ could be obtained and the mean equilibrium constant $\overline{K}$ could be calculated for the higher oligomers from their total amounts. At 23 °C the values $K_1 = 0.91$, $K_2 = 1.00$, $K_3 = 1.03$, and $\overline{K} = 1.04$ were found.

Further experiments showed that the enzyme is not specific for maltose but also catalyses establishment of the above equilibria with pure maltotriose or maltotetraose as substrate. Thus the general reaction is

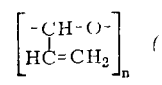
$$G_n + G_m \rightarrow G_{n+1} + G_{m-1}.$$

## Acid-Catalysed Degradation of Poly-3,4-acrolein

*R. C. Schulz, G. Wegner*, and *W. Kern*, Mainz (Germany)

Structurally homogeneous poly-3,4-acrolein *(1)* can be prepared by anionic polymerization of acrolein with sodium cyanide below 0 °C. Under these conditions, acrolein poly-

merizes exclusively at the C=O double bond. The polymers are colorless powders, dissolve in many organic solvents, and soften at 70 to 80 °C. In contrast to other polymeric



(1)

aldehydes, which often decompose spontaneously even at room temperature, poly-3,4-acrolein is remarkably stable, though it also is degraded by acids. This acid-catalysed degradation was followed viscometrically. The kinetic study showed that degradation proceeds almost exclusively by chain cleavage, which does not cause a "zip" reaction. The activation energy of chain cleavage amounts to 10.6 kcal/mole in dioxane and 12.8 kcal/mole in chloroform. Acid-catalysed depolymerization occurs only to a minor extent; it was followed by ultraviolet-spectroscopic determination of the monomeric acrolein formed on hydrolysis. The activation energy of depolymerization is 19.8 kcal/mole.

The stability of poly-3,4-acrolein towards acids is explained by formation of a resonance-stabilized cationic fragment, whereby the activation energy of depolymerization is greatly increased.

## Study of Structural Changes in Biopolymers by Chemical Relaxation

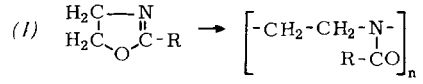
*G. Schwarz*, Göttingen (Germany)

Structural changes of biopolymers in solution generally comprise a very large number of individual steps. Use of chemical relaxation for study of the kinetics of such processes leads to relaxation curves with a complicated spectrum of relaxation times from which a mean relaxation time can be determined. A kinetic model of the structural change consisting of rapid growth steps and slow nucleation steps permits the mean value to be calculated theoretically. For certain conditions complete relaxation curves can also be calculated on this model. A mean relaxation time of the order of $10^{-7}$ second is obtained for the helix-coil transformation of polypeptides, and this is in agreement with current experimental results.

## Polymerization of 2-Oxazolines

*W. Seeliger* and *W. Thier*, Marl (Germany)

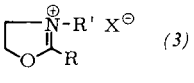
2-Oxazolines *(1)* can be converted into high-molecular poly-*N*-acylethyleneimines *(2)* by cationic catalysts.



(1) (2)

Polymerization of oxazolines is exothermal, the conversion of the imino ester into the amide structure being considered to provide the driving force.

A temperature of at least 110 °C is required for sufficiently rapid polymerization of the 2-oxazolines. Complete conversion is generally achieved within a few hours. Interruption of polymerization after incomplete conversion gives products with relatively low values of the reduced viscosity.



(3)

Compounds of formula *(3)* are suitable catalysts; they may be added as such or produced *in situ* by adding strong acids or their esters or anhydrides to the basic 2-oxazolines. R′ is then H, alkyl, or acyl, and $X^-$ is the weakly nucleophilic anion of a strong acid. Friedel-Crafts catalysts are also effective, and so are sulfuric acid and dialkyl sulfates, sulfonic acids and their alkyl esters, alkyl iodides, benzoyl *p*-toluenesulfonyl anhydride, iodine, crystalline salts of 2-oxazolines with *p*-toluenesulfonic or perchloric acid, $BF_3$ etherate, and *p*-nitrobenzenediazonium fluoroborate.

A mechanism for polymerization of 2-oxazolines is proposed in which the active end groups consist of oxazolinium cations that, formally from their oxonium limiting structures, alkylate the basic monomers and thus lead to the formation of new oxazolinium cations. According to this proposal, "living polymers" should be formed with stable end groups and narrow distributions of molecular weight.

Undiluted monomers are usually used for the polymerization, but solvents may also be added.

## Copolymerization in Systems with a Polymerization-Depolymerization Equilibrium

*P. Wittmer*, Ludwigshafen (Germany)

One of the conditions for validity of the well-known copolymerization equation [1] is irreversibility of all the growth reactions. If this condition is not fulfilled, the depolymerization reaction must be taken into account. The following copolymerization equation has been derived for the case where the propagation step in homopolymerization of one of the two monomers ($M_1$) is reversible:

$$\frac{d[M_1]}{d[M_2]} = \frac{1 + (r_1[M_1]/[M_2]) - (r_1K/[M_2])(1-x_1)}{1 + (r_2[M_2]/[M_1])}$$

Here K is the equilibrium constant between polymerization and depolymerization, and $x_1$ is the fraction of the active chains of the monomer $M_1$ with the sequence length 1. The following equation holds for $x_1$:

$$1-x_1 = \frac{r_1([M_1]+K)+[M_2]}{2r_1K} - \left[\left(\frac{[(r_1([M_1]+K)+[M_2]}{2r_1K}\right)^2 - \frac{[M_1]}{K}\right]^{1/2}$$

The equations contain three parameters, of which only two are freely disposable, namely, the two r values; the third (K) is determined by equilibrium measurements, carried out independently of the copolymerization system.

α-Methylstyrene was used as monomer whose polymerization reaches an equilibrium. The constants K for various polymerization temperatures (0–100 °C) were taken from the literature [2]. Methyl methacrylate and acrylonitrile were the comonomers; polymerizations were radical-induced in the absence of solvent. The new equations were found suitable to describe the copolymerization. The temperature-dependence of the r values can be represented by Arrhenius straight lines, as required by theory.

## Preparation of Star-Shaped Polymers by Anionic Polymerization

*J.-G. Zilliox*, *D. Decker*, and *P. Rempp*, Strasbourg (France)

The absence of spontaneous termination reactions in anionic polymerizations can be utilized for various syntheses. Star-shaped polystyrene molecules can be prepared by allowing "living" polystyrene to react with a polyfunctional deactivator, *e.g.* carbon tetrachloride, tribromomesitylene, or tetra(chloromethyl)siloxane [3]. The deactivation is, however,

[1] *L. Küchler*: Polymerisationskinetik. Springer, Berlin-Göttingen-Heidelberg 1951, p. 162.

[2] *H. W. McCormick*, J. Polymer. Sci. *25*, 488 (1957).

[3] See, *e.g.*, *S. P. Siao Yen*, Makromolekulare Chem. *81*, 152 (1965).

not always quantitative, and steric hindrance can also occur. In the best cases the number of polystyrene chains linked to each other is equal to the functionality of the deactivator.

A different method of preparing star-shaped molecules has been developed in the authors' laboratory: Divinylbenzene is treated with monofunctional "living" polystyrene and block-copolymerized. It is known that polymerization of divinylbenzene leads to a cross-linked insoluble polymer. However, in the present case the polymer remains completely soluble, provided that the amount of bifunctional monomer does not exceed 30 % of the tota amount of material. Solvated polystyrene branches are responsible for the solubility of the cross-linked stem which itself is insoluble.

The degree of branching depends on the experimental conditions and can reach high valucs. The polymeric products can be separated by fractional precipitation; successive fractions consist of star-shaped polymers with regularly decreasing degrees of branching.

[VB 977/294 IE]

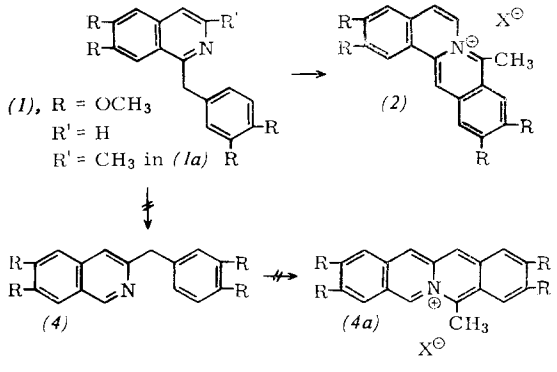
German version: Angew. Chem. *78*, 608 (1966)

## Acetylation of Benzylisoquinolines

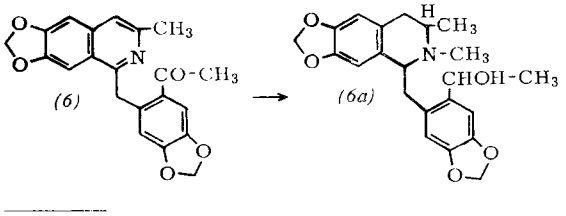
*W. Wiegrebe*, Brunswick (Germany)

According to *Awe*[1], the reaction of the 1-benzylisoquinoline alkaloid papaverine *(1)* with acetic anhydride and sulfuric acid that affords the berbine derivative "coralyn" *(2)* can be used to identify papaverine. However, 6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)-3-methylisoquinoline *(3)* cannot be converted into a coralyn derivative by acetylation. Several hypotheses have been forwarded to explain this failure of coralyn formation from *(3)*.

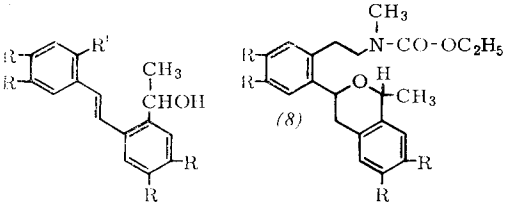
According to the paraberine hypothesis, coralyn has a paraberine and not a berbine structure. This hypothesis assumes, for example, that papaverine *(1)* rearranges to 6,7-dimethoxy-3-(3′,4′-dimethoxybenzyl)isoquinoline *(4)*, from which a paraberine *(4a)* is formed after acetylation. Compound *(4)* has been synthesized, but on acetylation does not give coralyn; this disproves the paraberine hypothesis.




Under the conditions of the acetylation, *(3)* gives 6,7-methylenedioxy-1-(3′,4′-diacetoxybenzyl)-3-methylisoquinoline *(5)* and 6,7-methylenedioxy-1-(2′-acetyl-4′,5′-methylenedioxybenzyl)-3-methylisoquinoline *(6)*; the structures of both these products have been demonstrated by chemical degradation and infrared and NMR spectroscopy and mass spectrometry[*]. For comparison with the tetrahydroisoquinolylalcohol *(6a)* formed from *(6)*, 1,2,3,4-tetrahydro-1-[2′-(1-hydroxyethyl)-4′,5′-dimethoxybenzyl]-6,7-dimethoxy-2-methylisoquinoline was prepared and subjected to degradation with ethyl chloroformate[2].

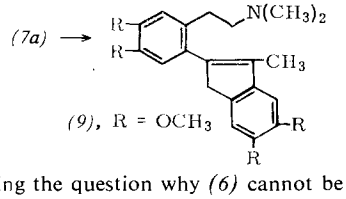



This produced mainly 3-[2′-(*N*-ethoxycarbonyl-*N*-methylamino)ethyl-4′,5′-dimethoxyphenyl]-6,7-dimethoxy-1-methylisochroman *(8)*, together with 2-[2-(*N*-ethoxycarbonyl-*N*-methylamino)ethyl]-2′-(1-hydroxyethyl)-4,4′,5,5′-tetramethoxy-*trans*-stilbene *(7)*. This stilbene is a by-product and not an intermediate in the formation of the isochroman *(8)*. The *N*,*N*-dimethylamino base *(7a)* corresponding to *(7)* is converted by acid into 2-[2-(2-dimethylaminoethyl)-4′,5′-dimethoxyphenyl]-5,6-dimethoxy-3-methylindene *(9)*.

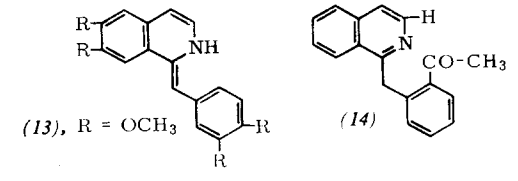



(7), R' = $CH_2$-$CH_2$-$N(CH_3)$-CO-$OC_2H_5$

(7a) R' = $CH_2$-$CH_2$-$N(CH_3)_2$




Regarding the question why *(6)* cannot be converted into a coralyn analogue, *Halpaap*[1] suggested that the ring closure is prevented by the 3-methyl group, whereas *Hertel*[1] contended that it is hindered by the methylenedioxy substituents in the benzyl residue. The latter view is, however, contradicted by the fact that 6,7-methylenedioxy-1-(3′-methylbenzyl)isoquinoline *(10)* and its 1-(3′,4′-methylene-dioxybenzyl)-6,7-dimethoxyisoquinoline *(11)* yield coralyn analogues. On the other hand, although 3-methylpapaverine *(1a)* can be converted into its 2′-acetylbenzyl derivate *(12)*, it does not react further to give a coralyn derivative, thus confirming *Halpaap*'s view. The position of the acetyl group in *(12)* was elucidated mainly by NMR spectra[3]. The NMR spectra of the bases and cations from *(1)* and *(12)* show that these substances do not possess the benzylidene structures *(13)* that have been discussed as possible intermediates in coralyn formation, despite their theoretical unlikelihood Coralyn formation occurs by way of a (2′-acetylbenzyl)isoquinoline *(14)*, in a manner resembling the transformation of berberine aldehyde to the corresponding quaternary salt.




[Lecture at Braunschweig (Germany), Jan. 24th, 1966]

[VB 984 IE]

German version: Angew. Chem. *78*, 647 (1966)

[1] *W. Awe*, *H. Halpaap*, and *O. Hertel*, Arzneimittel-Forsch. *10*, 936 (1960).

[*] We thank Drs. *Dolejš* and *Hanuš*, Prague (CSR), for measuring the mass spectra.

[2] *J. Knabe* and *U. R. Shukla*, Arch. Pharmaz. *295*, 871 (1962).

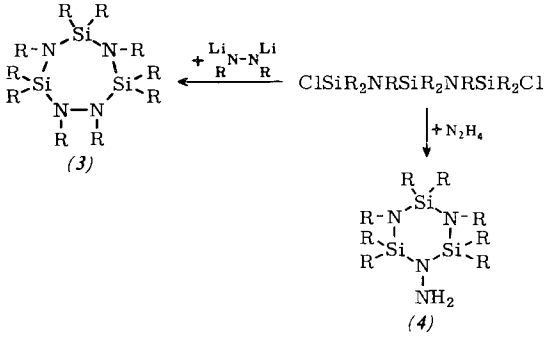
[3] *L. Pohl* and *W. Wiegrebe*, Z. Naturforsch. *20b*, 1033 (1965).

## Silyl Derivatives of Hydrazine and Hydroxylamine

*U. Wannagat*, Brunswick (Germany)

Pure 1,2-bis(trimethylsilyl)hydrazine *(1)* is obtained by reaction of hydrazine with chlorotrimethylsilane only below 20 °C and then only in moderate yield (ca. 25 %). Longer stirring and boiling under reflux lead to a mixture of the 1,2- and the 1,1-isomers *(2)*. The two products can be separated by gas chromatography and identified by infrared and Raman spectroscopy: *(2)*, $\nu_{as}$-SiNSi = 1005, $\nu_s$-SiNSi = 490, $\delta$-$NH_2$ = 1575 $cm^{-1}$. The two products are very similar in their physical properties, *e.g.* in melting point [*(1)* −64 °C, *(2)* −61 °C] and boiling point [*(1)* 149 °C, *(2)* 158 °C].

Analogous silylation of 1,1- and 1,2-dimethylhydrazine affords the monosilylated derivatives (R=$CH_3$),$R_2NNHSiR_3$, b.p.100 °C/721 mm, $\tau(SiCH_3)$=10.05 ppm,and $RHNNRSiR_3$, b.p. 109 °C/762 mm, $\tau(SiCH_3)$ = 9.96 ppm, which on further silylation by the above method yield the doubly silylated derivatives $R_2NN(SiR_3)_2$, b.p. 63 °C/13 mm, $\tau(SiCH_3)$ 9.99 ppm, and $R_3SiRNNRSiR_3$, b.p. 61 °C/13 mm, $\tau(SiCH_3)$ 9.87 ppm. Although the reaction of 1,5-dichlorooctamethyltrisilazane with the dilithium derivative of 1,2-dimethylhydrazine gives a seven-membered SiN ring compound, *viz.* decamethyl-1,2,4,6-tetraza-3,5,7-trisilacycloheptane *(3)* [R = $CH_3$, m.p. 42–43 °C, b.p. 67 °C/0.1 mm, $\tau(SiCH_3)$ 9.95 and 9.92 ppm in the ratio 2:1, $\tau(NCH_3)$ = 7.56 and 7.42 ppm in the ratio 1:1], the analogous reaction with hydrazine itself gives only the six-membered SiN ring compound, *N*-aminooctamethylcyclotrisilazane *(4)* [R = $CH_3$, m.p. 45 °C, b.p. 57 °C/0.05 mm] as is to be seen particularly from the infrared spectra.




Many of the silylated hydrazines show hypergolic behavior with fuming nitric acid (ignition time *ca.* 10 msec), inflame at once in fluorine, and explode when dropped into solutions of $O_3$ in liquid oxygen.

The following new silylated hydroxylamines have also been prepared: $(C_2H_5)_2NOSiR_3$. b.p. 35 °C/15 mm, from $(C_2H_5)_2NOH$; RO–NR–$SiR_3$, b.p. 98 °C/734 mm, from RO–NHR; and $(R_3Si)_2[NHO]$, b.p. 80 °C/97 mm, from $H_2NOH$; the last compound gives only one $R_3Si$ signal ($\tau$ = 9.94 ppm) in its $^1$H-NMR spectrum and is therefore presumably *N,N*-bis(trimethylsilyl)hydroxylamine. *O*-Silylated hydroxylamines are not cleaved at the Si–O bond by phenyl isocyanate.

[Lecture at Würzburg (Germany), Jan. 28th, 1966]

[VB 986 IE]

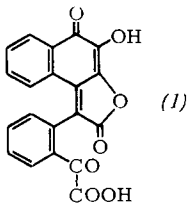
German version: Angew. Chem. *78*, 648 (1966)

## Constitution of the "Classical" 3-Hydroxy-1,2-naphthoquinone

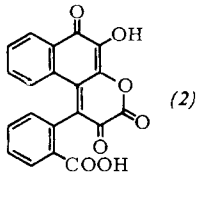
*H.-J. Teuber*, Frankfurt/Main (Germany)

*Zincke*[1] reported that autoxidation of naphthopyrogallol (1,2,3-naphthalenetriol) as well as oxidation of 1-amino-2,3-naphthalenediol[2] by iron(III) chloride gives a well-crystalline, ocher- or orange-colored compound which has hitherto been held to be 3-hydroxy-1,2-naphthoquinone[1–3].

This compound is best obtained from 2,3-naphthalenediol by oxidation with potassium nitrosobissulfate[4]. It is dimeric and has structure *(1)* or *(2)*.

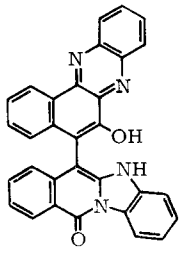



*(1)*

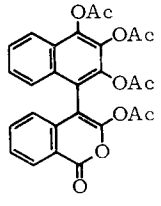



*(2)*

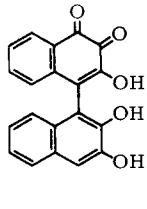
Since the compound is readily decarboxylated, like phenylglyoxylic acid, we prefer formula *(1)*. In agreement with this formulation are the spectra (the NMR spectrum, for instance, shows no aliphatic H), formation of naphthalene on distillation with zinc dust and of phthalic acid (not homophthalic acid!) on degradation with alkaline hydrogen peroxide, and absorption of only 1 mole of hydrogen on catalytic hydrogenation. Compound *(1)* – or *(2)* – condenses with 2 moles of *o*-phenylenediamine, giving *(3)*; with acetic anhydride it gives a tetraacetate, the isocoumarin derivative *(4)*, again with loss of one C atom; 1,2,3-triacetoxynaphthalene[5] is also formed in the latter reaction.




*(3)*




*(4)*




*(5)*

Compound *(1)* – or *(2)* – can be titrated as a dibasic acid (color change to purple); it is not obtained if the 4-position of 2,3-naphthalenediol is alkylated. Junction of the two naphthalene systems at positions 4′ and 1 in compounds *(1)* and *(2)* is indicated also by formation of compound *(1)* – or *(2)* – from the violet precursor *(5)* with potassium nitrosobissulfate or by disproportionation of the colorless dimeric 3-hydroxy-1,2-naphthoquinone[4].

[Lecture at Berlin, Feb. 8th, 1966]

[VB 991 IE]

German version: Angew. Chem. *78*, 647 (1966)

[1] *Th. Zincke* and *H. Noack*, Liebigs Ann. Chem. *295*, 6 (1897); *Th. Zincke* and *A. Ossenbeck*, *ibid.* *307*, 1 (1899).

[2] *P. Friedländer* and *L. Silberstern*, Mh. Chem. *23*, 513 (1902).

[3] *H. Erdtman*, Liebigs Ann. Chem. *513*, 240 (1934).

[4] *H.-J. Teuber* and *G. Steinmetz*, Chem. Ber. *98*, 666 (1965).

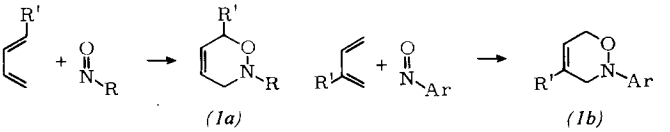
[5] *J. Hohn*, unpublished.

## Diene Syntheses of Heterocyclic Compounds

*G. Kresze*, Munich (Germany)

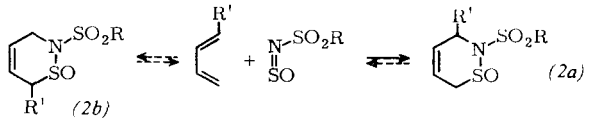
(2 + 4)-Cycloaddition is a particularly good method for the preparation of heterocyclic compounds when the dienophile contains hetero-atoms.

Nitroso compounds (aromatic nitroso and α-halogeno-nitroso compounds) react most readily. A monosubstituted diene affords mainly or exclusively the 3,6-dihydro-1,2-oxazine *(1a)* or *(1b)*.



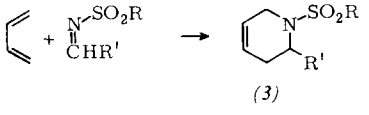

*(1a)* *(1b)*

Moreover, diene syntheses with *N*-sulfinyl compounds, and in particular *N*-sulfinylsulfonamides, lead to substituted 3,6-dihydro-1,2-thiazine 1-oxides when the reaction is under kinetic control. In some cases, however, an equilibrium mixture *(2a)* ⇄ *(2b)* results.



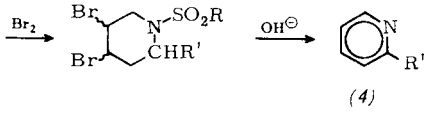
*(2b)* *(2a)*

*N*-Sulfonylimines, which can be obtained from *N*-sulfinylsulfonamides and a few aldehydes, are active as dienophiles if the carbon atom to which the imino group is attached carries a substituent that acts as an electron acceptor. The



*(3)*

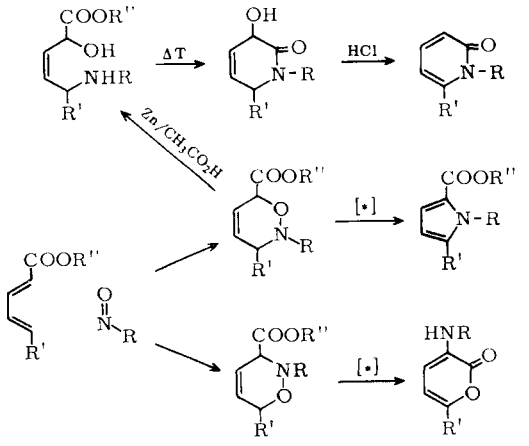
R' = $CCl_3$, COOR''



*(4)*

1,2,3,6-tetrahydropyridines obtained with dienes in good yield can be converted into pyridine derivatives *(4)* by bromination and subsequent removal of HBr and sulfinic acid.

Adducts of dienecarboxylic esters and nitroso compounds can be converted into other heterocyclic compounds:



The first step in the conversion of the oxazine derivatives involves an inverse β-fragmentation:

which appears to be a general reaction.

[Lecture at Aachen (Germany) on May 6th, 1966]

[VB 992 IE]

German version: Angew. Chem. *78*, 648 (1966)

[*] Chromatography on $Al_2O_3$ or treatment with bases in protic solvents.

# SELECTED ABSTRACTS

**A new synthesis of isocyanates under mild conditions,** from primary amines, carbon monoxide, and $PdCl_2$, is reported by *E. W. Stern* and *M. L. Spector*. The $PdCl_2$ is reduced to metal in the reaction. Aniline *e.g.*, afforded phenyl isocyanate in 68 % yield; n-butylamine afforded n-butyl isocyanate (49 % yield). Presumably a complex is formed among the amine, carbon monoxide, and the palladium compound, its decomposition leading to the observed products. / J. org. Chemistry *31*, 596 (1966) / –Bu. [Rd 486 IE]

**A solution of dichloroketene,** $Cl_2C{=}C{=}O$, was obtained for the first time by *W. T. Brady*, *H. G. Liddell*, and *W. L. Vaughn* when they treated trichloroacetyl chloride with zinc (activated with Cu) in anhydrous ether or ethyl acetate. Dichloroketene can be kept in these solvents for several days at 5 °C. It could not be isolated in substance because of its great tendency to polymerize, but it partially co-distils with octane or decane at reduced pressure. The infrared spectrum of the distillate shows a band at 1940 $cm^{-1}$, assigned to the C=C=O group. Chemical identification (and at the same time determination of the yield) of dichloroketene was achieved in reactions with ammonia, benzylamine, or aniline to give the corresponding dichloroacetamides in yields of up to 96 %. / J. org. Chemistry *31*, 626 (1966) / –Bu.

[Rd 485 IE]

**2,4,6-Triisopropylbenzenesulfonyl chloride was used to effect internucleotide linkages** by *R. Lohrmann* and *H. G. Khorana*. The $C_3'$–$C_5'$ internucleotide linkage was achieved with good yields. *R. Lohrmann*, *D. Söll*, *H. Hayatsu*, *E. Ohtsuka*, and *H. G. Khorana* synthesized the 64 possible ribotrinucleotides derivable from adenosine, cytidine, guanosine, and uridine, yields of trinucleoside diphosphates averaging 70–80 %. / J. Amer. chem. Soc. *88*, 819, 829 (1966) / –De.

[Rd 489 IE]

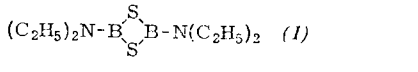
**Thiols can be selectively and irreversibly removed from aqueous solutions by poly[N-vinylphenylmaleic imide].** *E. G. Richards*, *D. L. Snow*, and *C. W. F. McClare* suggest using the polymer as column filling or adding it in portions to the solution, as a means of removing thiols and SH-proteins from biological preparations. The polymer is readily prepared from polyaminostyrene and maleic anhydride. The pale brown powder, when used as column filling at pH 7, has a capacity of *ca.* 1.3 mmole of SH per ml of column volume, measured with 2-mercaptoethanol. Nucleotides and transfer-RNA are not retained on the column; proteins are retained in accord with their SH content. / Biochemistry *5*, 485 (1966) / –Hö.

[Rd 472 IE]

**Twelve new buffers** for biochemical reactions in the pH range 6.1–8.3 are introduced by *N. E. Good et al.* There have hitherto been few suitable buffers available for this range. The substances proposed (with their $pK_a$ values at 30 °C) are: 1. 2-morpholinoethanesulfonic acid (6.15); 2. *N*-(carbamoylmethyl)iminodi(acetic acid) (6.6); 3. 1,4-piperazinedi(ethanesulfonic acid) (6.8); 4. 2-(carbamoylmethylamino)ethanesulfonic acid (6.9); 5. *N,N,N*-trimethyl-2-ammonioethylammonium dichloride (= cholamine) (7.1); 6. 2-[bis(2-hydroxyethyl)amino]ethanesulfonic acid (7.15); 7. 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (7.55); 8. 2-*N*-[tris(hydroxymethyl)methyl]aminoethanesulfonic acid (7.5); 9. *N*-(carbamoylmethyl)glycine (7.7); 10. *N*-[tris-(hydroxymethyl)methyl]glycine (8.15); 11. Glycine amide hydrochloride (8.2); 12. *N,N*-bis(2-hydroxyethyl)glycine (8.35). Reduction of hexacyanoferrate(III) by illuminated chloroplasts was used as test reaction for biological suitability as well as oxidation of succinate by oxygen with help of plant mitochondria (followed manometrically), and protein biosynthesis in cell-free extracts of *Escherichia coli*. / Biochemistry *5*, 467 (1966) / –Hö. [Rd 473 IE]

**Lithium hydridotris-(t-butoxy)aluminate** is a selective reducing agent for the conversion of phenyl esters into aldehydes under mild conditions, as shown by *P. M. Weissman* and *H. C. Brown* for phenyl esters of aliphatic carboxylic acids. The yields are around 70%. The method is not applicable to aromatic, α,β-unsaturated, or cyclopropanecarboxylic acids. Examples: Phenyl cyclohexanecarboxylate → cyclohexanecarbaldehyde; phenyl hexanoate → hexanal / J. org. Chemistry *31*, 283 (1966) / –Bu. [Rd 462/671 1E]

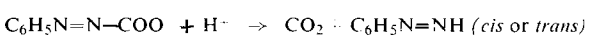
**Cyclic boron-sulfur compounds** have been described by *J. A. Forstner* and *E. L. Muetterties*. Hydrogen, alkanes, and exclusively the dithiadiboretane derivative *(1)* are formed on treatment of hydrogen sulfide with triethylamine-borane at 200 °C.



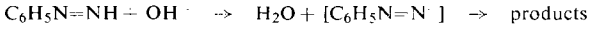
*(1)*

The product was resublimed and recrystallized from pentane. It is soluble in chloroform and carbon tetrachloride and melts at 70 °C in a vacuum. Molecular-weight determinations (cryoscopy in benzene and ebulliometry in $CCl_4$) confirm the molecular size proposed. The proton resonance spectrum shows a quartet at −3.3 ppm and a triplet at 1.2 ppm. Treatment of hydrogen sulfide with trimethylamine-borane gives the known compound $[(CH_3)_2NBS]_3$ containing a six-membered ring, instead of a compound with a four-membered ring. / Inorg. Chem. *5*, 164 (1966) / –Sch. [Rd 480 1E]

**Phenyldiimine** *(1)*, which has been assumed as intermediate *inter alia* in the oxidation of phenylhydrazine and the decarboxylation of phenylazoformic acid, has been detected in solution by *E. M. Kosower* and *Pih-kuei C. Huang*. On mixing of a degassed solution of the phenylazoformate ion *(2)* with phosphate buffer of pH 7.10, a new absorption spectrum, assigned to *(1)*, appears with maxima at 2140, 2700, and 4000 Å. The half-life of *(1)* at pH 7.3 is 80000 sec;

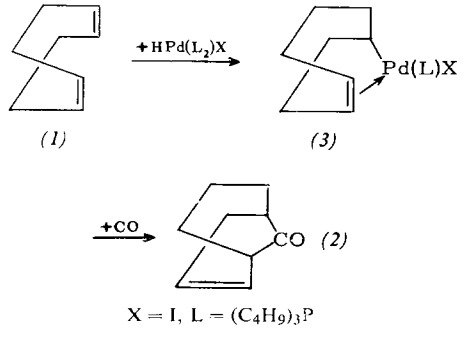


*(2)* *(1)*



at pH 13.7 compound *(1)* is completely destroyed in 100 sec, the main products being benzene, azobenzene, and hydrazobenzene. / J. Amer. chem. Soc. *87*, 4645 (1965) / –Ma. [Rd 454/663 1E]

**Transannular addition of carbon monoxide to cycloocta-1,5-diene** *(1)* was observed by *S. Brewis* and *P. R. Hughes*. Reaction of *(1)* with CO in tetrahydrofuran at 150 °C and 1000 atm in the presence of 1% of a palladium-containing catalyst

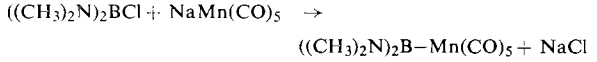



*(1)* *(3)* *(2)*

X = I, L = $(C_4H_9)_3P$

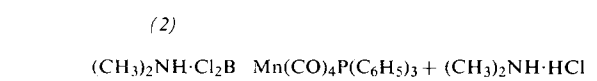
gave bicyclo[3.3.1]non-2-en-9-one *(2)* in 40–50% yield together with 45–50% of cycloocta-1,3-diene. Presumably *(2)* is formed *via* the adduct *(3)*. / Chem. Commun. *1966*, 6 / –Ma. [Rd 455/664 1E]

**Bis(dimethylamino)boron-pentacarbonylmanganese** *(1)* was obtained by *H. Nöth* and *G. Schmid* on treating sodium pentacarbonylmanganate with chlorobis(dimethylamino)-boron in tetrahydrofuran (yield 75%).

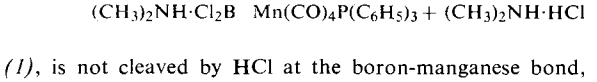


*(1)*

Compound *(1)* crystallizes as orange-red prisms, which, when fresh, decompose with melting from 60 °C. One mole of carbon monoxide is removed on treatment with triphenylphosphine, yielding bis(dimethylamino)boron-tetracarbonyl-(triphenylphosphine)manganese *(2)* as yellow crystals of m.p. 124 °C in 80% yield. Other reactions of compound *(1)* include cleavage of the boron-manganese bond with $Br_2$, $H_2$, or HCl, as well as hydrolysis. The complex *(2)*, in contrast to

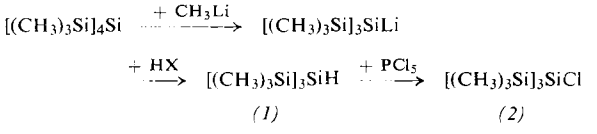


*(2)*



*(1)*, is not cleaved by HCl at the boron-manganese bond, but instead at the boron-nitrogen bond. / J. organomet. Chemistry *5*, 109 (1966) / –Sch. [Rd 478 1E]

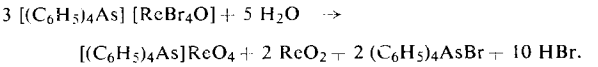
**Chlorotris(trimethylsilyl)silane** *(2)* is formed, according to *H. Gilman* and *R. Harrell*, in 50% yield in a three-stage synthesis.



*(1)* *(2)*

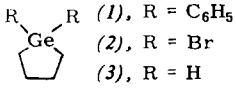
The chlorosilane *(2)*, b.p. 70–72 °C/0.5 mm Hg, m.p. 51–52 °C, can be obtained in 80–90% yield when *(1)* is treated with an excess of $CCl_4$. Chlorination of *(2)* at low temperatures leads to 2,2-dichlorohexamethyltrisilane, $[(CH_3)_3Si]_2SiCl_2$ *(3)* (yield 75%, b.p. 76–77 °C/10 mm); hydrolysis with aqueous tetrahydrofuran gives tris(trimethylsilyl)silanol, $[(CH_3)_3Si]_3SiOH$ (yield 68%; b.p. 81 °C/15mm). Compound *(3)* can be converted with methylmagnesium iodide into octamethyltrisilane and by $LiAlH_4$ into 1,1,1,3,3,3-hexamethyltrisilane (yield 60%; b.p. 65 °C/45 mm). / J. organomet. Chemistry *5*, 199 (1966) / –Sch. [Rd 479 1E]

**Oxotetrahalogenorhenates(V)** have been prepared by *F. A. Cotton* and *S. J. Lippard*. Reduction of potassium perrhenate with zinc in the presence of an excess of acid affords a new class of compound of general composition $L(ReX_4O)$, L being $(C_6H_5)_4As$, $(n\text{-}C_4H_9)N$, or $(C_2H_5)_4N$, and X being Cl, Br, or I. They probably contain a square-pyramidal ion $(ReX_4O)^-$ with strong π-bonding between oxygen and rhenium. $[(C_6H_5)_4As][ReBr_4O]$ *(1)* forms red prisms that are soluble in acetone, ethanol, acetonitrile, chloroform, or tetrahydrofuran but insoluble in diethyl ether or hydrocarbons. With $(C_6H_5)_3P$ in acetonitrile, *(1)* gives $ReBr_3(C_6H_5)_3P)_2O$, with HCl in acetone $[(C_6H_5)_4][ReCl_4O]$, with hot aqueous HBr $[(C_6H_5)_4As]_2[ReBr_6]$, and with sulfoxides in acetonitrile $[(C_6H_5)_4As]ReO_4$. The last-mentioned compound is also obtained by reaction with water:



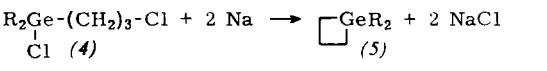
Compound *(1)* is diamagnetic. Its infrared spectrum indicates reversible addition of acetonitrile to form $[(C_6H_5)_4As][ReBr_4O(CH_3CN)]$. / Inorg. Chem. *5*, 9 (1966) / –Sch [Rd 474 1E]

**Germacyclopentanes and -butanes** have been prepared by *P. Mazerolles, J. Dubac,* and *M. Lesbre*. Treatment of dibromodiphenylgermane with Grignard compounds of 1,4-dibromobutane in benzene leads to compound *(1)* (70 % yield), and subsequent cleavage with bromine to *(2)* (80 % yield);



*(1)*, R = $C_6H_5$
*(2)*, R = Br
*(3)*, R = H

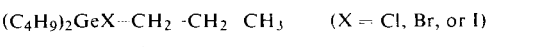
reduction with $LiAlH_4$ then gives germacyclopentane *(3)* (90 %) which is a liquid boiling at 91–92 °C. Chlorination of *(1)* with sulfuryl chloride affords 1,1-dichlorogermacyclopentane, b.p. 94 °C/64 mm Hg, in 90 % yield; by using $HgCl_2$, 1-chlorogermacyclopentane, b.p. 154 °C/745 mm, is obtained in 77 % yield. Synthesis of the cyclobutane derivatives *(5)* is achieved by treatment of chlorogermanium compounds *(4)* with sodium in boiling xylene.



$R_2Ge(Cl)-(CH_2)_3-Cl$ *(4)* + 2 Na → $GeR_2$ *(5)* + 2 NaCl

[*(5a)*, R = $C_4H_9$, yield 75 %, b.p. 111–112 °C/18 mm; *(5b)*, R = $C_2H_5$, yield 35 %, b.p. 77–78 °C/80 mm].

Ring scission of *(5a)* by HX affords compounds *(6)* quantitatively.

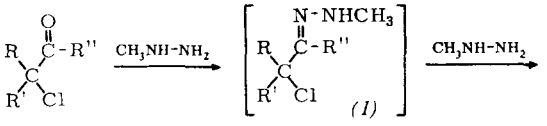


$(C_4H_9)_2GeX-CH_2-CH_2-CH_3$ (X = Cl, Br, or I)

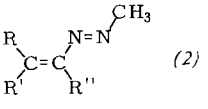
*(6)*

On reaction with sulfur, compound *(5a)* gives 2,2-dibutyl-1-thia-2-germacyclopentane, b.p. 130 °C 4 mm, in 84 % yield. / J. organomet. Chemistry *5*, 35 (1966) / –Sch. [Rd 475 IE]

**The synthesis of α,β-unsaturated aliphatic azo compounds,** previously unknown, is reported by *B. T. Gillis* and *G. D. Hagarty*. Reaction of α-chloroaldehydes or α-chloroketones with two equivalents of methylhydrazine (with or without solvent) leads by 1,4-dehydrochlorination of the intermediate hydrazone *(1)* to α,β-unsaturated methylazo compounds *(2)*, which have characteristic absorption spectra. Examples: 2-(methylazo)propene, b.p. 61–64 °C, yellow liquid, yield 31 %; 1-(methylazo)cyclohexene, b.p. 101–105 °C/80 mm Hg,



$CH_3NH-NH_2$ → [$R-C(=N-NHCH_3)-C(R')(Cl)-R''$] *(1)* → $CH_3NH-NH_2$



*(2)*

yellow, 61 %; 1-(methylazo)isobutene, b.p. 75–80 °C/200 mm, yellow, 35 %. / J. Amer. chem. Soc. *87*, 4576 (1965) / –Ma. [Rd 451/660 IE]

**Infrared spectra of cesium and tetraalkylammonium salts containing the anions $HCl_2^-$ and $DCl_2^-$** have been measured by *J. C. Evans* and *G. Y-S. Lo*. The salts were obtained by condensation of HCl or DCl onto the ordinary chlorides at −90 °C. The unstable Cs salts were studied at −78 °C, the ammonium salts at 25 °C. The spectra of the salts, dissolved in benzene, methylene dichloride, or acetonitrile, or suspended in Nujol, showed the structures of the anions to depend on the nature of the cations. The tetraethyl-, tetrapropyl-, and tetrapentyl-ammonium salts contain linear, symmetrical $HCl_2^-$ ions with a single potential minimum; for the cesium, tetramethylammonium, and trimethylhexadecylammonium salts the distances between the H or D atom and the two Cl atoms differ. / J. physic. Chem. *70*, 11 (1966) / –Hz. [Rd 467 IE]

**Kinetic data for irreversible electrochemical reductions** have been calculated from polarographic maxima by *A. Saraby-Reinjes* and *J. Th. G. Overbeek*. If these data are to be determined from the height of the diffusion-controlled polarographic steps, surface-active substance such as gelatin must be added to suppress the polarographic maxima; these, however, materially alter the kinetics of the reaction. The authors have found a simple empirical relation for the concentration polarization:

$$\log(c/{}^{\circ}c) \propto i_c$$

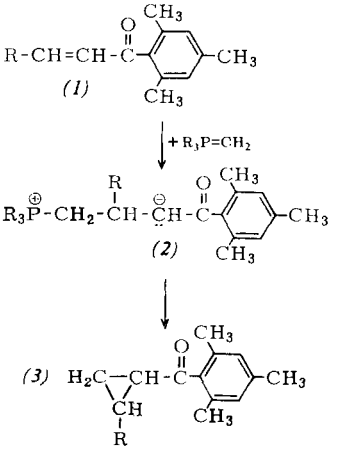
(c, °c concentrations of depolarizer in the bulk of the solution and at the electrode surface, respectively; $i_c$ cathode current).

which permits the current-potential curve to be evaluated up to currents double the value of the limiting diffusion current. In this way the following data for the reduction of bivalent cobalt and manganese in solutions containing lithium or magnesium perchlorate as supporting electrolyte were determined:

0.002M $Co(NO_3)_2$ in 0.02 M $LiClO_4$: $\alpha n_a = 0.753_5$; $\log k_o = 11.13$
0.02 M $Mg(ClO_4)_2$: $\alpha n_a = 0.730$; $\log k_o = 11.10$
0.002 M $MnSO_4$ in 0.04 M $LiClO_4$: $\alpha n_a = 1.783$; $\log k_o = 8.05$
0.02 M $Mg(ClO_4)_2$: $\alpha n_a = 1.744$; $\log k_o = 7.86$

where $k_o$ is the rate constant of the transfer reaction in cm/sec, α is transfer constant, $n_a$ the number of electrons involved in the rate-determining step. / Trans. Faraday Soc. *62*, 182 (1966) / –Hz. [Rd 465 IE]

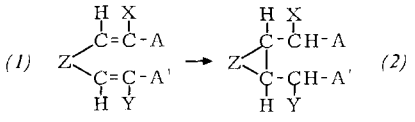
**The Wittig reaction with α,β-unsaturated ketones can involve also formation of a three-membered ring.** *J. P. Freeman*, carrying out this reaction with the ketone *(1)*, obtained the cyclic ketone *(3)*, R = $C_6H_5$, b. p. 150–155 °C/0.1 mm, $n_D^{20}$ = 1.5754, in 50 % yield by way of the betaine *(2)*.



*(1)* → (+ $R_3P=CH_2$) → *(2)* → *(3)*

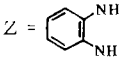
However, 1,3-diphenyl-2-propen-1-one (chalcone), which is sterically less hindered, reacts as expected to form 1,3-diphenylbutadiene, which dimerizes to 1,3,4-triphenyl-4-styrylcyclohexene. Compound *(3)* was also prepared from ethyl 2-phenylcyclopropanecarboxylate and mesitylmagnesium bromide in 56 % yield. / J. org. Chemistry *31*, 538 (1966) –Bu. [Rd 483 IE]

**Electrolytic-reductive cyclization of activated olefins** is a new route to cyclic compounds, according to *G. D. Anderson* and *M. M. Baizer*. For example, electrolysis of 40 g of diethyl deca-2,8-diene-1,10-dioate *(1a)* in a mixture of acetonitrile, tetramethylammonium *p*-toluenesulfonate, and water at 2 A and −1.91 to −1.96 V cathode potential gives 13.4 g of diethyl *trans*-cyclohexane-1,2-diacetate and 5.3 g of the *cis*-isomer. Analogously, from 40 g of the tetraethyl ester of *o*-bis(β-dicarboxyvinylamino)benzene *(1b)* was obtained 34.4 g



*(1)* *(2)*

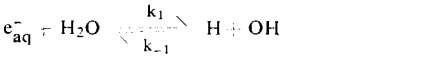
*(a)*: A = A' = $COOC_2H_5$, X = Y = H, Z = $(CH_2)_4$
*(b)*: A = A' = X = Y = $COOC_2H_5$,



of the tetraethyl ester of 2,3-bis-(dicarboxymethyl)-1,2,3,4-tetrahydroquinoxaline *(2b)*. Free-radical intermediates probably are not involved in the coupling reaction. (A,A' = electron-withdrawing groups; X,Y: electron-withdrawing groups or H). / Tetrahedron Letters *1966*, 511 / −Ma.

[Rd 452/661 IE]

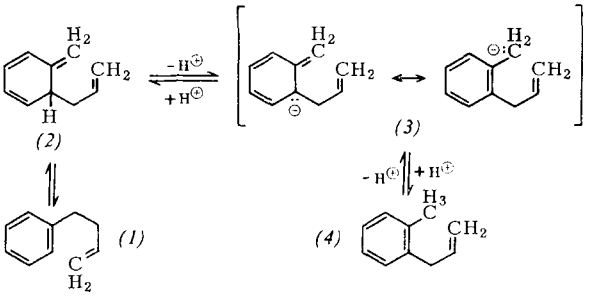
**The kinetics of reaction of the hydrated electron with water** at room temperature were studied by *E. J. Hart*, *S. Gordon*, and *E. M. Fielden* by means of electron pulse radiolysis. Reactions of $e^-_{aq}$ with, *e.g.*, $H_3O^+$, $O_2$, and $H_2O_2$ (which are about $10^9$ times faster than that with water) were suppressed by use of extremely pure, triple distilled water, adjustment of pH with carbonate-free KOH, and pre-irradiation. The rate constant $k_1$ of the reaction



in $H_2$-saturated solution of pH 8.3–9.0 at 25 °C is 16 ± 1 $mole^{-1}$ $sec^{-1}$ (concentration of impurities less than $5\times10^{-9}$ M); the constant of the reverse reaction, $k_{-1}$, is $2.3\times10^7$ $mole^{-1}$ $sec^{-1}$. / J. physic. Chem. *70*, 150 (1966) / −Hz.

[Rd 466 IE]

**Claisen rearrangement of compounds containing no heteroatoms** has been described by *W. von E. Doering* and *R. A. Bragole*. To explain why the Claisen rearrangement of C–H compounds has not been observed, it has generally been assumed that the necessary cleavage of a C–C bond would make the activation energy too high. The authors held that a more probable cause was the great difficulty of re-aromatization of compound *(2)* with shift of a hydrogen atom. Accordingly they carried out the rearrangement in a strongly basic medium (K t-butoxide in t-butyl alcohol) at 350 °C, since this difficulty should be overcome by deprotonation of *(2)* to *(3)*. Equilibria are set up between *(1)* and the four



*(2)* *(3)* *(1)* *(4)*

other possible phenylbutenes, and also between *(4)* and the two other *o*-tolylpropenes, so that eight compounds are involved in the equilibirum. However, a different mechanism, according to which the compound *(1)* is deprotonated at the *ortho*-position by the base, also explains the reaction route. / Tetrahedron *22*, 385 (1966) / − Bu.

[Rd 484 IE]

# BOOK REVIEWS

**Ullmanns Encyklopädie der technischen Chemie** (Ullmann's Encyclopaedia of Technical Chemistry). Vol. 15: Saccharin to Silicones. Chief editor *W. Foerst*. Editor *Hertha Buchholz-Meisenheimer*. Verlag Urban und Schwarzenberg, Munich-Berlin 1964. 3rd, completely revised Edit., xii + 794 pp., 309 figs., DM 182.– (ca. $ 45.–) (sold only as the complete work).

The new volume of Ullmann contains 26 articles under main headings. Of these, the six largest account for as much as 72% of the volume. Such large articles, each heavily subdivided, have proved their value for the organisation of the work. Here they are on the following subjects: sulfur and sulfur compounds (Schwefel und Schwefelverbindungen) (193 pp.), lubricants (Schmiermittel) (139 pp.), pesticides (Schädlingsbekämpfung) (81 pp.), nitric acid (Salpetersäure) (65 pp.), silicon compounds (Siliciumverbindungen) (51 pp.), and silver (Silber) (40 pp.).

The article on sulfur and sulfur compounds gives a detailed review of the whole field. It is the result of collaboration between 19 authors from Farbwerke Hoechst, BASF, Farbenfabriken Bayer, Metallgesellschaft, Lurgi, the University of Heidelberg, Ruhrgas, Theo Goldschmidt A.G., Gewerkschaft Elwerath, and elsewhere. In spite of this variety the connections and unity within the article have not been lost – a sign of good collaboration and first-class editorial organisation.

For the paper on lubricants, Esso placed four authors from their research laboratory at Hamburg-Harburg at the disposal of the editor. Their contribution is both detailed and didactically instructive. Ten pages are devoted to theoretical ideas, which are brought completely up to date; further sections deal with details of this highly varied field, which stretches from lubrication by solids such as graphite and molybdenum sulfide to lubrication by gases, from oil for watches to oil for motors. The pressure of practical demands has made progress in this field very rapid and in part heterogeneous, and this article is very valuable because it gives the non-specialist an orderly technical perspective without sacrifice of material content

The third large article, on pesticides, is compiled by nine authors from Geigy A.G. It is in no sense confined to characterisation of substances used as pesticides; on the contrary, it goes deeply into the ramifications of biological relationships. Relevant problems are described; and legal requirements, questions of toxicology, and – with particular success – the technical evaluation and importance of pesticides are also treated. The subject is a new one; the most important advance, namely the discovery of synthetic contact insecticides, was made only 25 years ago; yet today pesticides are a determining factor in world nutrition and about one billion people are protected against malaria by means of contact insecticides.

Among the smaller articles, particular mention may be made of that on sera and vaccines (31 pp.), compiled by six authors of Behringwerke, Marburg, with Prof. *Günther* of the Paul-Ehrlich Institute in Frankfurt/M. This also is written in depth as well as in detail. The formation of antibodies is discussed, as well as, for instance, the isolation of sera from horses. Particular interest centers on the evaluation and control of sera and vaccines.

Of the small articles, all rich in content, the following deserve special mention: acid-base theories (Säure-Base-Theorien) (2 pp.) by Prof. *Seel*, Saarbrücken; shoe-polish (Schuhpflegemittel) (7 pp.); writing and drawing materials (Schreib- und Zeichenmaterialien) (15 pp.). The last two articles are also by experts from the appropriate industries. – Further titles include: hydrochloric acid (Salzsäure) (17 pp.), sapogenins (6 pp.), oxygen (Sauerstoff) (12 pp.), abrasion and abrasives (Schleifen und Schleifmittel) (7 pp.), welding and cutting (Schweißen und Schneiden) (15 pp.), and silk (Seide) (9 pp.).

It is good to see that industry is sufficiently convinced of the value of Ullmann for leading firms to feel obliged to place authoritative authors at the disposal of the editor and to present the results of their research in this frame. This has lead to a complete scientific account of industrial research which, incidentally, includes significant theoretical contributions from industrial sources. Of the total of 83 authors in the present volume, only 11 are from universities and only 4 (!) from technical colleges. In spite of this, the treatment does not lean unduly towards industrial practice: fundamental research is always fully considered. Neighboring fields, such as historical connections and legal requirements, are also well treated, the sections on toxicology by Prof. *Oettel* of BASF, which are appended to each article, being particularly noteworthy.

It should, however, be pointed out that, with a few exceptions, industry has been very reserved about financial and economic data. This can be understood where it concerns a firm's own new processes. But there are very many processes, *e.g.* most of the inorganic ones, that are traded on the world market with contractual guarantees of installation and running costs with regard to size and local conditions. Concrete comparison of the various processes could be drawn if the various advantages and disadvantages had been evaluated more actuarially.

Summing up, it can be said that in this volume, as in its predecessors, the purpose of Ullmann is excellently fulfilled, namely, to give an ordered and clear reference work for the growing wealth of practical research.

*H. Sachsse* [NB 429/336 IE]

**Kunststoffbestimmungsmöglichkeiten** (Characterization of Plastics). By *Anneliese Krause* and *A. Lange*. Carl Hanser Verlag, Munich 1965. 1st edit., 199 pp., 30 tables, linen, DM 34.– (ca. $ 8.50).

This is the first book to provide a collection of the methods and data needed for analysis of plastics in a way that is simple and intelligible to the non-specialist and yet substantially complete and easy to follow. A chapter giving general remarks on the types of plastics is followed by a review of the methods available for qualitative and quantitative analysis of individual plastics and their structural units; there follow chapters on additives and on quality control. Very valuable features are that each chapter includes the necessary characteristics, in tabular form, as well as detailed instructions for analysis and calculation of the results. – Listing benzene as a solvent for polyethylene (table 21) probable must be regarded as a typographical error. Unfortunately, infrared spectroscopy is not taken into account, although beyond doubt it permits rapid and sure identification of plastics. In spite of this shortcoming this book, which is adressed to the plastics industry as well as to experts and students, will be of great help in the analysis of plastics.

*G. Greber* [NB 435/342 IE]

**Grundriß der Technischen Organischen Chemie** (Fundamentals of Technical Organic Chemistry). By *A. Rieche*. S. Hirzel Verlag, Leipzig 1965. 3rd improved edit., xviii + 550 pp., 152 figs., 1 table, linen, DM 24.60 (ca. $ 8.–).

This new edition appears only three years after the previous one. The text has not been greatly changed, but the author has taken in the latest advances in chemistry and technology in many places.

The term "organic chemistry" is widely interpreted. It stretches from the technology of coal – beginning with its mining – over border areas such as manufacture of carbide, to the processing of agricultural raw materials. The term "technical chemistry" is also widely interpreted. Emphasis is on the materials. Numerous technical processes are described in detail with the aid of clear flow sheets, and summarising sections on chemical technology are scattered throughout the text. However, the weight placed on various fields and stages of development of chemical technology is very varied, and this makes it difficult for the beginner to obtain a balanced picture of the present chemical industry.

In its 530 pages of text the book presents an astonishing amount of material. It is remarkable how the author has remained master of such a wide field down to details. It is, however, questionable whether the student can work through such a book and retain much of its content in his memory. The reviewer, therefore, assesses the value of this book primarily as an easily accessible – and very cheap – reference work for a first introduction into a given field of work, the detailed and reliable index being of considerable help in this respect.

In preparation for his task in industry the student would, however, be better served if the book would present concrete examples of the problems met in industry and their solution. It is to be hoped that a textbook will soon be written which starts from the material and thus remains lively and yet illustrates the fundamentals of chemical processes in a deductive manner.

*H. Kindler* [NB 437/344 IE]

**Biochemistry of Quinones.** Edited by *R. A. Morton*. Academic Press Inc., New York-London 1965. 1st Edit., xvii + 585 pp., numerous figs., £5.17.6 (about $16.50).

Books are the only organized form in which the virtually limitless riches of biochemical information can be presented. In the absence of a better principle it is still customary to use the time-hallowed divisions of organic chemistry as a basis for assembling biochemical information.

An example of this is provided by the present volume where the chemistry and biological relations of some quinones are treated, in manifold variations, by 19 authors in 15 articles. Yet, when it comes to making a book out of these (sometimes excellent) articles, the greatest service has, in the reviewer's opinion, been provided by the printer who numbered the pages consecutively and by the binder who placed them between two covers.

There is, indeed, in this book an appreciable excess of the overlap, repetition, and omission – in comparison with what is promised by the title and the preface – to which one has become accustomed in modern multi-author monographs. Take, for instance, plastoquinone: there is a careful and completd account of it by *Langemann* and *Isler* in a chapter "Chemistry of Isoprenoid Quinones", and a still more detailed neighbouring article by *Redfearn* specially devoted to this quinone, then it occurs in a chapter on the biosynthesis of "biologically active quinones" (*i.e.* isoprenoid quinones), and finally it is presented comprehensively, yet again with its history, preparation, and function, in "Quinones in Photosynthetic Reactions" by *Arnon* and *Crane*. The same applies to ubiquinone, vitamin K, and vitamin E quinone. This is the result of dividing the contents both quasi-vertically into chapters on individual quinones, with general chemical and biological aspects as sub-headings,

and horizontally with general chemical and biological chapter headings, individual quinones occurring in subheadings.

Thus, in contrast to its title and pretty dust-cover, and in spite of its size, this book is restricted substantially to strongly lipophilic quinones with isoprenoid side chains. For these compounds, which are important as constituents of biologically functioning particles, it provides comprehensive and valuable documentation. -- The reader is advised to begin at page 89.

*K. Wallenfels* [NB 473/326 IE]

**Oligosaccharides.** A comprehensive account of all known sugars of the oligosaccharide class of compounds. By *R. W. Bailey*. Pergamon Press, Oxford-London-New York-Paris 1965. 1st edit., vi + 178 pp., bound $ 3.0.0.

The development of chromatographic methods for separation of oligosaccharide mixtures has led, particularly in recent years, to the isolation of numerous new compounds of this type. Since the results are recorded in journals appertaining to different disciplines the increasing number of new oligosaccharides makes it continually harder to determine whether a particular compound has or has not been described. The object of the present book is to ease this situation.

Nomenclature and the methods of isolation and determination of structure are first reviewed. The main part of the book contains a systematic list of all (about 480) the oligosaccharides that contain up to ten monosaccharide units and were known up to the end of 1962; this occupies some 100 pages. Short entries record the physical constants, source, isolation, and, as far as realized, the chemical synthesis. Each oligosaccharide is given a number which is used in the indexes.

An enormous amount of material (over 1000 references to original papers) has been brought together in this book, sifted, and splendidly handled The classification is clear and easy to follow, and the presentation intelligible despite its concise form. It affords a source of information that is rapid and fully sufficient for first orientation, this being aided by the excellent arrangement of the index. For instance, "Compound No 337" is found in the index of trivial names under raffinose, gossypose, and melitriose, and again in the general subject index as $6^G$-α-galactosylsucrose (the name being abbreviated according to *W. J. Whelan*'s proposal) among the oligosaccharides related to D-glucose, D-galactose, and D-fructose. This book is essential for the chemist working in the field and should be in every library. It only remains to be hoped that the classification and nomenclature used in it will be adopted, not only in the specialist journals, but also in textbooks.

*F. W. Lichtenthaler* [NB 434/341 IE]

**Oxidation Mechanisms.** By *T. A. Turney*. Butterworth & Co., Ltd. London 1965. 1 st Edit., viii + 207 pp., 35 s. (about $ 4.–).

The two recent monographs by *Waters* and *Stewart* dealing with oxidation mechanisms are now followed by a third, from a New Zealand author. It is similar in size to its predecessors but differs in that inorganic ions as well as organic compounds are treated.

The organic part is certainly too short. *Malaprade*, *Harries*, *Rieche*, *O. Dimroth*, *Hock*, *Bartlett*, *Roček*, *Swern*, *Prileshajew*, and *Teuber* are missing from the author index of about 600 names, entries such as cumene, decalin, peracids, and quinone from the subject index, and biological oxidation is not mentioned at all, the reaction of ozone with olefins is omitted, and the enormous influence of the configuration of a glycol on the velocity of its fission by periodate or lead tetra acetate is not mentioned; the reader is not told that the reaction with $OsO_4$ implies a *cis*-hydroxylation. This list could be expanded. One gets the impression that the author has confined himself almost entirely to the Anglo-Saxon and particularly the English literature.

On the other hand, oxidations occurring in inorganic chemistry are handled better and more completely. Even the division of the material, with its chapter headings "Cation,cation oxidations", "Cation,substrate oxidations", *etc.*, is better suited to inorganic than to organic oxidations since the latter often involve neutral molecules.

The claim on the dust-cover that "Without doubt, this is an exceptionally informative treatment of the suject for all chemistry students reading for Honours Ph. D. degrees. It will also be of value to industrial chemists concerned with oxidation processes" seems to the reviewer to be greatly exaggerated.

*R. Criegee* [NB 459/312 IE]

**High-Temperature Compounds of Rare Earth Metals with Nonmetals.** By *G. V. Samsonov*. Consultants Bureau Enterprises, Inc., New York 1965. 1st Edit., xiii + 280 pp., numerous figs., $ 17.50.

This monograph is an expanded and improved English translation of the Russian edition that appeared in 1964. The author, who is represented by many contributions to this field, deals with borides, carbides, nitrides, silicides, and sulfides of scandium, yttrium,lanthanum, and lanthanides. Each chapter is divided into sections: structure and properties, general methods of preparation, description of all the compounds, areas of use, literature citations. For example, in the chapter on carbides one finds:

(1) Crystal structure of compounds of the types $M_3C$, MC, $M_2C_3$, and $MC_2$; densities; specific electrical resistance; magnetic behavior. There are comparative observations on variation of the metallic component, and general viewpoints are brought out.

(2) Review of preparation from M + C or $M_2O_3$ + C.

(3) Reports on all the known carbides, from Sc to Lu; preparation and properties; phase diagram for La/C. Here the monograph takes on the character of a list of references.

(4) Short indications of possible uses.

The title "High-Temperature Compounds..." leads one to expect extensive applications in the high-temperature region. But this development peters out quite early. Often only laboratory experiments re reported and proposals mentioned. Information about the use of hexaborides ($LaB_6$) as cathode material is somewhat more extensive; and additionally the use of the substances described as semiconductors, neutron absorbers, and crucible materials is considered.

The book makes the impression of being complete (references up to 1964) and expertly compiled. It can afford valuable information to those interested in this field. Printing and production are good.

*H. Schäfer* [NB 467/320 IE]

**Stereochemistry, Mechanism and Silicon.** By *L. H. Sommer*. McGraw-Hill Book Comp., New York-St.Louis-San Francisco-Toronto-London-Sydney 1965. 1st Edit., xvi + 189 pp., 78 s. (ca. $ 9.50).

Monographs on organosilicon chemistry have hitherto been of the comprehensive, general type. The rapid growth of knowledge has, however, brought a further need for monographs on special problems and partial areas.

Therein lies the value of *L. H. Sommer*'s book on the relations between stereochemistry and reaction mechanism at the silicon center of organosilicon molecules. The author is Professor of Chemistry at Pennsylvania State University and has long been known for his valuable contributions to the preparative and theoretical chemistry of organosilicon com-

pounds, having worked in this field since 1958 with a large number of collaborators.

In this book the author begins with an account of the undamental experiments of his school on the preparation of optically active silicon compounds and then details the reactions in which Si–O, Si–halogen, and Si–H bonds play a part, finally discussing the stereochemistry and reaction mechanism at silicon centers. This leads up to a classification of all the reactions that can occur at a silicon atom.

The reader will be grateful for the concise and clear description of this field and for the collection of so many results. The book constitutes a valuable enrichment of the monograph literature of modern silicon chemistry.

*W. Noll* [NB 468/321]

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# Classification and Analysis of NMR Spectra

BY DR. B. DISCHLER

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*The use of nuclear magnetic resonance as the basis of a spectroscopic method in organic analysis is steadily growing* [1]. *The object of the present article is to present a general picture of the classification and interpretation of the NMR spectra obtained at high resolutions. In simple cases complete interpretation is possible with the aid of only a few equations; otherwise it is often necessary to use a laborious mathematical procedure, which is discussed here. For a more profound study, the reader is referred to more detailed publications* [2–6].

## I. Introduction

Nuclear magnetic resonance arises as a result of transitions between the energy levels of a nuclear magnetic dipole in a static magnetic field. The existence of discrete states can be understood in terms of the quantum theory. The observation of nuclear magnetic resonance requires the presence of an external alternating magnetic field of suitable frequency, by which detectable transitions are induced.

When nuclear magnetic resonance signals were first observed, it was found that this "nuclear Zeeman effect" could be explained by the simple Equation (1):

$$1945: \quad h\nu_o = \frac{\mu}{I} H \qquad (1)$$

where h is Planck's constant; $\nu_o$ the resonance or Larmor frequency, $\mu$ the magnetic moment of the nucleus, I the nuclear spin, and H the strength of the external magnetic field.

With better resolution it became possible to recognize differences in the shielding of the external magnetic field by the electrons of atoms of identical species in different chemical environments. This "chemical shift" was taken into account by Equation (2).

$$1949: \quad h\nu_i = \frac{\mu}{I} H_o (1-\sigma_i) \qquad (2)$$

where i is a subscript for numbering the nuclei in a molecule, $H_o$ the field strength of the external magnetic field at resonance, and $\sigma$ a shielding parameter ($10^{-4}$–$10^{-5}$ for protons).

Later the indirect nuclear spin interaction caused by spin polarization of the electron cloud was discovered. A complete description of the spectrum therefore requires the introduction of a spin Hamiltonian operator, which is given by:

$$1951: \quad \mathbf{H} = \sum_{i=1}^{n} \nu_i \mathbf{I}_z(i) + \sum_{i=1}^{k-1} \sum_{k=z}^{n} J_{ik} \mathbf{I}(i) \mathbf{I}(k) \qquad (3)$$

where $\mathbf{I}(i)$ is the angular momentum operator for the nucleus i, $\mathbf{I}_z(i)$ the z component of $\mathbf{I}(i)$ [the negative z-direction is given by the direction of the static magnetic field], and $J_{ik}$ is the parameter for spin-spin coupling between the nuclei i and k.

This energy operator will be discussed further in Section III.

## II. Types of NMR Spectra

It is usual and convenient to divide nuclear resonance spectra into types. A short formula is used to characterize both the spectrum and the arrangement (the symmetry) of the nuclei in the molecule (see Figs. 1 and 2).

[1a] *K. H. Hauser*, Angew. Chem. *68*, 729 (1956).

[1b] *J. D. Roberts*, Angew. Chem. *75*, 20 (1963); Angew. Chem. internat. Edit. *2*, 53 (1963).

[2] *J. A. Pople, W. G. Schneider*, and *H. J. Bernstein*: High-resolution Nuclear Magnetic Resonance. McGraw Hill, New York 1959.

[3] *L. M. Jackmann*: Applications of Nuclear Magnetic Resonance Spectroscopiy in Organic Chemistry. Pergamon Press, London 1959.

[4] *P. L. Corio*, Chem. Reviews *60*, 363 (1960).

[5] *J. D. Roberts*: An Introduction to the Analysis of Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra. Benjamin, New York 1961.

[6a] *J. Ranft*, Fortschr. Physik *9*, 149 (1961).

[6b] *H. Strehlow*: Magnetische Kernresonanz und chemische Struktur. Steinkopff, Darmstadt 1962.

The characterization requires that all the nuclei in the molecule should be reduced to the "spin system". This spin system consists of the nuclei having the spin $^1/_2$ (*e.g.* $^1$H, $^{19}$F, $^{31}$P) that interact with one another by indirect spin coupling [7].

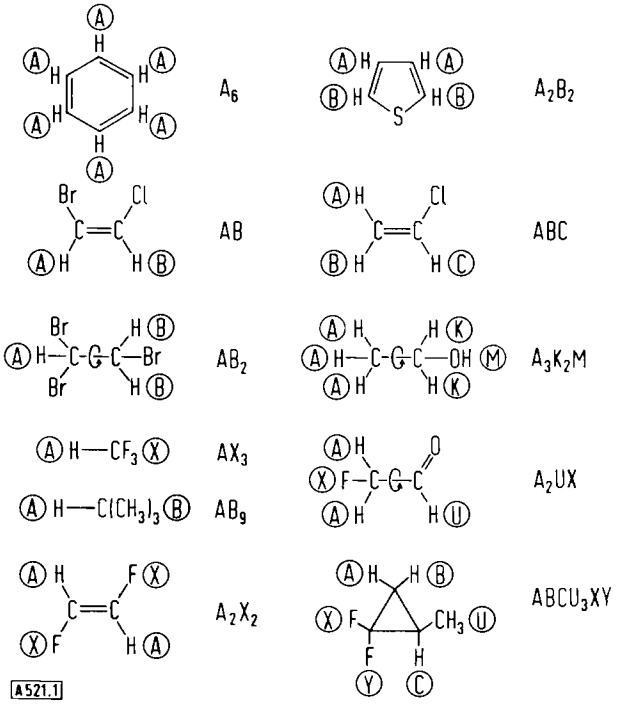



Fig. 1. Designation of NMR spin systems.

If the approximate values of the Larmor differences $\nu_o\delta_{ik}$ [8] and the coupling parameters $J_{ik}$ are known, the type to which a spectrum belongs can be given by two rules:

1. Chemically non-equivalent nuclei in a molecule are assigned different letters [9].

2. The choice of the letter is determined by the magnitude of the spin-spin coupling relative to the Larmor difference.

The first nucleus, *i.e.* that with the highest spin coupling (and any other equivalent nucleus), is always denoted by A and the other nuclei by

(a) a subsequent letter from the beginning of the alphabet (B, ...) if $J_{AB}$ is comparable in magnitude with $\nu_o\delta_{AB}$;

(b) a letter from the middle of the alphabet (M, ...) if $J_{AM}$ is approximately one order of magnitude smaller than $\nu_o\delta_{AM}$ [10];

(c) a letter from the end of the alphabet (X, ...) if $J_{AX}$ is two or more orders of magnitude smaller than $\nu_o\delta_{AX}$ [11].

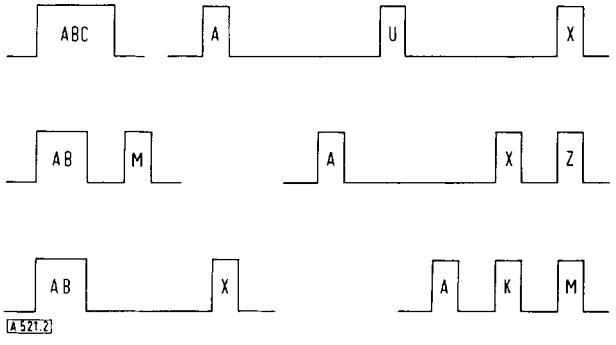



Fig. 2. Types of NMR spectra for three chemically non-equivalent nuclei, schematically represented by envelope curves.

Case (a) corresponds to the so-called complex spectra, in which the Larmor differences are important as well as the coupling parameters. In Case (b), the signals of the non-equivalent nuclei occur in separate groups, in which the line splitting and the line intensities depend only slightly on the Larmor differences. In Case (c), the resonance signals of the non-equivalent nuclei are so far apart that they are usually recorded as separate groups of lines; within these sub-spectra, the splittings and intensities of the lines are independent of the Larmor differences, *i.e.* they are determined only by the spin coupling. Thus the use of Rule 2 takes into account both the external appearance of the spectra and the various effects of the Larmor differences on the line splittings and intensities.

Rules 1 and 2 are sometimes not sufficient to give an unambiguous designation for more complex spin systems [12]; an extension of the rules is therefore desirable [13].

[7] The spin system does not include, for example, carbon and oxygen nuclei (spin = 0), except when the isotopes $^{13}$C and $^{17}$O are involved. Moreover, nuclei with spin $> ^1/_2$ (chlorine, bromine, *etc.*) are not normally included, since they have a quadrupole moment ($Q \neq 0$) and do not exhibit spin coupling because of quadrupole relaxation.

[8] The quantity known as the "Larmor difference" is defined by $\nu_i - \nu_k = \nu_o\delta_{ik}$.
($\nu_i$, $\nu_k$ = Larmor frequencies at constant magnetic field $H_o$ in the absence of any spin coupling; $\nu_o$ = the frequency of the radio-frequency transmitter; $\delta_{ik}$ = a dimensionless parameter related to the $\tau$ scale [22] by $\delta_{ik} = \tau_i - \tau_k$.)

[9] As a result of symmetries in the molecular structure, the nuclei in the spin system may have:
(a) equal Larmor frequencies, *i.e.* $\nu_i = \nu_k$,
(b) equal spin coupling parameters, *i.e.* $J_{ij} = J_{kj}$, for all i, k, and j with $\nu_j \neq \nu_i = \nu_k$.
If condition (a) is satisfied, the nuclei i and k are described as "chemically equivalent" or "isochronous". If condition (b) is also satisfied, the nuclei i and k are described as "magnetically equivalent". The special significance of this latter property will be seen in Section IIIe.
In the examples of the $AB_2$ type in Figures 1 and 7, the isochronous B protons are *magnetically* equivalent ($J_{AB} = J'_{AB}$), whereas in the examples of the $A_2B_2$ type in Figures 1 and 10, the A and B protons are *chemically*, but not *magnetically* equivalent ($J_{AB} \neq J'_{AB}$); see also [12].

[10] Rule 2b is a subsequent refinement, and has not yet been generally accepted. Some authors use the letter K instead of M.

[11] The condition for 2c is automatically satisfied when the nuclei present are different (*e.g.* $^1$H and $^{19}$F).

[12] Regarding nomenclature in $A_2B_2$ spin systems, it should be noted that notations such as $A_2'B'_2$, AA'BB', or AA*BB* are occasionally used in order to indicate that the nuclei are not magnetically equivalent [9]. However, the usual notations $A_2B_2$ and $A_2X_2$ are preferable. There is no danger of confusion, since there are very few $A_2B_2$ systems with magnetically equivalent nuclei. Two rare exceptions are cyclopropene and difluoromethane, which may be denoted by $A^*{}_2B^*{}_2$ or $A^*{}_2X^*{}_2$ [14b].

[13] The existing rules may be supplemented as follows. The omission of one or two letters in the alphabetic sequence should correspond to cases (b) and (c) of Rule 2. This suggestion is followed in the last three examples in Figures 1 and 2.

## III. Basic Principles for the Mathematical Treatment of NMR Spectra

In the quantum-mechanical picture, the lines of a nuclear magnetic resonance spectrum correspond to transitions between the stationary states of a spin system. The three fundamental equations are:

$$\mathbf{H}\Psi_p = E_p\Psi_p \tag{4}$$

$$f_{qp} = (E_p - E_q)/h \tag{5}$$

$$I_{qp} = \text{const.}\,|\Psi_p\,\mathbf{H}^{(x)}\,\Psi_p|^2 \tag{6}$$

The general equation of state [Equation (4)] is used to calculate the energy eigenvalues $E_p$ and the eigenfunctions $\Psi_p$ of the stationary states for a given Hamiltonian operator **H**. The line frequency $f_{qp}$ for a transition from the state $\Psi_q$ of energy $E_q$ to the state $\Psi_p$ with energy $E_p$ is given by the Bohr frequency condition [Equation (5)]. The corresponding intensity $I_{qp}$ is proportional to the matrix element with the operator of the transition probability $\mathbf{H}^{(x)}$ [Equation (6)].

### (a) The Spin Hamiltonian Operator

**H** in Equation (4) is replaced by the spin Hamiltonian operator from Equation (3). For nuclei with spin $^1/_2$, the complicated angular momentum operator is given by Equations (7), which together with Equation (3) give Equation (8).

$$\mathbf{I}_z(i)\,\Psi = m_i\Psi \tag{7a}$$

$$\mathbf{I}(i)\,\mathbf{I}(k)\,\Psi = \tfrac{1}{4}(2\mathbf{P}_{ik} - \mathbf{1})\,\Psi \tag{7b}$$

$$\mathbf{H} = \sum_{i=1}^{n} \nu_i\, m_i\, \mathbf{1} + \tfrac{1}{4}\sum_{i=1}^{k-1}\sum_{k=2}^{n} J_{ik}\,(2\mathbf{P}_{ik} - \mathbf{1}) \tag{8}$$

$m_i$ is the magnetic quantum number; $\mathbf{P}_{ik}$ the permutation operator, which permutes the subscripts of the nuclei i and k, and **1** the identity operator (without effect).

The first term in Equation (8) gives the "nuclear Zeeman energy" which is proportional to the resonance frequency $\nu_i$ [or the magnetic field strength H*, see Equation (1)]. The second term gives the energy due to indirect spin coupling, which is proportional to the coupling parameter $J_{ik}$.

### (b) The Spin Functions

The functions on which the Hamiltonian operator **H** is allowed to act are the product spin functions.

The spin functions corresponding to the two orientations of a single nucleus ($I = {}^1/_2$) are denoted by the symbols $\alpha$ and $\beta$ [15]. For a spin system consisting of two nuclei there are four product spin functions: $\alpha\alpha$, $\alpha\beta$, $\beta\alpha$, and $\beta\beta$. The first factor in the product spin function is then the spin function of the first nucleus, the second that of the second nucleus, and so on. Thus the permutation operator $\mathbf{P}_{12}$ [see Equation (8)] has the following effect:

$$\mathbf{P}_{12}\alpha\alpha = \alpha\alpha;\ \mathbf{P}_{12}\beta\alpha = \alpha\beta;\ \mathbf{P}_{12}\alpha\beta = \beta\alpha;\ \mathbf{P}_{12}\beta\beta = \beta\beta.$$

In general the stationary states are described by linear combinations of product functions. For example, the following functions occur in any $A_2$ spin system (cf. Fig. 3).

$$\frac{1}{\sqrt{2}}(\alpha\beta + \beta\alpha) \quad \text{and} \quad \frac{1}{\sqrt{2}}(\alpha\beta - \beta\alpha)$$

### (c) The Eigenvalue Problem

The entire calculations of nuclear magnetic resonance spectra have been programmed for electronic computers, so that now the theoretical spectrum corresponding to a given set of parameters can be obtained without effort (see Section V d, e). The course of the calculation is shown in Scheme (9).

$$\underset{\text{Parameter}}{\boxed{\nu_i,\ J_{ik}}} \overset{a}{\longleftrightarrow} ((H_{pq})) \overset{b}{\longrightarrow} (E_p, \Psi_q) \overset{c}{\longleftrightarrow} \underset{\text{Spectrum}}{\boxed{f_{qp},\ I_{qp}}} \tag{9}$$

Here the step a denotes the calculation of the complete energy matrix, $\mathbf{H}_{pq}$ being equal to $\varphi_p\mathbf{H}\varphi_q$,

b denotes reduction to the diagonal form by solution of the eigenvalue problem, and

c denotes calculation of the frequencies and intensities of the allowed transitions.

The values of the parameters $\nu_i$ and $J_{ik}$ are inserted in the Hamiltonian operator [Equation (8)]. The desired eigenvalues $E_p$ and eigenfunctions $\Psi_p$ that satisfy Equation (4) must then be calculated in the usual manner by means of secular equations, *i.e.* the energy matrix $((H_{pq}))$ is calculated with a set of starting functions and brought into the diagonal form by a unitary transformation. The diagonal elements are then the desired eigenvalues, and the transformation matrix consists of the eigenvectors that link the eigenfunctions with the starting functions.

### (d) Transition Probability and Selection Rules

The calculation of the line intensities by means of Equation (6) involves an operator $\mathbf{H}^{(x)}$, which is defined as follows for the resonance absorption of radio-frequency energy:

$$\mathbf{H}^{(x)} = \sum_{i=1}^{n} (1-\sigma_i)\,\mathbf{I}_{+(i)} \tag{10}$$

In Equation (10) $\mathbf{I}_+$ is a "shift operator" with the effect that

$$\mathbf{I}_+\,\alpha = 0 \tag{11a}$$

$$\text{and } \mathbf{I}_+\,\beta = \alpha \tag{11b}$$

Equation (11b) states that the nuclear spin is "flipped" from the $\beta$ into the $\alpha$ orientation [15]. No absorption can occur in the state $\alpha$ [Equation (11a)]. The transition $\beta \rightarrow \alpha$ leads to a change in the magnetic quantum number m from $-{}^1/_2$ to $+{}^1/_2$, *i.e.* $\Delta m = +1$. Equations (10) and (11) give the selection rule [Equation (12)]:

$$\sum_{i=1}^{n} \Delta m_i = +1 \tag{12}$$

$$\Delta m_i = 0 \text{ or } +1.$$

[14a] *J. A. Pople* and *T. Schaefer*, Molecular Physics *3*, 547 (1960).

[14b] *P. Diehl* and *J. A. Pople*, Molecular Physics *3*, 557 (1960).

[14c] *P. Diehl*, Helv. chim. Acta *48*, 567 (1965).

[15] It was assumed in Equations (3) and (8) that the vector of the static magnetic field points in the negative z direction; this is usually the case. In the state $\alpha$ ($m = +{}^1/_2$), the spin is then antiparallel to the magnetic field.

Equation (12) is applicable if the transition is between only two energy levels described by simple product spin functions. However, the eigenfunctions are mostly linear combinations, for which the less accurate selection rule of Equation (13) is used for the sake of simplicity [16]. A further condition for allowed transitions is given later [Equation (15)].

$$\Delta\left(\sum_{i=1}^{n} m_i\right) = \Delta F_z = +1 \qquad (13)$$

$F_z$ is the z-component of the total spin.

### (e) Some Important Rules

The signal due to isochronous nuclei [9] is usually split because of spin coupling. There are compounds, however, in which no splitting occurs in spite of spin coupling. For example, the "spectra" of unsubstituted benzene and methane consist of a single line each (see Rule 2). Moreover, it is a well-known fact that the spin coupling between the protons of a methyl group that can rotate is not detectable, but is by no means zero (see Rule 1).

The nuclei in these structures, are magnetically equivalent [9], and the following two rules are generally valid [17]:

**Rule 1.** The spin coupling between magnetically equivalent nuclei does not affect the spectrum.

**Rule 2.** If a spin system contains only one type of chemically equivalent (isochronous) nuclei, these are always magnetically equivalent [18a], and the "spectrum" consists of a single signal, irrespective of the couplings present.

An explanation for the peculiarities described in the two rules is found in the occurrence of "good" quantum numbers.

If two operators are commutable [Equation (14a)], their eigenvalues g are known as "good" quantum numbers [Equation (14b)]. The reason for their importance in quantum mechanics is the fact that they cause certain matrix elements to disappear [Equation (14c)].

$$\mathbf{GH}\Psi = \mathbf{HG}\Psi \qquad (14a)$$

$$\mathbf{G}\Psi_p = g_p\Psi_p;\ \mathbf{G}\Psi_q = g_q\Psi_q \qquad (14b)$$

$$\Psi_p\mathbf{H}\Psi_q = 0 \text{ when } g_p \neq g_q \qquad (14c)$$

If **H** in Equation (14c) is taken as the operator of the transition probability $\mathbf{H}^{(x)}$ from Equation (10), it follows from Equation (6) that all transitions in which at least one "good" quantum number changes are forbidden. For magnetically equivalent nuclei, the parameters for the mutual spin coupling occur only in the form of good quantum numbers. Thus owing to the substraction involved in the calculation of the allowed frequencies [Equation (5)], these coupling parameters cannot influence the spectrum.

The Hamiltonian operator can also commute with some other operators, *e.g.* the $\mathbf{F}_z$ operator of the total spin [see Equation (13)]. The energy matrix $((H_{pq}))$ therefore breaks down into independent sub-matrices for the various values of $F_z$.

The molecule under examination often possesses elements of symmetry, and the operators **H** and $\mathbf{H}^{(x)}$ can then commute with certain symmetry operators **S**. Symmetry eigenvalues s corresponding to these, *e.g.* with the values +1 and −1 for symmetric and antisymmetric functions, respectively, can then be defined as good quantum numbers.

Another good quantum number is the "particle spin" **I***, which is obtained when a group of magnetically equivalent [9] nuclei are considered together as a "spin particle" [18b]. In a freely rotating methyl group, for example, there are only states with $I^* = {}^3/_2$ or $I^* = {}^1/_2$. Thus in the magnetic field there are two molecular species, which cannot be interconverted by nuclear resonance. The situation is similar to that of ortho- and para-hydrogen in optical spectroscopy.

Owing to the ability of **S** and **I*** to commute with $\mathbf{H}^{(x)}$, another selection rule for allowed transitions in addition to Equations (12) and (13) results:

$$\Delta I^* = \Delta s = 0 \qquad (15)$$

Since **S** and **I*** may also commute with the Hamiltonian operator, the matrix elements $H_{pq}$ disappear whenever the condition of Equation (15) is not satisfied by the functions involved.

There is a simple, but very useful, summation rule [Equation (16)] for the line intensities. This rule is based on the energy-level diagram and requires that the total intensity for n nuclei of spin $= {}^1/_2$ be normalized to $n2^{n-1}$ [19].

**Rule 3.** The sum of the intensities of all transitions that terminate in the state $\Psi_t$ differs from the sum of the intensities of all transitions that start at $\Psi_t$ by exactly twice the value of the z component of the total spin in the state $\Psi_t$.

$$\sum_q I_{qt} = \sum_p I_{tp} + 2F_z(\Psi_t) \qquad (16)$$

The states p and q over which the sums are to be taken are given by the energy-level diagram; q passes through at most $\binom{n}{r+1}$ values and p through $\binom{n}{r-1}$ values, where $r = 2F_z(\Psi_t)$.

## IV. Examples of Simple Spin Systems

In the equipment used to record the following spectra, the magnetic field strength was varied and the radio frequency $\nu_0$ was kept constant.

### (a) The AB System

Figure 3 shows a number of calculated spectra for two coupled non-equivalent nuclei. The energy-level

[16] As an example of this, transition 9 in the $AX_2$ scheme in Figure 6 is forbidden according to Equation (12), though it appears to be allowed according to Equation (13).

[17] *H. S. Gutowsky, D. W. McCall,* and *C. P. Slichter,* J. chem. Physics *21,* 279 (1953).

[18a] In $A_n$, the spin coupling with all other (imaginary) nuclei is zero.

[18b] *D. R. Whitman, L. Onsager, M. Saunders,* and *H. E. Dubb,* J. chem. Physics *32,* 67 (1960).

[19] *G. Giomousis* and *J. D. Swalen,* J. chem. Physics *36,* 2077 (1962).

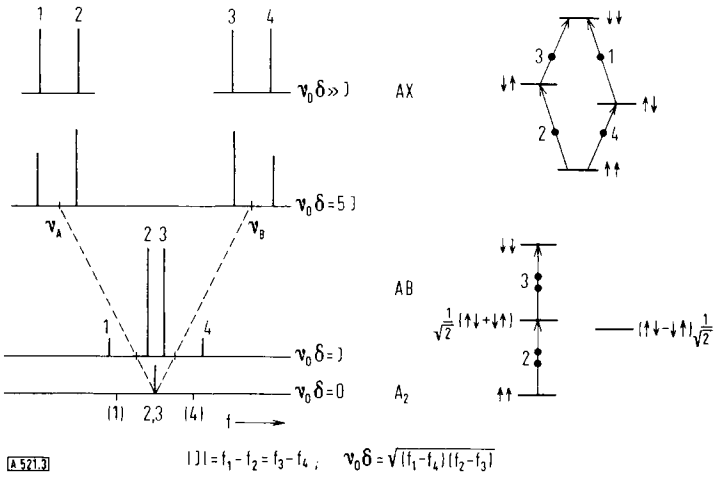



Fig. 3. Calculated spectra for the two-spin system AB, with energy-level diagrams and spectra for the limiting cases AX and $A_2$ [20].

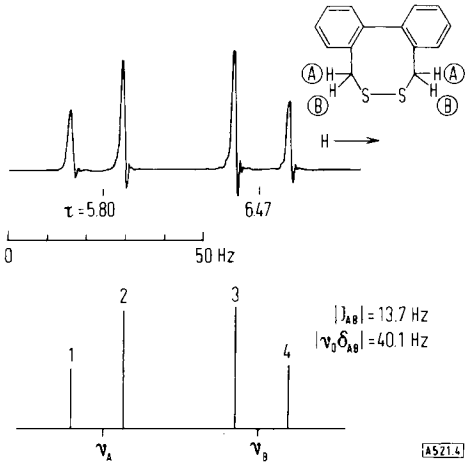



Fig. 4. Resonance of the methylene protons of 1,2-dibenzo[*d*, *f*,]dithiacyclooctadiene [21] in $CS_2$ at $\nu_0$ = 60 MHz and 24 °C ($\delta$ = 0.67 ppm.; J = 13.7 Hz).

In the rigid eight-membered ring, the protons are situated in sterically different positions, with a Larmor difference of 40.1 and a spin coupling of 13.7 Hz. These values were used for the calculation of the control spectrum (Fig. 4, bottom). The resonance of the protons of the *o*-phenylene residue is situated at a lower field strength, and is not shown [22].

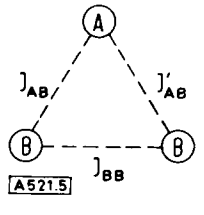



Fig. 5. Spin coupling in the $AB_2$ system (schematic).

diagram is given for the limiting cases AX and $A_2$. The forms of the spectra depend on the ratio $J_{AB}:\nu_0\delta_{AB}$. In the proton magnetic resonance spectrum of 1,2-dibenzo[*d*,*f*] dithiacyclooctadiene [21], the methylene protons in the eight-membered ring give rise to an AB spectrum (Fig. 4).

### (b) The $AB_2$ System

In the three-spin $AB_2$ system (Fig. 5), $J_{AB} = J'_{AB}$ because of symmetry. Consequently, the two B nuclei are magnetically equivalent [9] and form a spin particle with the possibilities $I^*_B = 1$ and $I^*_B = 0$. The BB coupling is not observed (cf. Section IIIe, Rule 1), and the energy-level diagram breaks down vertically into six and two states (cf. Fig. 6).

In the limiting case of an $A_3$ system ($\nu_0\delta_{AB} = 0$) there is a further vertical division. The good quantum numbers are then:

$I^*_A = 3/2$, $s_{23} = +1$ [Fig. 6, (a)];
$I^*_A = 1/2$, $s_{23} = +1$ [Fig. 6, (b)];
$I^*_A = 1/2$, $s_{23} = -1$ [Fig. 6, (c)] [23].

On this basis it is possible to deduce the following properties of the $AB_2$ spectrum:

1) Line 3 must remain invariant owing to the fact that it is isolated; its frequency is always $\nu_A$ and its intensity is 1;

2) as the limiting case $A_3$ is approached, Lines 1, 2, and 8 become weaker and weaker and are ultimately forbidden;

3) the "combination line" 9 is particularly weak, since it is forbidden in both limiting cases $AX_2$ and $A_3$.

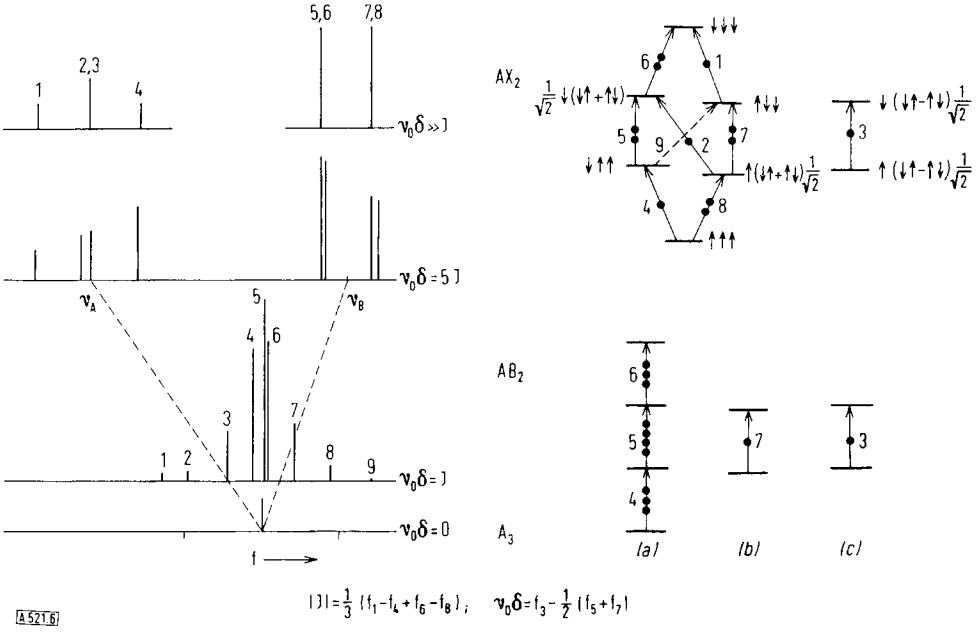



Fig. 6. Calculated spectra for the three-spin system $AB_2$ with the energy-level diagrams and spectra for the limiting cases $AX_2$ and $A_3$ [20].

[20] The arrows by the energy levels show the spin orientation, the static magnetic field being directed upward. The number of "beads" shown on the transitions corresponds to the intensity.

[21] *A. Lüttringhaus et al.*, Chem. Ber., in press.

[22] The Larmor frequencies in the spectrum are given relative to the tetramethylsilane signal on the dimensionless $\tau$ scale, where $\tau_i = 10 - 10^6(\nu_i - \nu_{TMS})/\nu_0$ ppm.

[23] The symmetry operation corresponding to the eigenvalue $s_{23}$ is $P_{23}$.

[24] *Corio* [4] gives Tables for AB, $AB_2$, $AB_3$, and $A_2B_3$, most of which are reproduced by *Strehlow* [6b].

Apart from the normalization factor, the $AB_2$ spectrum depends only on the ratio $J_{AB}:\nu_0\delta_{AB}$. Some calculated $AB_2$ spectra are to be found in the literature as a function of this ratio [24,25]. They show that there is no crossing of lines, *i.e.* the order of the lines always permits an unambiguous assignment.

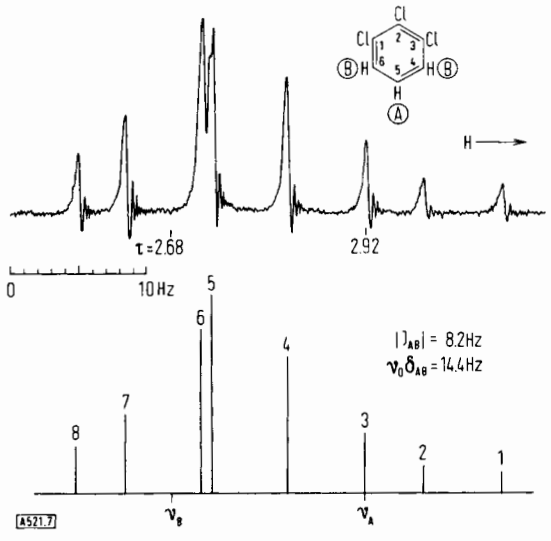



Fig. 7. Magnetic resonance of the protons of 1,2,3-trichlorobenzene in $CCl_4$ at $\nu_0 = 60$ MHz and 24 °C as an example of an $AB_2$ spectrum ($\delta = 0.24$ ppm.; $J = 8.2$ Hz).

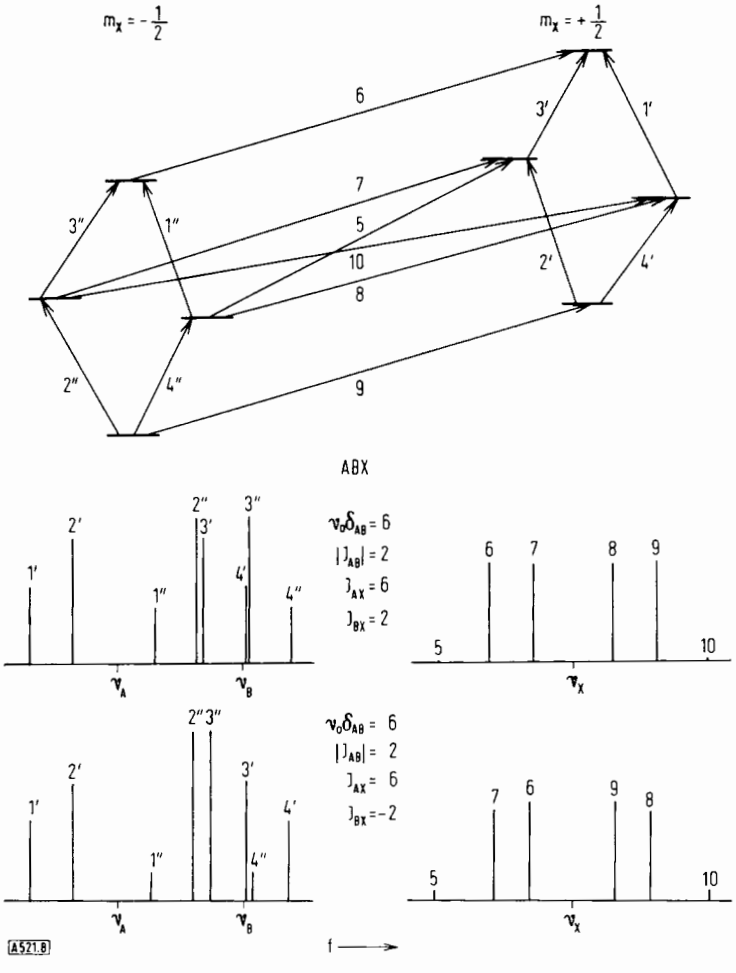



Fig. 8. Term diagram and two calculated spectra for the three-spin system ABX.
The influence of the signs of $J_{AX}$ and $J_{BX}$ can be recognized in the two calculated spectra.

Figure 7 shows the $AB_2$ spectrum of the protons in 1,2,3-trichlorobenzene.

### (c) The ABX System

New features of the ABX system in comparison with the above examples are first the dependence of the spectrum on the relative signs of the spin coupling parameters J, second the resulting problem of the assignment of the lines, and third the fact that the problem can be simplified [14] if the ABX system is broken down into two AB systems. The energy-level diagram can thus be subdivided into two parts with the magnetic quantum numbers $m_x = +1/2$ and $m_x = -1/2$ (see Fig. 8). The two subschemes are linked only by the transitions of the nucleus X; otherwise they represent two AB systems similar to that discussed in Section IVa. Here, however, the spectrum contains "effective" Larmor frequencies ($\nu'_A$, $\nu'_B$, $\nu''_A$, $\nu''_B$), which depend on the spin coupling with the X nucleus in the following manner:

Subsystem I ($m_X = +1/2$):

$$\nu'_A = \nu_A + \tfrac{1}{2}J_{AX};\quad \nu'_B = \nu_B + \tfrac{1}{2}J_{BX} \tag{17}$$

Subsystem II ($m_X = -1/2$):

$$\nu''_A = \nu_A - \tfrac{1}{2}J_{AX};\quad \nu''_A = \nu_B - \tfrac{1}{2}J_{BX} \tag{18}$$

In the analysis of the ABX spectrum, all the parameters can be found from the two AB subspectra. The defining equations are:

$$|J_{AB}| = f'_1 - f'_2 = f'_3 - f'_4 = f''_1 - f''_2 = f''_3 - f''_4 \tag{19}$$

$$\nu_0\delta_{AB} = \frac{1}{2}(D' + D'') \tag{20}$$

$$J_{AX} = f'_o - f''_o + \frac{1}{2}(D' - D'') \tag{21}$$

$$J_{BX} = f'_o - f''_o - \frac{1}{2}(D' - D'') \tag{22}$$

The symbols used have the following meanings:

$$D' = \nu'_A - \nu'_B = +\sqrt{(f'_1 - f'_4)(f'_2 - f'_3)} \tag{23}$$

$$D'' = \nu''_A - \nu''_B = +\sqrt{(f''_1 - f''_4)(f''_2 - f''_3)} \tag{24}$$

$$f'_o = \tfrac{1}{2}(\nu'_A + \nu'_B) = \tfrac{1}{2}(f'_1 + f'_4) = \tfrac{1}{2}(f'_2 + f'_3) \tag{25}$$

$$f''_o = \tfrac{1}{2}(\nu''_A + \nu''_B) = \tfrac{1}{2}(f''_1 + f''_4) = \tfrac{1}{2}(f''_2 + f''_3) \tag{26}$$

The resonance lines of the X nucleus permit the calculation of two additional quantities:

$$J_{AX} + J_{BX} = f_6 - f_9 \tag{27}$$

$$J_{AX} - J_{BX} = \frac{1}{2\nu_0\delta_{AB}}(f_5 - f_{10})(f_7 - f_8) \tag{28}$$

Whereas the spectrum is affected only by the magnitude of the coupling parameter $J_{AB}$, the relative signs of $J_{AX}$

[25] *K. B. Wiberg* and *B. J. Nist*: The Interpretation of NMR Spectra. Benjamin, New York, 1961. – This book contains tables and spectra for the AB, $AB_2$, $AB_3$, $AB_4$, and $A_2B_3$ system types and a collection of spectra whose form depends on more than one parameter (ABX, ABC, and $A_2B_2$ systems).

and $J_{BX}$ affect the frequencies and intensities throughout the spectrum (see Fig. 8).

The proton magnetic resonance spectrum of 1,2,4-trichlorobenzene (Fig. 9) appears to be an ABC spectrum, but is in fact of the ABM type ($\nu_0\delta_{AM} = 8.4\ J_{AM}$; $\nu_0\delta_{BM} = 14.2\ J_{BM}$; cf. Section II). In an ABM analysis, there are no simple defining equations similar to those that apply to ABX systems [Equations (19)–(28)]. However, it has been found that these equations can be used to good approximation, since the parameters obtained are practically the same as those obtained by precise ABM analysis [26].

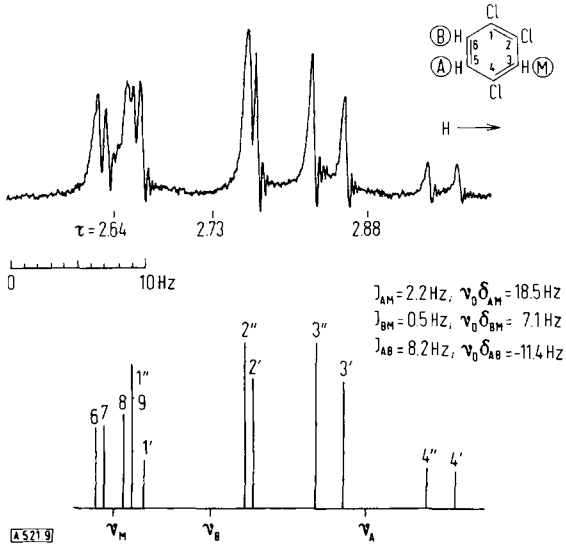



Fig. 9 Magnetic resonance of the protons of 1,2,4-trichlorobenzene in $CCl_4$ at $\nu_0$ = 60 MHz and 24 °C. The spectrum is of the ABM type and can be approximately analysed as an ABX type.

## V. Methods for the Analysis of NMR Spectra

The information about a molecule that can be obtained using nuclear magnetic resonance spectroscopy are usually based on the screening parameter $\sigma$ and the spin coupling constant J. Thus, analysis of an NMR spectrum, *i.e.* the determination of the numerical values of these quantities from the observed positions of the lines, is the reverse of the problem of calculating the spectrum corresponding to a given set of parameters (cf. Section IIIc). Scheme (9) should now be followed from right to left. This is possible for steps a and c, but there is no simple solution for the inversion of step b. Various approaches to the solution of this principal difficulty in the analysis of complex spectra have been suggested. The most important methods will de bescribed briefly in this section.

### (a) The Method of Moments

For any spectrum in which the line intensities and the distances of the frequencies from an arbitrary reference point $f_0$ have been determined, the "spectral moments" can be calculated by summation of simple products [27]. It has been shown by theory [28] that these moments can be equated to expressions containing the Larmor frequencies and coupling parameters. The advantage of this method is the fact that assignment of the lines is not necessary. It has the disadvantage that a complete analysis is impossible except for the simplest types of spectra, since it gives only the parameters that are explicitly contained in the spectral moments. However, the method is extremely useful, for example, when only the chemical shifts in $A_2B_2$ spectra are required (see Section VI, Table 2) or when the overlapping of the lines is too serious to permit the use of other methods, *e.g.* in broad-line NMR spectra of solids.

### (b) Direct Analyses

A very simple case is encountered with "multiplet spectra" (first-order spectra), *e.g.* of the type $A_rX_t$ with magnetically equivalent [9] nuclei. The coupling parameters can be read off directly from the multiplet splittings, and the Larmor frequencies from the multiplet centers. In other direct analyses, the parameters are obtained by substitution of the line frequencies in defining equations; this possibility exists for spectra of the types AB, $AB_2$, and ABX [see Figs. 3 and 6, and Eqs. (19) to (28)], or of the types $A_2X_2$, $A_2B_2$, $A_2B_2X$, and $AB_2X$ (see Table 4).

### (c) The Algebraic Method

In the algebraic method [29–31], the parameters are calculated from the solution of a system of equations. Such a system of equations is assigned to each eigenvalue problem or to its secular equation (Viéta's square root law). Other equations follow from the invariant rules for unitary transformations. The system of equations is solved numerically after insertion of the experimental energy eigenvalues. The observed line frequencies must first be converted into the eigenvalues with the aid of the energy-level diagram. Although explicit expressions have been derived even for complex systems such as $AB_2C_2$ [29], the practical use of this method is mainly confined to the type ABC [30, 31], since the experimental errors mount up too rapidly in the long equations obtained for larger systems.

[26] *G. Englert* and *W. Brügel*, unpublished results.

[27] The spectral moment of the n-th order with respect to a frequency $f_0$ is defined by

$$\langle f^n \rangle = \frac{\sum_k (f_k - f_0)^n I_k}{\sum_k I_k},$$

where $I_k$ = is the intensity. For example, for $A_2B_2$ spectra with $f_0$ in the center of symmetry[28]:

$$(\nu_0\delta_{AB})^2 = 4\langle f^2 \rangle;\ J_{AB}^2 + J_{AB}'^2 = \frac{\langle f^4 \rangle}{\langle f^2 \rangle} - \langle f^2 \rangle$$

[28] *W. A. Anderson* and *H. M. McConnell*, J. chem. Physics *26*, 1496 (1957).

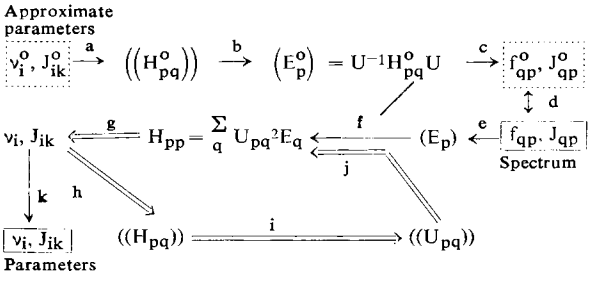
[29] *D. R. Whitmann*, J. molecular Spectroscopy *10*, 250 (1963).

[30] *W. Brügel*, *Th. Ankel*, and *F. Krückeberg*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *64*, 1121 (1960).

[31] *S. Castellano* and *J. S. Wangh*, J. chem. Physics *34*, 295 (1961).

### (d) The Iteration Method

The principle of the iteration method is shown in the following scheme [32, 33]. An approximate set of parameters ($\nu_i^o$, $J_{ik}^o$) is established, *e.g.* by comparison with similar substances, from theoretical data, or by a preliminary analysis. These parameters are then used to calculate an approximate spectrum (Steps a, b, and c), and the assignment of the lines is transferred to the experimental spectrum (Step d). It is then possible to determine the eigenvalues $E_p$ from the experimental frequencies $f_{qp}$ (Step e). The crucial step now is the transformation of these eigenvalues back into the matrix elements $H_{pp}$ (Step f). This is carried out in approximation by means of the unitary transformation matrix U with which the eigenvalue problem was previously solved for the approximate parameters, *i.e.* U is given by the matrix of the approximate eigenvectors.




A set of parameters ($\nu_i$, $J_{ik}$) is then calculated from the diagonal elements $H_{pp}$ (Step g). This set is better than the approximate set ($\nu_i^o$, $J_{ik}^o$), since the experimental eigenvalues $E_p$ are more accurate than the approximation $E_p^o$. The eigenvalue problem is now solved with the new parameters (Steps h and i) and transformed back with the aid of the improved eigenvectors $U_{pq}$ (Step j). The cycle g-h-i-j-g is repeated until no further improvement of the parameters is obtained (Step k).

### (e) The Fitting Method

An attempt may be made to find a set of parameters to fit any spectrum by simple trial and error. The better the agreement between the frequencies and intensities calculated from the tentative parameters and the experimental spectrum, the closer is the set of parameters used to the correct values (trial and error fitting). This method can be regarded as an analytical procedure only if it is carried out systematically, *e.g.* by calculation of a succession of theoretically possible spectra and determination of the correct parameters by interpolation. It works well if only a few independent parameters are involved [4] or if a series of similar spectra are to be analysed [34, 35].

In another method [36], the correct set of parameters is calculated by the method of least squares. A set of approximate parameters is used as in Section Vd to calculate a theoretical spectrum, and partial derivatives of these approximate frequencies with respect to the individual parameters are determined numerically. The deviations of the calculated line frequencies from the experimental values and the partial derivatives give the corrections for the approximate parameter (minimum condition). As in Newton's approximation, the results converge towards the correct values if the starting values are reasonably good.

## VI. Comparison of Various Analytical Methods Using the $A_2B_2$ Spectrum of o-Dichlorobenzene

The proton magnetic resonance spectrum of *o*-dichlorobenzene (cf. Fig. 10) has been analysed several times by a number of different processes. It can be seen from Table 1 that the spin coupling parameters were obtained with an accuracy of only 0.1–0.2 Hz. The methods described in [34, 35, 38, 39] are exact analyses and would give accurate parameters for accurate line frequencies. Thus the deviations in the coupling constants are due only to the limited accuracy of the practical measurements. Since the measurements always involve some inaccuracy, the influence of these errors on the accuracy of the parameters must be taken into account in a comparison of the analytical methods.

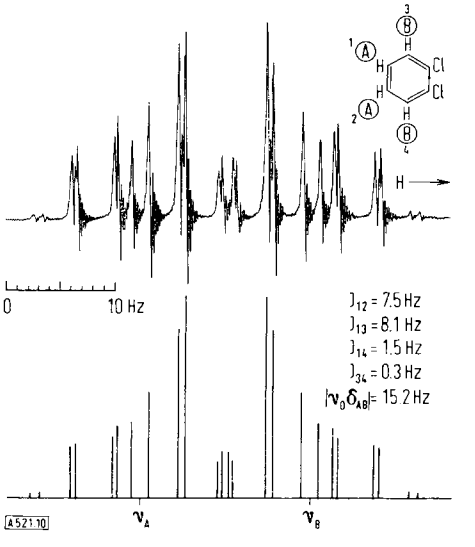



Fig. 10. Magnetic resonance of the protons of *o*-dichlorobenzene in $CCl_4$ at $\nu_0$ = 60 MHz and 24 °C [45b]. For the analysis of this $A_2B_2$ spectrum, see Part VI.

It can be seen from Table 2 that the various methods differ in this respect. The values in Table 2 all refer to


[32] *J. D. Swalen* and *C. A. Reilly*, J. chem. Physics *37*, 21 (1962).
[33a] *R. A. Hoffman* and *S. Gronowith*, Arkiv Kemi *15*, 45 (1959).
[33b] *R. A. Hoffman*, J. chem. Physics *33*, 1256 (1960).
[34] *J. Martin* and *B. P. Dailey*, J. chem. Physics *37*, 2594 (1962).
[35] *M. Grant*, *R. C. Hirst*, and *H. S. Gutowsky*, J. chem. Physics *38*, 470 (1963).
[36] *S. Castellano* and *A. A. Bothner-By*, J. chem. Physics *41*, 3863 (1964).
[37] *J. A. Pople*, *W. G. Schneider*, and *H. J. Bernstein*, Canad. J. Chem. *35*, 1060 (1957).
[38] *B. Dischler* and *G. Englert*, Z. Naturforsch. *16a*, 1180 (1961).
[39] *D. R. Whitman*, J. chem. Physics *36*, 2085 (1962).

the same spectrum [40], and the same approximate parameters were used where necessary (in accordance with [37]). The quality of the analysis was assessed on the basis of the frequency deviation $\overline{\Delta f}$ [41] between the calculated spectrum and the experimental spectrum.

The analysis by the iteration process NMRIT [44] was carried out following the scheme in Section Vd. Divergence began after two iterations, though the approximate parameters (from [37]) had been distinctly improved. The analysis was repeated with these improved values, and the final set of parameters was obtained after seven iterations. The error limits were calculated from the program, with the assumption that the experimental eigenvalues are accurate to ± 0.1 Hz.

Table 1. Results of the analysis by various methods of independently recorded spectra of *o*-dichlorobenzene.

| Ref. | $\nu_o$ (MHz) | Concn. (%) | $J_{12}$ (Hz) | $J_{13}$ (Hz) | $J_{14}$ (Hz) | $J_{34}$ (Hz) | $\nu_o\delta$ (Hz) | $\delta$ (ppm) |
|---|---|---|---|---|---|---|---|---|
| [28] | 30 | 100 | — ± 1.0 | ≤ 8,1 [a] | — [a] | — | 7.8 ± 0.5 | 0.26 |
| [37] | 40 | 100 | 8.3 | 8.3 | 1.7 | 0 | 10.1 | 0.252 |
| [38] | 56.4 | 100 | 7.7 | 7.9 | 1.6 | 0.5 | 14.60 | 0.259 |
| [39] | 60 | 100 | 7.44 | 8.17 | 1.61 | 0.36 | 15.23 | 0.254 |
| [34] | 60 | ≤ 5 [b] | 7.5 | 7.9 | 1.7 | 0.5 | 16.16 | 0.286 |
| [35] | 60 | 95 [c] | 7.5 | 8.1 | 1.5 | 0.3 | 15.80 | 0.263 |
| Average (lines 3 to 6) | | | 7.54 | 8.02 | 1.60 | 0.42 | — | — |

[a] $\sqrt{J_{13}^2 + J_{14}^2}$ = 8.1 Hz [27]; [b] Mole-%, in cyclohexane; [c] Vol-%, in cyclohexane.

Table 2. Results of spectral analysis by various methods for the same experimental spectrum of *o*-dichlorobenzene.

| Method | Iteration steps | $\overline{\Delta f}$ [41] (Hz) | $J_{12}$ (Hz) | $J_{13}$ (Hz) | $J_{14}$ (Hz) | $J_{34}$ (Hz) | $\nu_1 - \nu_2$ (Hz) | $\nu_3 - \nu_4$ (Hz) | $\nu_o\delta$ (Hz) |
|---|---|---|---|---|---|---|---|---|---|
| Moment method [27] | 0 | — | — | ≤ 8.4[a] | [a] | — | — | — | 15.3 |
| Direct analysis [42] | 0 | 0.091 | 7.44 ± 0.20 | 8.12 ± 0.20 | 1.57 ± 0.20 | 0.26 ± 0.20 | — | — | 15.15 ± 0.20 |
| Algebraic [39] | 0 | 0.099 | 7.44 ± 0.05 | 8.17 ± 0.05 | 1.61 ± 0.05 | 0.36 ± 0.05 | — | — | 15.23 ± 0.05 |
| Iteration [44] | 9 | 0.097 | 7.55 ± 0.10 | 8.10 ± 0.07 | 1.51 ± 0.06 | 0.37 ± 0.10 | 7.562 ± 0.037 | 7.553 ± 0.037 | 15.12 ± 0.07 |
| Fitting [45a] | 9 | 0.076 | 7.53 ± 0.04 | 8.09 ± 0.10 | 1.52 ± 0.04 | 0.33 0.18 | 7.628 ± 0.002 | 7.606 ± 0.015 | 15.24 ± 0.02 |
| Average (lines 2 to 5) | | | 7.49 | 8.12 | 1.55 | 0.33 | — | — | 15.18 |

[a] $\sqrt{J_{13}^2 + J_{14}^2}$ = 8.4 Hz.

The following points should be mentioned in connection with the values given in Table 2:

The second moment of the spectrum gives a very reliable value for the Larmor difference $\nu_o\delta_{AB}$, and with the aid of the fourth moment [27] it is found that $J_{AB}^2 + J'^2_{AB} = 70.6$. It follows that $J_{AB} = J_{13} = 8.0$–$8.3$ cps if a value between 1.5 and 2.5 Hz is assumed for $J'_{AB} = J_{14}$. The moment method does not yield any information about the values of $J_{AA} = J_{12}$ and $J_{BB} = J_{34}$.

The direct analysis [38] was carried out using defining equations [42] but without the use of approximate parameters. The limits of error correspond to the maximum deviation between the frequencies of the experimental and calculated spectra.

In the algebraic analysis carried out by *Whitman* [39], summation rules [43] for frequencies and intensities were used in the assignment of the lines. The estimated accuracy value of ± 0.05 Hz [39] is very optimistic.

The analysis by the iteration process NMRIT [44] was carried out following the scheme in Section Vd. Divergence began after two iterations, though the approximate parameters (from [37]) had been distinctly improved. The analysis was repeated with these improved values, and the final set of parameters was obtained after seven iterations. The error limits were calculated from the program, with the assumption that the experimental eigenvalues are accurate to ± 0.1 Hz.

In the fitting method LAOCOON II [45], a comparison spectrum was first calculated from the approximate parameters. The correctly assigned experimental line positions were then introduced, but the expected convergence was not observed. In a second attempt, the four innermost lines, which showed particularly marked deviation from the comparison spectrum, were omitted. This gave a useful set of parameters in five steps, and these parameters were then used in four further steps using all the lines, in order to obtain the final values. The limits of error given by the program is the change in the parameters at which the mean frequency deviation $\overline{\Delta f}$ [41] would be exactly doubled. These "probable" errors are only indirectly connected with the inaccuracy of the parameters, which is, for example, about 10 times greater at $\nu_1$.

The fitting method gives the best results, both with regard to $\Delta f$ [41] and in relation to the average values in Tables 1 and 2, *i.e.* in this example at least, the errors in the measurements are best averaged out by LAOCOON II. This is as expected, since in this method the genuine information from the line positions is used exactly in accordance with their significance for the individual parameters. Though line positions are also used directly in the direct analysis method, the distribution of the weigths is rigid and unequal, as in any defining equation

[40] The spectrum published by *Whitman* [39] contains uncertainties of up to 0.2 Hz in the frequencies; this is desirable for the test of Table 2. Better accuracy can now be obtained if the spectrum is recorded several times and the results averaged.

[41] The root mean square error for t lines is:

$$\Delta f = \left[\frac{1}{t}\sum_{k=1}^{t}\left(f_k^{exp} - f_k^{calc}\right)^2\right]^{1/2}$$

[42] *B. Dischler* and *W. Maier*, Z. Naturforsch. *16a*, 318 (1961); *B. Dischler*, ibid. *20a*, 888 (1965).

[43] Cf. Rule 3 in Part IIIe. The following trivial rule applies to frequencies: The distance between two energy levels is independent of the transitions chosen. In Figure 3, for example, $f_1 + f_4 = f_2 + f_3$.

[44] Thanks are due to Dr. *W. Brügel*, Hauptlaboratorium BASF, Ludwigshafen, for the analysis by NMRIT [32].

[45a] The analysis with LAOCOON II (Least-squares Adjustment Of Calculated On Observed NMR spectra). [33] was kindly carried out by Dr. *H. Günther*, Institut für Organische Chemie, Universität Köln.

[45b] Dr. *H. Günther* also supplied the depicted spectrum of *o*-dichlorobenzene, which was recorded with a Varian A60 spectrometer.

of generally validity. With the analytical and iteration methods some of the original accuracy is lost in the conversion of frequencies into energies. In view of the uncertain convergence behavior encountered in the methods of[44] and [45a], it seems advisable to use two steps: for example, a set of parameters may be calculated by the simple direct method[42], and these may then be further improved, if necessary, by the fitting method[45a].

In order to make a general assessment of the efficiencies of the various analytical methods, it would naturally be necessary to work out a large number of examples.

## VII. Suggestions for the Analysis

### (a) Arrangement in Order of Difficulty

The very different mathematical requirements involved in the analysis of the individual spectra have here been arranged in order of difficulty. Table 3 shows the criteria used in the assessment, and Table 4 shows a selection of analyses that have been carried out.

Table 3. Classification of spectral analyses according to their difficulty.

| Difficulty grading | I | II | III | IV | V | VI |
|---|---|---|---|---|---|---|
| Without calculation | + | | | | | |
| Directly analysable | ∓ | + | + | + | | |
| Assignment required | | | + | + | + | + |
| Central spectrum required | | | | + | + | + |
| Difficult calculation | | | | | + | + |
| Good approximate parameters required | | | | | | + |

Table 4. Examples of investigated spectra, arranged to illustrate the various degrees of difficulty in accordance with Table 3.

| Type of spectrum | Difficulty grading | Method of analysis b) direct c) algebraic d) iteration e) fitting *) simplification by division into subspectra (cf. Sect. IVc) b) | c) | d) | e) |
|---|---|---|---|---|---|
| Multiplets | I | [17] | | | |
| AB | II | [46] | | | |
| $AB_2$ | II | | | | [47, 4] |
| ABX | III | [48] | | | |
| $AB_2X$ | III | [49] | | | |
| $A_2X_2$ | III | [50, 51] | | | |
| $A_2B_2$ | IV | [38, 42] | [52, 39] | [33a] | [34, 35] |
| $A_2B_2X$ | IV | [38]* | | | [53] |
| $ABU_3X$ | IV | [14a]* | | | |
| ABC | V | | [30, 31] | [54] | [55] |
| ABCX | V | | [56]* | | |
| ABCD | VI | | | [57] | [58, 36] |
| $AB_2C_2$ | VI | | | | [36] |

[46] *W. A. Anderson*, Physic. Rev. *102*, 151 (1956).

[47] *E. L. Muetterties* and *W. D. Phillips*, J. Amer. chem. Soc. *79*, 322 (1957).

[48] *H. S. Gutowsky*, *C. H. Holm*, *A. Saika*, and *G. A. Williams*, J. Amer. chem. Soc. *79*, 4596 (1957).

[49] *R. J. Abraham*, *E. O. Bishop*, and *R. E. Richards*, Molecular Physics *3*, 485 (1960).

[50] *H. M. McConnell*, *A. D. McLean*, and *C. A. Reilly*, J. chem. Physics *23*, 1152 (1955).

[51a] *G. W. Flynn* and *J. D. Baldeschwieler*, J. chem. Physics *38*, 226 (1963).

[51b] *G. W. Flynn*, *M. Matsushima*, *J. D. Baldeschwieler*, and *N. C. Craig*, J. chem. Physics *38*, 2295 (1963).

### (b) Experimental Aids

Substitution by isotopes is useful in NMR spectroscopy. For instance proton magnetic resonance spectra can be simplified by partial deuteration of the substances, since the lines due to the hydrogen atoms that have been replaced by deuterium disappear, and the H–D spin coupling constants are smaller by a factor of 1/0.154 than the corresponding H–H coupling constants.

If the measuring frequency is increased from 60 to 100 MHz, the Larmor differences are almost doubled, whereas the spin couplings remain unchanged. Thus the spectrum approaches the multiplet type, which is easier to interpret and to analyse. Conversely, a change in frequency from 60 to 15 MHz leads to a more complex spectrum, owing to the smaller Larmor differences. Comparison of the spectra obtained with all three frequencies often makes it possible to decide between several combinations of signs in the spin couplings[49]. The Larmor differences can also be varied within certain limits by solvent effects[58]; this permits the unambiguous determination of the signs of the coupling parameters in systematic studies[59].

An important aid is nuclear magnetic double resonance (NMDR). In normal operation the spectrum is recorded in a radio-frequency field $H_1$, the strength of which is kept so small that the energy-level diagram remains stationary, so that the Dirac perturbation theory, on which the calculation of Equations (5), (6), (10), and (12) is based, is valid. In double resonance, a second radio-frequency field $H_2$ is applied parallel to $H_1$; the much greater field strength of $H_2$ leads to a change in the energy-level diagram whenever its frequency $\nu_2$ coincides exactly or approximately with a resonance line.

In "spin decoupling" experiments[60,61], the multiplet splitting caused by one or more X nuclei is caused to disappear by the application of the Larmor frequency $\nu_X$ with saturation field strength. In addition to simplifying the spectrum, spin decoupling yields information on the interrelationship between certain lines.

This interrelationship between lines is specially studied in "perturbation field experiments"[62], where the frequency of a single resonance line is applied permanently.

[52] *B. D. Nageswara-Rao* and *P. Venkateswarlu*, Proc. Indian Acad. Sci., Sect. A *54*, 1 (1961).

[53] *R. E. Richards* and *T. Schaefer*, Proc. Roy. Soc. (London), Ser. A *246*, 429 (1958).

[54] *C. A. Reilly* and *J. D. Swalen*, J. chem. Physics *32*, 1378 (1960).

[55] *C. S. Johnson Jr.*, *M. A. Weiner*, *J. S. Waugh*, and *D. Seyferth*, J. Amer. chem. Soc. *83*, 1306 (1961).

[56] *W. Brügel*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *66*, 159 (1962).

[57] *C. A. Reilly* and *J. D. Swalen*, J. chem. Physics *34*, 980 (1961).

[58] *S. Clough*, Molecular Physics *2*, 349 (1959).

[59] *H. Dreeskamp* and *E. Sackmann*, Z. physik. Chem. N.F. *34*, 261 (1962).

[60] *A. L. Bloom* and *J. N. Shoolery*, Physic. Rev. *97*, 1261 (1955).

[61] *W. A. Anderson* and *R. Freeman*, J. chem. Physics *37*, 85 (1962).

[62] *R. Freeman* and *W. A. Anderson*, J. chem. Physics *37*, 2053 (1962).

The field strength must be large enough to perturb the energy levels involved in the resonance in question, the perturbation being either (a) energetic [62] or (b) in the occupation numbers [61,63], depending on the relaxation time. It is then found that for (a), the lines due to all transitions that begin or terminate at these two levels are split into two equally strong components [62] with a perturbation parameter that depends almost linearly on the field strength $H_2$, while for (b) these lines undergo characteristic intensity changes [64]. Since the lines in which the same levels are involved are known in perturbation field experiments, this method assists in obtaining a definite assignment of the lines.

The observation of multiple quantum transitions ($\Delta m = 2, 3 \ldots$) which occur near the saturation intensity of $H_1$ [65,66] yields additional information about the energy-level diagram, which may allow a particular choice in the signs of spin coupling parameters.

The proton magnetic resonance spectrum of gaseous 1,1-difluoroethylene (at 10–26 atm) contains both sharp and broad lines [51a]; this is in agreement with theoretical calculations which assume an interaction between the spin of the fluorine nuclei and the molecular rotation as the relaxation mechanism. The different line widths are of great assistance in the assignment of the lines, *i.e.* in the determination of the relative signs of coupling parameters [51].

## VIII. Outlook

For n nuclei of spin $^1/_2$, the number of energy levels increases with $2^n$, and the number of lines roughly with $n^3$ (see Table 5). As the size of the spin system becomes larger, the number of lines increases so rapidly that they can no longer be resolved. Moreover, the average intensity of the lines rapidly decreases. Analysis thus becomes very difficult or even impossible. It is therefore to be expected that the simpler spin systems studied so far (see Table 4) will still occupy the foreground in the future.

Table 5. Numerical data for increasingly complex spin systems with nuclear spin $^1/_2$.

| Example | A | AB | ABC | ABCD | – | – |
|---|---|---|---|---|---|---|
| Nuclei | 1 | 2 | 3 | 4 | 8 | n |
| Parameters ($\nu_i$, $J_{ik}$) [a] | 1 | 3 | 6 | 10 | 36 | $n+\binom{n}{2}$ |
| Matrix elements [b] | 2 | 6 | 20 | 70 | 12870 | $\sum_{i=0}^{n}\left[\binom{n}{2}\right]^2$ |
| Energy levels | 2 | 4 | 8 | 16 | 256 | $2^n$ |
| Allowed transitions [c] | | | | | | |
| max. | 1 | 4 | 15 | 56 | 11440 | $\sum_{i=0}^{n-1}\binom{n}{i}\binom{i+1}{n}$ |
| min. | 1 | 2 | 5 | 10 | 186 | $2^n-\binom{n}{g}$; $g=\frac{n}{2}$ or $\frac{n-1}{2}$ |
| Total intensity | | | | | | |
| normalized [d] | 1 | 4 | 12 | 32 | 1024 | $n^{2n-1}$ |
| experimental | 1 | 2 | 3 | 4 | 8 | n |

[a] For $n > 1$, the number of independent parameters is always two less, since the form of the spectrum depends only on the ratio of the Larmor differences to coupling parameters.

[b] These values take into account the breakdown into submatrices $F_z$.

[c] The number of these is variable, owing to the selection rule Equation (15). The minimum number is found, for example, in $A_n$ systems, and the maximum number in the above examples.

[d] The normalization is based on the summation rule (cf. Section IIIe, Rule 3).

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# Problems of Iron Metabolism with Special Reference to Biochemical, Physiological, and Clinical Aspects

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*A brief account of the functions and chemical structures of the principal iron compounds found in the human body is followed by a discussion of the physiology of iron metabolism, starting with its resorption, continuing with its transport and assimilation by the body cells, and concluding with its elimination. Special attention is paid to the problems of intracellular and extracellular transport of iron. A number of diseases with characteristic disturbances of the iron metabolism are also briefly described.*

Wherever respiration occurs, iron is present in some form. Iron is essential to the elementary metabolic processes in the cell. In the catalytic processes of the respiratory chain it acts as an electron carrier, and it is responsible for the transport of molecular oxygen in higher organisms. These important functions depend

on the ability of iron to exist in coordination compounds in different oxidation and bonding states [1].

The adult human body contains 4 to 5 g of iron. Several iron fractions, listed in Table 1, are distinguished according to the function of the iron.

Table 1. Body components containing iron.

| Occurrence | Iron bound as | Mode of linkage | Function | Iron content | |
|---|---|---|---|---|---|
| | | | | Total [a] | % of body iron |
| Blood system | Hemoglobin | Heme | $O_2$ transport | 3 g | 65.4 |
| | Plasma | Transferrin | Fe transport | 4 mg | 0.1 |
| Tissues | Functional iron (myoglobin, cell hemes) | Heme | Cell respiration | 650 mg | 13.9 |
| | Storage iron | Ferritin Hemosiderin | Iron pool Detoxication | 1 g | 21.5 |
| | | | | 4.65 g | 100.0 |

[a] Approximate values.

## A. Iron Compounds Present in the Human Body

### I. Hemoproteins

The compounds of this group (hemoglobin, myoglobin, *etc.*) all contain the iron(II)-protoporphyrin complex heme as specific prosthetic group. Their function involves the transport of oxygen and cell respiration.

The incorporation of metal atoms into the porphyrin ring system leads to extremely stable chelates. Biologically, the most important metal-porphyrin complexes are those of iron. Iron can bind six ligands in octahedral arrangement. In heme, the iron is situated in the center of the planar protoporphyrin ring; in hemoglobin, for example, the fifth coordination site is occupied by a nitrogen atom of a histidine residue of the globin, while the sixth is occupied by water. The hemoproteins can be divided into two groups according to function.

#### 1. Respiratory Enzymes

In cytochrome c, the protein component is bound by covalent sulfide linkages to side chains of the porphyrin-iron system. This linkage is much stronger than, for example, the protein linkage of the heme in hemoglobin. Moreover, the "heme" group in cytochrome c evidently is shielded by the protein chain to such an extent that the iron cannot react with oxygen. Cytochrome c is not autoxidable at physiological pH-values; further, the porphyrin component differs from that of hemoglobin in two of its side chains.

Many points concerning the structure and function of cytochrome b still remain unclear.

The respiratory enzymes also include catalase, which decomposes hydrogen peroxide into water and oxygen, and the peroxidases, which catalyse the oxidation of substrates by hydrogen peroxide.

[1] *G. L. Eichhorn* in: Iron Metabolism, an International Symposium. Springer, Berlin-Göttingen-Heidelberg 1964, p. 9.

#### 2. Hemoproteins that Store and/or Transport Molecular Oxygen

Hemoglobin (molecular weight 66000), the principal constituent of erythrocytes, consists of four subunits, each containing one heme molecule. The iron content of hemoglobin is 0.335 to 0.338 %. The four heme groups are situated on the surface of the peptide chains [2], the spatial arrangement of which was elucidated only a few years ago [2, 3].

Iron(II) myoglobin contains only a single peptide chain having a molecular weight of 17000. The structure of this protein was also established fairly recently [4]. Oxygen is bound as in hemoglobin, but myoglobin is saturated at considerably lower oxygen pressures. It stores oxygen in muscles and is particularly important in sea animals with lungs, when these animals remain submerged for long periods.

## II. Iron Proteins Responsible for the Storage and Transport of Iron

#### 1. Ferritin and Hemosiderin

Iron is stored in ferritin and hemosiderin in the liver, spleen, and bone marrow. Ferritin is a water-soluble, crystallizable iron protein built up from apoferritin and micelles of a colloidal iron(III) hydroxide-phosphate complex. According to *Granick* and *Michealis* [5], the iron content of ferritin isolated from horse spleen varies between 17 and 23 %. The iron micelles are situated within the protein envelope [6]. Electron microscopy gives a value of 55 to 60 Å for the diameter of the iron micelles, and 94 to 110 Å for that of the protein envelope [6–8]. The iron micelles are seen in the electron microscope to consist of four subunits with diameters of 27 to 30 Å. The values found for the molecular weight of the apoferritin from horse spleen vary from 327000 to 480000, depending on the method of determination [9–11]. The iron in ferritin is trivalent, but it is incorporated and released in the bivalent form [12].

The nature of hemosiderin is still a subject of controversy. Unlike ferritin, it is insoluble in water. In the optical microscope it can be observed in the form of granules, in which the iron is also trivalent. The iron

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[3] *V. M. Ingram* and *A. O. W. Stretton,* Nature (London) *184,* 1903 (1959).

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[12] *M. W. Loewus* and *R. A. Fineberg,* Biochim. biophysica Acta *26,* 441 (1957).

content according to most of the results reported is 30 to 40 %, *i.e.* much higher than in ferritin. The protein components of hemosiderin and ferritin show a number of similarities in their amino-acid composition [13].

### 2. Transferrin

Transferrin is the specific iron-transport protein of blood plasma. It is a glycoprotein; values of 90000 [14] and 86000 [15] have been reported for its molecular weight. Starch-gel electrophoresis after incubation of transferrin with neuraminidase leads, depending on the enzyme concentration, to the gradual formation of four slower bands. It has been concluded from this result that the transferrin molecule contains four neuraminic acid groups in addition to peptide chains [16].

Two atoms of iron can be reversibly bound by one molecule of transferrin, *i.e.* the binding capacity of 1 mg of transferrin is 1.30 µg of iron [15]. Magnetic measurements [17] have shown that the bound iron is present in the trivalent form. The nature of the bonding is not yet clear [18,19].

By the reversible binding of iron, transferrin is responsible for the transport of iron in the plasma and in the extracellular fluid, and for the transfer of iron between resorption, storage, and consumer organs [20]. It is therefore of the utmost importance to the correct functioning of the iron metabolism.

By starch-gel electrophoresis 15 genetically determined transferrin types [21] of different specific migration rates can be distinguished. These transferrin types are of special interest in human genetics.

## B. Physiology of Iron Metabolism

In view of the extent of the material available on the physiology of iron metabolism, a detailed description will not be given here. Instead, the most important principles will be discussed briefly with the aid of the scheme of iron metabolism in Fig. 1. Some hypotheses currently under discussion have also been included.

### I. Resorption

Tracer studies using $^{59}Fe$ (half-life 47 days) have shown that most of the iron ingested orally is resorbed in the cranial section of the duodenum [22,23]. However,

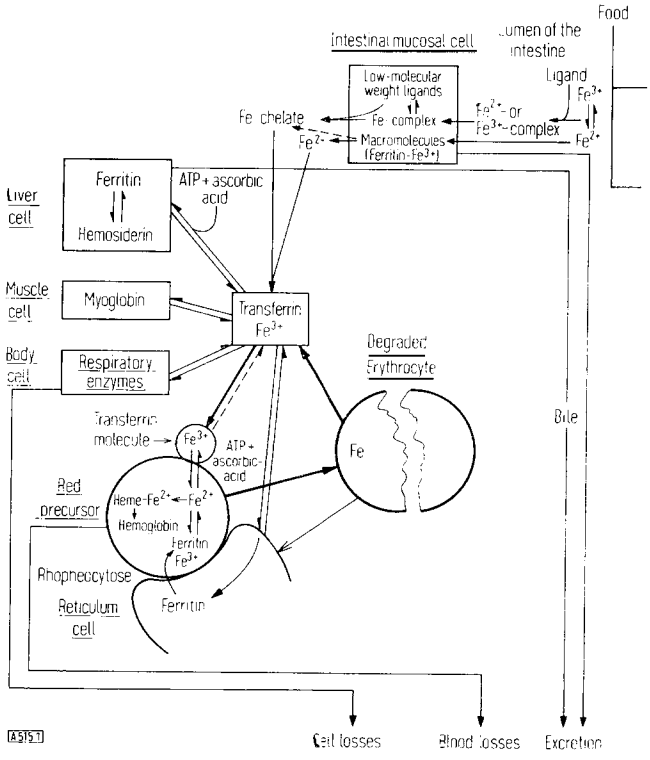


Fig. 1. Scheme of the physiology of iron metabolism.

other sections of the gastrointestinal tract, including the large intestine [24] are also able to absorb iron. Inorganic iron compounds are more readily absorbed than iron contained in the food. The iron present in various foods is absorbed to different extents.

Owing to experimental difficulties, no accurate quantitative data are available on the utilization of iron in the food. According to *Moore* [25], Europeans and North Americans absorb an average of 5 to 10 % of the iron in their diet. Thus from a daily iron intake of 12 to 15 mg in the food, 0.6 to 1.5 mg is absorbed. This does not include the iron consumed in water, beer, wine, and other beverages.

The general view is that iron is resorbed in the bivalent form [26]. Ascorbic acid [27] and substances containing thiol groups [28] increase resorption because of their ability to keep iron in the bivalent form. A number of organic acids is also claimed to promote resorption by increasing the acidity of the medium and the solubility of the iron [29]. Finally, resorption is also increased by amino acids [30] and by sorbitol [31]; however, this increase cannot be explained by increased acidity or by a reducing action.

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[27] *S. M. Greenberg*, *R. G. Tucker*, *A. E. Heming*, and *J. K. Mathues*, J. Nutrit. *63*, 19 (1957).

[28] *L. Heilmeyer* in *R. O. Wallerstein* and *S. R. Mettier*: Iron in Clinical Medicine. University of California Press, Berkeley, 1958, p. 24.

[29] *J. Groen*, *W. A. van den Broeck*, and *H. Welchmann*, Biochim. biophysica Acta *1*, 315 (1947).

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[31] *J. F. Herndorn*, *E. G. Rice*, *R. G. Tucker*, *E. J. van Loon*, and *S. M. Greenberg*, J. Nutrit. *64*, 615 (1958).

These observations have recently led to the view that the iron passes through the intestinal epithelial cells [*] in a complex of low molecular weight. *Charley et al.* [32] have shown that not only bivalent, but also trivalent iron is rapidly resorbed if it is administered as the chelate with fructose. The experiments were carried out with 32 M fructose solutions containing a mixture of $^{59}FeCl_3$ with carrier $FeCl_3$, and with $FeSO_4$ in 0.9 % NaCl solution with $^{59}FeCl_3$ at iron concentrations of 0.5 mg/ml. The time taken for the iron to pass from the lumen of the intestine into the peripheral blood circulation was no longer than the time normally required by the bloodstream. Thus the passage through the epithelial cells appears to be very fast. The passage of low-molecular weight iron complexes through the cell membrane has been observed also in other biological systems such as liver slices and reticulocytes [33–35].

In addition to these views on the resorption path, there is the old mucosal block theory developed by *Hahn* [36] and *Granick* [37, 38], according to which the iron is passed through the mucosal cells with the aid of ferritin. The iron resorption is thought to cease when the ferritin in the mucosal cell is saturated, so that the organism is prevented from becoming overloaded with iron. However, this theory has been disproved [39]: by simultaneous determination of the quantity of iron offered and the quantity resorbed (with the aid of $^{59}Fe$) and of the ferritin content of the mucosal cells, it was shown that the iron resorption increases in proportion to the ferritin concentration in the intestinal mucosal cell even after the ferritin has been saturated. Nevertheless it is still believed that ferritin is involved in the resorption of iron.

Several authors [32,40,41] believe that the saturation of transferrin in the blood plasma with iron plays an important part in the resorption of iron. This view is based on experiments which show that $^{59}Fe$-fructose or $^{59}FeSO_4 \cdot 7H_2O$ administered enterally after saturation of the plasma transferrin with iron no longer pass into the peripheral blood. Other research groups [42,43], however, concluded from experimental evidence that the resorption of iron is independent of the degree of saturation of the plasma transferrin. According to this view, if the transferrin is saturated with iron, any further iron absorbed, which is probably not bound to the transferrin in the portal blood, is immediately intercepted and retained by the liver, so that it does not enter the peripheral blood. This interpretation agrees with the results of both groups of workers.

In studies on healthy persons, *Brown, Dubach,* and *Moore* [44] also came to the conclusion that the saturation of the transferrin has no influence on the resorption of iron. On the basis of our own investigations, particularly on a case of congenital atransferrinemia (which is discussed more fully in Section C.IV) we agree with this last interpretation.

The role of pancreatic secretion in iron resorption has only recently been re-examined, though a connection was mentioned by *Taylor, Stiven,* and *Reid* [45] as early as 1935. *Davies* and *Badenoch* [46] found increased iron resorption in severe cases of chronic pancreatitis. *Callender* [47] also observed increased iron resorption in chronic liver diseases; the resorption could be lowered by administration of pancreatin. It was concluded from these results that pancreatic juice contains a substance that inhibits iron resorption. It has recently been suggested that hemochromatosis may be caused by a genetic defect in the region of the pancreas, coupled with a deficiency or absence of iron resorption inhibitor.

## II. Iron Transport and Iron Turnover

Iron is transported by the specific transport protein, discovered by *Holmberg* and *Laurell* [48] in 1944, and independently by *Schade* and *Caroline* [49] in 1946, and named by these two groups transferrin and siderophilin, respectively. The reversible binding of iron by transferrin permits the rapid transfer of the metal between the resorption, storage, and consumer organs. The normal concentration of transferrin in plasma is 200 to 320 ppm. For practical reasons, the transferrin concentration usually is given as the total iron-binding capacity of the serum. This is the quantity of iron that is specifically bound by 100 ml of serum. The iron-binding capacity normally is only 0.25 to 0.30 ppm. Thus when the iron level in the serum is 0.1 ppm, the transferrin is only about one-third saturated with iron. Above the saturation limit, toxic reactions occur because of the presence of free iron ions.

Most of the iron transported in the plasma is derived from the degradation of hemoglobin. The economic control of the iron metabolism is particularly clear from the fact that the iron liberated by the breakdown of erythrocytes is largely re-used for the formation of fresh hemoglobin. For an erythrocyte life of 110–120 days, the daily iron requirement of the blood-forming tissue is 23 to 30 mg. Thus 8 to 10 times the quantity of iron present in the plasma (3 to 4 mg) would be needed to satisfy this requirement alone. This turnover is further increased by the exchange of stored iron, iron in myoglobin, and iron in cell hemin, as well as the iron that is absorbed and eliminated. The total iron turnover is calculated to be 0.36 to 0.52, and on an average [*] 0.42 mg of Fe per day per kg of body weight [50,51].

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[*] Intestinal epithelial cell = intestinal mucosal cell.


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[33] *A. Mazur, S. Green,* and *A. Carleton,* J. biol. Chemistry *235,* 595 (1960).

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[48] *C. G. Holmber* and *C.-B. Laurell,* Acta physiol. scand. *10,* 307 (1945).

[49] *A. L. Schade* and *L. Caroline,* Science (Washington) *104,* 340 (1946).


[*] Based on a body weight of 70 kg.


[50] *L. Heilmeyer* and *W. Keiderling,* Strahlentherapie *100,* 169 (1956).

The rate of iron exchange in the plasma and the daily or hourly plasma iron turnover can be determined with the aid of $^{59}Fe$ (as $^{59}FeCl_3$ or $^{59}Fe$ citrate). The biological half-life[**] of iron bound by transferrin normally is 70 to 140 minutes.

Using $^{59}Fe$ samples with high specific activities, *Pollycove* studied the iron exchange among the iron fractions in the body[52]. He postulated the existence of a "labile iron pool"[53] (a labile, easily exchangeable iron reserve in the storage organs), and calculated its size from the rate of migration of the $^{59}Fe$ out of the plasma. No iron compound corresponding to this pool has so far been detected with certainty. *Pollycove* also calculated the quantity of ferritin (mobilizable stored iron) held in the storage organs together with the labile iron pool and hemosiderin, as well as the mean effective time for the hemoglobinization of the erythron[***] and the average life of the latter. Some important data are given in Figs. 2 to 4 and in Table 2[54].

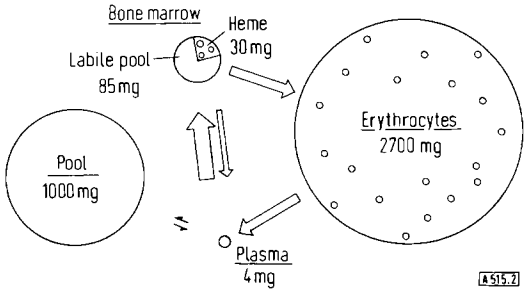


Fig. 2. Scheme of the iron exchange between the iron distribution sites [54]. The numerical values agree approximately with those of Table 1 (the erythrocyte iron is given here instead of hemoglobin iron; the two quantities are practically the same). The size of the circle is proportional to the component of the body iron fractions, and the area of the arrow to the rate of exchange.

The use of $^{59}Fe$ for the determination of the rate of migration of iron from the plasma, the daily or hourly iron turnover, the iron utilization by the erythrocytes, and the distribution of the iron in the organs is now applied in clinical diagnosis, and has led to valuable discoveries concerning disturbances of the iron metabolism.

## III. Assimilation of Iron by the Cells

Investigations on the uptake of iron by the body cells have so far been confined to red precursors[*] and liver cells. *Mazur* and *Carleton*[33] studied the incorporation

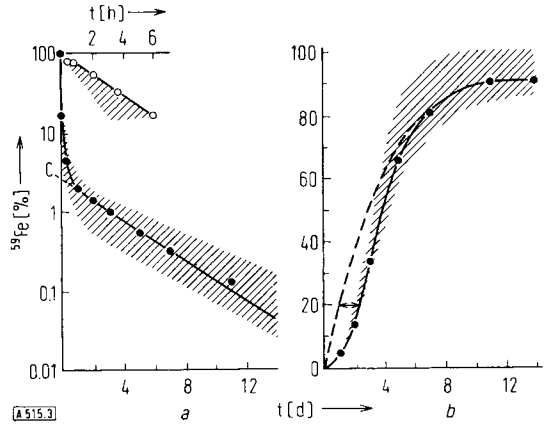


Fig. 3a. $^{59}Fe$ content of the plasma of a healthy male weighing 70 kg. Hemoglobin: 17.1 g/100 ml of blood. Hemoglobin synthesis: 6.6 g/day. Mean life time of erythrons: 122 days. C: mean effective time for the hemoglobinization of the erythron (according to [54]).
Ordinate: Percentage of $^{59}Fe$ remaining in the plasma.
Abscissa: Time after intravenous injection of $^{59}Fe$ (top: hours; bottom: days).
Shaded area: Normal range.

Fig. 3b. Absorption of $^{59}Fe$ by the erythrocytes (measured) (——) and the erythrons (calculated) (- - - - -). Double arrow: mean effective time for the hemoglobinization of erythrons. Test subject as for Fig. 3a (according to [54]).
Ordinate: Percentage of $^{59}Fe$ incorporated.
Abscissa: Time (days) after intravenous injection of $^{59}Fe$.

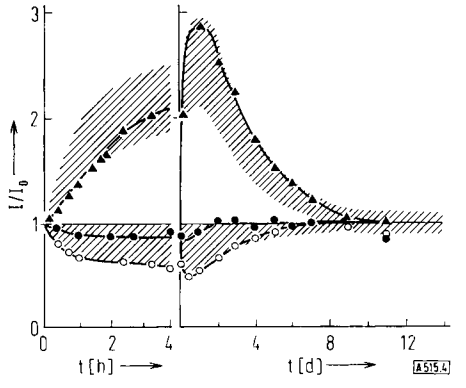


Fig. 4. Surface radioactivity measured on a healthy subject (according to [54]).
▲: bone marrow (sacrum); ●: liver; ○: spleen.
Shaded area: normal ranges (top) for sacrum and (bottom) for liver and spleen.
Ordinate: Relative radioactivity of the body surface ($I/I_0$).
Abscissa: Time (left: hours; right: days) after intravenous injection of $^{59}Fe$.

Table 2. Plasma iron exchange [54] (see Fig. 2).

| Iron taken up from | mg/day | Iron given up to | mg/day |
|---|---|---|---|
| Erythrocytes | 21 | Erythropoetic labile iron pool | 32 |
| Storage iron | 1 | Storage iron | 1 |
| Extracellular fluid | 1 | Extracellular fluid | 1 |
| Absorption | 1 | Excrements and losses | 1 |
| Erythropoetic labile iron pool | 11 | | |
| | 35 | | 35 |

of plasma-bound iron into the ferritin of liver slices and liver cell homogenizates. They found that the incorporation of iron in this case involves the assistance of ATP and ascorbic acid, the liberation of the transferrin-bound iron being accompanied by the formation of a complex from two moles of ATP, one mole of ascorbic

[51] *W. Keiderling, H. A. E. Schmidt, M. Lee,* and *K. Th. Frank,* 5th Congress Europ. Hematology Soc. 1955. Springer, Heidelberg 1956, pp. 127, 779.

[**] The biological half-life in this case is half of the residence time of transferrin-bound iron circulating in the bloodstream.

[52] *M. Pollycove* and *R. Mortimer,* J. clin. Invest. *40,* 753 (1961).

[53] *M. Pollycove* and *M. Maqsood,* Nature (London) *194,* 152 (1962).

[***] The term "erythron" includes all stages in the development and aging of the erythrocyte. The time for the hemoglobinization of the erythron is the time required for the synthesis of the hemoglobin in the red precursors until the erythrocytes have reached maturity.

[54] *M. Pollycove* in [1], p. 148.

[*] Red precursors are nucleated red cells, which normally occur only in the bone marrow. Young red cells are found in the peripheral blood. These do not contain cell nuclei, but only nuclear detritus.

acid, and the transferrin molecule. A similar mechanism was proposed for the incorporation of iron into the red precursors [55]. It was assumed that following its release from the transferrin, the iron is coupled to ferritin before being used for the synthesis of hemoglobin.

The transfer of iron from transferrin to the hemoglobin-forming cells has recently been followed by tracer techniques. *Jandel*, *Katz*, and other workers [15,56–59] carried out incubation experiments with $^{131}$I-transferrin to which $^{59}$Fe was coupled. It was found that the transferrin becomes fixed specifically on the surface of young red cells [*]. The transferrin molecule adheres to the cell surface for about one minute. During this time, the iron is split off from the transferrin by an endothermic process and is then taken up by the cell. The affinity of the iron-containing transferrin molecule for the hypothetical receptors on the cell surface was found to be greater than that of iron-free molecules. This result explains the displacement of transferrin molecules that have given up their iron to the cell by iron-containing molecules reaching the cell surface later. The number of receptors has been calculated to be 50000 per reticulocyte. However, *Morgan* and *Laurell* [60] found that transferrin with or without iron is firmly bound to the reticulocyte surface, and that the iron resorption is proportional to the iron concentration, irrespective of the transferrin concentration.

The path followed by iron from its absorption by the red precursors to its incorporation into hemoglobin is largely unknown. It is not certain whether ferritin acts as an intermediate [55], possibly as the substrate of the labile iron pool postulated by *Pollycove* [55], or whether the iron undergoes further intracellular transport, possibly again *via* complexes of low molecular weight. *Goldberg et al.* [61,62] showed that the incorporation of iron into the protoporphyrin is catalysed by a specific enzyme, heme synthetase.

Another theory of the transfer of iron to the red precursors was developed by *Bessis* and *Breton-Gorius* [63,64] on the basis of impressive electron micrographs of "rhopheocytosis" [*]. Ferritin molecules are assumed to be transferred from the reticulocytes in the bone marrow directly to the erythroblasts. It is still uncertain whether the reticulocytes obtain their iron from the transferrin or directly from the hemoglobin of erythrocytes that have been broken down (erythrophagocytosis).

The course of the iron exchange between transferrin and the other body cells, particularly those of the reticuloendothelial system, has not yet been elucidated. As has been shown by our experiments, however, an essential function of transferrin appears to be the prevention of iron uptake by body cells that do not form hemoglobin and to protect the organism against siderosis.

#### IV. Elimination of Iron

According to *Finch* [65], the daily iron loss is approximately 0.6 mg for the human male, and about 2 to 3 times as much for the female after puberty. During pregnancy the iron loss increases to 3–4 mg per day owing to placental iron transport. The iron is generally lost as protein, bile and other secretions, and body cells. The loss of body cells accounts for the major part of the daily iron loss.

Assuming that the supply of iron is normal and that there is no disturbance of resorption, a negative iron balance can occur only as a result of bleeding. For a normal diet containing 12 to 15 mg of iron, 5 to 10 % of which are resorbed, adult males and non-menstruating females do not develop iron deficiency or hemochromatosis, and according to *Moore* [25], this is the best available evidence that the quantity of iron eliminated is between 1 and 1.5 mg per day.

### C. Pathology of Iron Metabolism

Though iron deficiency can be accompanied by many diseases, only a few outstanding forms can be described here.

#### I. Iron Metabolism in Infected Persons

The starting point for the ferrokinetic studies on infected persons was the observation that enterally or parenterally administered iron has little or no effect on the hyposideremia (lowering of the serum iron concentration) that accompanies the onset of inflammatory disease. Thus special conditions must prevail in infected persons.

The ferrokinetic studies consist of four parts: 1. Quantitative determination of the serum iron, and determination (by the isotope technique) of 2. the rate of migration of iron from the plasma, 3. the rate of incorporation of iron into the erythrocytes, and 4. the distribution of iron in the bone marrow, liver, spleen, and heart. From the iron concentration and the rate of migration of $^{59}$Fe from the plasma, it is possible to calculate the iron turnover per unit time, if the plasma volume is known. The tracer method can be used for the investigation, not only of the intermediate, but also of the exogenous processes of iron metabolism.

The resorption ratio and the rate of resorption were determined for guinea pigs after oral administration of

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[58] *J.H.Jandl* and *J.H.Katz*, Trans.Ass.Amer.Physiol. *1961*, 72.

[59] *J. H. Katz* and *J. H. Jandl* in [1], p. 103.

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[61] *A. Goldberg*, *H. Ashenbrucker*, *G. E. Cartwright*, and *M. M. Wintrobe*, Blood *11*, 821 (1956).

[62] *A. Goldberg*, Brit. J. Haematol. *5*, 150 (1959).

[63] *M. Bessis* and *J.Breton-Gorius*, Rev.Hématol.*14*, 165 (1959).

[64] *M. Bessis* and *J. Breton-Gorius*, Blood *19*, 635 (1963).

[*] The term "rhopheocytosis" refers to the supply of iron to the nucleated red precursor stages in bone marrow by transfer of ferritin molecules from the reticulocytes to the red precursors without cleavage of the ferritin-iron complex.

[65] *C. A. Finch* in [1], p. 452.

$^{59}FeSO_4$, first under normal conditions, and then after parenteral application of diphtheria toxin. The animals treated with the toxin absorbed more iron from the gastro-intestinal tract than the control animals [66–68]. We have recently confirmed this increase in iron resorption in humans by iron balance studies on 19 adult patients with florid infections [69]. Radical changes occur in the intermediate iron metabolism. The rate of migration of iron from the plasma is markedly increased, so that though the plasma iron concentration is generally much lower than normal, the iron turnover is increased, sometimes by a factor of more than four (see Table 3).

Table 3. Plasma iron turnover on infection (normal range 0.36 to 0.52 mg Fe per 24 h per kg body weight).

Cases 1–14: florid infections; cases 15–19: declining infections.

| Case | Disease | Iron turnover (mg/24h/kg) |
|---|---|---|
| 1 | Tuberculous meningitis | 1.78 |
| 2 | Pulmonary TB | 1.64 |
| 3 | Tuberculous peritonitis | 1.56 |
| 4 | Endocarditis lenta | 1.08 |
| 5 | Monocytic angina | 1.08 |
| 6 | Monocytic angina | 1.06 |
| 7 | Pulmonary TB | 1.02 |
| 8 | Pulmonary TB | 0.98 |
| 9 | Pulmonary TB | 0.86 |
| 10 | Endocarditis (sensibilization phase) | 0.70 |
| 11 | Pulmonary TB | 0.63 |
| 12 | Angina | 0.62 |
| 13 | Mesenteric gland TB | 0.58 |
| 14 | Pulmonary TB | 0.58 |
| 15 | Encephalomeningitis | 0.50 |
| 16 | Pulmonary TB | 0.49 |
| 17 | Miliary TB | 0.47 |
| 18 | Angina | 0.32 |
| 19 | Pulmonary TB | 0.27 |

The migration rate and the iron turnover are normally determined by the erythropoietic activity of bone marrow. The increase in turnover on infection, on the other hand, is due less to the hemoglobin iron fraction than to the stored fraction (ferritin). Measurement of the radioactivity on the surface of the body showed that the $^{59}Fe$ administered does not travel to the hematopoiesis sites in the bone marrow, but to the reticuloendothelial tissues, especially in the liver and in the spleen. The incorporation of iron into hemoglobin is reduced in infected persons, whereas the rate of release is higher, since the life of erythrocytes is shorter.

The change in the iron metabolism on infection can be summarized as follows: The iron resorption from the gastro-intestinal tract is increased; the rate of migration and the turnover of plasma iron is increased; the rate and extent of utilization of iron for the formation of hemoglobin is reduced; and the rate of liberation of hemoglobin iron from the circulating erythrocytes, which have a shorter life, is increased. Most of the extra iron in infected persons travels into the reticuloendothelial system and accumulates as hemosiderin in the inflamed region [70].

As was shown by *Heilmeyer* and co-workers [71], iron salts, ferritin, and hemosiderin seem to have a protective action against various toxins. To all appearances, iron plays an important part in non-specific protection against infection. It therefore seems reasonable that the intermediate iron metabolism should change during an infection, in such a way that the iron is mobilized from the plasma, from the gastro-intestinal tract, and even from the erythropoiesis, and displaced into the protective cell system.

According to *Schäfer* [72], a single stimulation of the reticuloendothelial system, *e.g.* by injection of a storable substance (colloidal silver) leads to similar changes in the intermediate iron metabolism as an infection. Frequent repetition of injections of this type leads to blockage of the reticuloendothelial system, *i.e.* the system fails to respond to further stimuli. This is accompanied by the disappearance of the normal day-night rhythm of the serum iron level, which normally reaches its highest value during the morning and its lowest value in the late afternoon. In two children whose reticuloendothelial system was blocked by transfusion hemosiderosis, the day-night rhythm was found to have spontaneously disappeared. These findings indicate that the reticuloendothelial system does not greatly affect the intermediate iron metabolism even in normal circumstances. It has not yet been established whether the system is the sense organ of higher centers, or how the stimuli are transmitted.

## II. Iron Metabolism in Cases of Iron Deficiency

In cases of true iron deficiency, the total iron content of the body is reduced. This leads to a decrease, not only in the content of hemoglobin iron and stored iron, but also in the content of cell hemin iron, a fact that could explain a number of clinical symptoms. The principal causes of iron deficiency are malnutrition and loss of blood, an important factor in women being menstruation.

Iron resorption tests in cases of iron deficiency give high values. Though the plasma iron level is low, the rate of loss of iron from the plasma is increased, so that the iron turnover may in some cases be only slightly reduced, or may even be normal. The iron passing through the plasma is nearly all incorporated into hemoglobin. Thus the iron metabolism in cases of iron deficiency is characterized by displacement of nearly all the mobilizable iron into the erythropoietic tissue, where it is made available for the synthesis of hemoglobin.

Recent studies by *Heilmeyer* [73] have shown that interesting changes in the porphyrin metabolism occur during iron deficiency. The protoporphyrin and coproporphyrin concentrations in the erythrocytes increase, as do the concentrations of δ-aminolevulinic acid and coproporphyrin in the urine, but less porphobilinogen is eliminated. In incubation

[66] *W. Keiderling*, Schweiz. med. Wschr. *1958*, 965.

[67] *W. Keiderling* and *H. A. E. Schmidt* in *W. Keiderling*: Eisenstoffwechsel. Beiträge zur Forschung und Klinik. G. Thieme, Stuttgart 1959, p. 155.

[68] *W. Keiderling*, *M. Lee*, and *H. A. E. Schmidt*, Verh. dtsch. Ges. inn. Med. *1962*, 356.

[69] *W. Keiderling*, *W. Dischler*, *H. Wagner*, and *O. Lorenz*, Dtsch. med. Wschr. *1964*, 719.

[70] *F. Wöhler* in [67].

[71] *L. Heilmeyer*, *W. Keiderling*, and *F. Wöhler*, Dtsch. med. Wschr. *1958*, 1965.

[72] *K. H. Schäfer* in [1], p. 280.

[73] *L. Heilmeyer* in [1], p. 201.

experiments with hemolysates of erythrocytes from iron-deficient patients, the synthesis of porphyrins from δ-aminolevulinic acid was slower and less profuse than in normal hemolysates. However, if δ-aminolevulinic acid and protoporphyrin are added to a hemolysate from healthy erythrocytes, the rate of synthesis decreases in the same manner as in the iron-deficient hemolysate. Thus in cases of severe iron deficiency, where the quantity of iron available for the synthesis of heme is reduced, the synthesis of porphyrin also appears to be inhibited, in order to protect the organism from an accumulation of the toxic porphyrins.

### III. Iron Metabolism in Hemochromatosis

Idiopathic hemochromatosis is dominated by a very marked increase in the stored iron fraction. This leads to a series of characteristic changes in the exogenous and intermediate iron metabolism. The serum iron concentration is greatly increased, so that the transferrin, which is generally present only in small concentrations, is almost completely saturated with iron. The iron resorption is increased, as has also been shown by investigations with $^{59}Fe$ [74]. The loss of iron from the plasma is slower, but the higher serum iron level still gives a higher turnover. Most of the iron passing through the plasma goes to the storage organs (liver, spleen), as shown by radioactivity measurements at the surface of the body, and by the decreased incorporation into the erythrocytes [75]. However, the reduced iron utilization is due not to a decrease in the erythropoietic activity of the bone marrow, but to the marked increase in the iron pool.

The pathogenesis of hemochromatosis is still unknown, though interesting theories have been revived regarding the possibility that the pancreatic secretion [44] or the bile contributes in some way to the high iron resorption. Another possibility that has been discussed is that of disturbances in the regulation of ferritin synthesis, the excess of ferritin produced being subsequently converted into hemosiderin.

### IV. Iron Metabolism in Atransferrinemia

The case of congenital atransferrinemia studied in Freiburg [76] involved a girl aged seven years, who was retarded in her physical development and who had been found to have a severe anemia that did not respond to therapy at the age of only $3^1/_2$ months. Clinical observations included hepatosplenomegaly and megalocardia. Both the peripheral blood and the bone marrow punctate showed signs of severe iron deficiency, while the liver biopsy indicated severe siderocirrhosis.

The plasma iron concentration was only 0.014 ppm (normal range 0.08–0.13 ppm). As can be seen from Fig. 5, ferrokinetic investigation with $^{59}Fe$ showed extreme acceleration of iron loss from the plasma, an increased plasma iron turnover, and a very marked decrease in the uptake of iron by the erythrocytes. Determination of the $^{59}Fe$ distribution by measurements on the body surface showed a marked increase in activity above the liver, whereas very little $^{59}Fe$ was absorbed by the spleen, and none by the bone marrow. The iron resorption, as found in iron balance investigations with $^{59}Fe$, was higher than normal.

In the autopsy following the sudden death of the patient excessive iron deposits were found in the liver, heart, kidneys, pancreas, and thyroid gland.

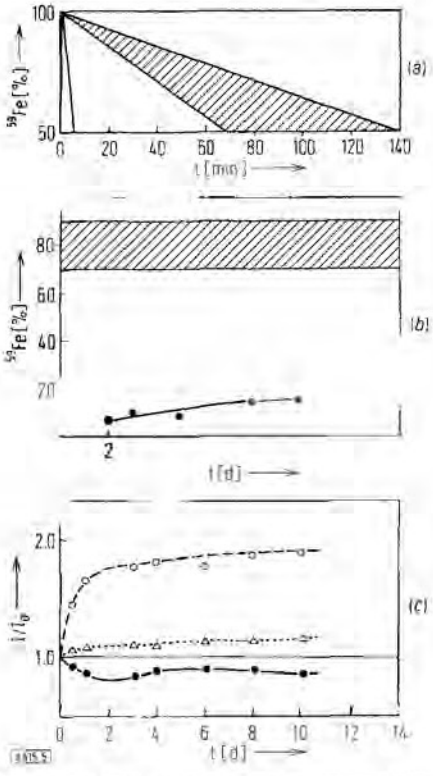


Fig. 5. Ferrokinetics in a girl aged 7 years suffering from transferrin deficiency.

(a) Migration of $^{59}Fe$ from the plasma.
Ordinate: $^{59}Fe$ remaining in plasma (%).
Abscissa: Time (min) after injection of autologous plasma incubated with $^{59}Fe$ citrate.
Shaded area: normal range.

(b) Incorporation of $^{59}Fe$ into the erythrocytes.
Ordinate: $^{59}Fe$ incorporated into the erythrocytes.
Abscissa: Time (days) after injection of autologous plasma incubated with $^{59}Fe$ citrate.
Shaded area: normal range.

(c) Surface radioactivity.
○ liver; △ spleen; ● sacrum.
Ordinate: Relative radioactivity of the body surface.
Abscissa: Time (days) after injection of autologous plasma incubated with $^{59}Fe$ citrate.

This informative case shows clearly the importance of transferrin to the correct operation of the iron metabolism. When the iron transport system breaks down the iron evidently passes unhindered into the tissues, where it is stored as hemosiderin and leads to cirrhoses and brown induration. The supply of iron to the bone marrow, on the other hand, is insufficient, leading to the paradoxical situation of severe iron deficiency anemia and marked siderosis of the organs. The results also show that transferrin is of minor importance in iron resorption.

[74] *J.-C. Dreyfus* and *G. Schapira* in [1], p. 296.

[75] *W. Keiderling, I. Reissner, W. Dischler*, and *G. Hoffmann* in *W. Keiderling* and *G. Hoffmann*: Radioisotope in derHämatologie. First internat. Symposium. F.-K. Schattauer, Stuttgart 1963, p. 81.

[76] *L. Heilmeyer, W. Keller, O. Vivell, W. Keiderling, R. Betke, F. Wöhler*, and *H. E. Schultze*, Dtsch. med. Wschr. *1961*, 1745.

## V. Iron Metabolism in Sideroachrestic Anemias

The sideroachrestic anemias are divided into idiopathic forms, in which a congenital (hypochromic sideroachrestic hereditary anemia)[77,78] and an acquired type (refractory sideroblastic anemia)[79,80] are distinguished, and into symptomatic forms in lead poisoning and other types of poisoning, in pyridoxin deficiency, and occasionally in blood neoplasia and in the initial stages of myelosclerosis[81]. These diseases initially give the appearance of anemia; complications occur later as a result of abnormal deposition of iron in the liver.

A pathogenetic feature common to all forms is disturbance of the utilization of iron in the synthesis of hemoglobin. The development of the diseases was studied by determination of the heme precursors (uroporphyrin, coproporphyrin, protoporphyrin) in the erythrocytes, and by incubation experiments with hemolysates of bone marrow and peripheral blood with added heme precursors and δ-aminolevulinic acid or porphobilinogen[81,82].

The combination of iron, protoporphyrin, and globulin in the red precursors normally is preceded by the formation of these three substances in approximately stoichiometric amounts. After the synthesis in the erythrocytes all but very small quantities of the substances are consumed. In refractory sideroblastic anemia and in many symptomatic forms, the combination of iron and protoporphyrin is upset, so that porphyrin and iron accumulate in the erythrocytes. It is not certain whether the disturbance is due to iron deficiency, damage to the structure of the mitochondria, or disturbance of the intracellular iron metabolism. In pyridoxin deficiency and in hypochromic sideroachrestic hereditary anemia, the supply of protoporphyrin is retarded as a result of disturbance of the porphyrin synthesis, the disturbance in the case of hypochromic sideroachrestic hereditary anemia probably being mainly in the transition from coproporphyrin to protoporphyrin.

However, the disturbance of hemoglobin synthesis leads to an accumulation of iron, not only in the erythropoietic system, but also in the reticular cells of the bone marrow and in the liver. After the disease has lasted for some years, other organs such as the pancreas, lymph nodes, and heart muscle become overloaded with iron, and this can give rise to the symptoms of a secondary hemochromatosis.

Ferrokinetic investigation with $^{59}Fe$ shows normal loss of iron from the plasma, increased iron turnover, and a marked decrease in the rate of incorporation of iron into the erythrocytes. Most of the injected $^{59}Fe$ accumulates in the liver, and very little iron is taken up by the spleen and the bone marrow[78,80].

## Closing Remarks

Recent research on iron metabolism has yielded new and impressive results. Particularly interesting work has been done on the intracellular transport of iron, which may involve complexes of low molecular weight, and which is evidently very important in the resorption, of iron by the intestinal mucosal cells and in the absorption of iron by the hemoglobin-forming cells. Special attention is also due to the synthetic routes taken by the individual iron fractions in the body. Though we are still far from knowing the nature of the reaction sequences involved, the results obtained so far have helped towards a better understanding of iron metabolism and its disturbances.

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[78] *L. Heilmeyer, J. Emmrich, H. H. Hennemann, W. Keiderling, M. Lee, R. Bilger*, and *H. Schubothe*, Folia haematol. NF *2*, 61 (1958).

[79] *S. E. Bjorkman*, Blood *11*, 250 (1956).

[80] *L. Heilmeyer, W. Keiderling, R. Bilger*, and *H. Bernauer*, Folia haematol. NF *2*, 49 (1958).

[81] *L. Heilmeyer*: Die Störungen der Bluthämsynthese. G. Thieme, Stuttgart 1964.

[82] *L. Heilmeyer*, Schweiz. med. Wschr. *1962*, 1285.

# Acrylonitrile from Propylene, Ammonia, and Atmospheric Oxygen

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*Acrylonitrile was produced in a pilot plant from propylene, ammonia, and atmospheric oxygen in a fixed-bed reactor in the presence of a Bi/Mo/Si oxide shell catalyst. The propylene conversion, which can amount to about 70% under optimal conditions, was studied as a function of structural properties and the chemical composition of the catalyst, and of the composition of the starting mixture. Acrylonitrile of adequate purity for use in polymerizations could be obtained by multi-stage processing of the crude product.*

Acrylonitrile attained a certain importance in Germany during the second world war owing to its use as a raw material for the polyacrylonitrile fiber produced by the former I.G. Farbenindustrie and as an additive in the production of Buna N. It was originally synthesized from ethylene oxide and hydrocyanic acid and later, more economically, from acetylene and hydrocyanic acid. A few years ago the production of acrylonitrile from acetaldehyde and hydrocyanic acid, *via* lactonitrile, also gained some importance.

The production of acrylonitrile by the direct reaction of propylene, ammonia, and oxygen in accordance with the equation

$$CH_3{-}CH{=}CH_2 + NH_3 + {}^3/_2O_2 \rightarrow CH_2{=}CH{-}CN + 3\,H_2O$$

was described as early as 1949 in a patent application by Allied Chemical and Dye Corp., New York (USA)[1]. A few years later, the Distillers Company, Edinburgh (UK), published a process for the reaction of acrolein with ammonia and oxygen, the acrolein being obtained by the air oxidation of propylene[2]. In this case, the same reactants as are used in the Allied Chemical and Dye Corp. process are converted into acrylonitrile by a two-step reaction. However, the yields obtained in both cases were low, so that the processes could not yet be used economically.

At the beginning of 1959, Standard Oil of Ohio (SOHIO), Cleveland (Ohio, USA) published a process in which acrylonitrile is produced from the same raw materials, *i.e.* propylene, ammonia, and oxygen, in a conversion of about 50%[3]. A new feature of this process was the use of a bismuth/molybdenum catalyst with silica as a porous support. It thus became feasible to use this synthesis on an industrial scale, and experience gained over the next five years showed that it is economically far superior to all other processes. Fifteen plants using the SOHIO process are already in operation, and after completion of all plants currently under construction, it is expected that this process is used for 75% of the acrylonitrile production of the western world.

[1] U.S. Pat. 2481826 (1949).

[2] Brit. Pat. 709337 (1954); German Pat. 897560 (1953).

[3] U.S. Pat. 2904580 (1959).

Since ammonia is a cheap industrial product, and propylene is formed in the cracking of nearly all petroleum products, acrylonitrile has become a cheap organic base chemical. This has led to the development of many new applications, as is illustrated *e.g.* by the recent increase in production of copolymers of acrylonitrile. It is probable that in addition to polymerization and copolymerization, other reactions of acrylonitrile, leading to products of low molecular weight, will also become important.

## Laboratory Experiments

Following the publication of the SOHIO process, the examples of the synthesis of acrylonitrile in a fluidized bed described in Belgian Patent No. 571200 were repeated in our laboratory at the beginning of 1960. Since we also wished to study the ammonoxidation of propylene at low throughputs, and since the fluidized-bed process appeared to be difficult to use for small reaction units, we used fixed-bed reactors with which a great deal of experience had already been gained at our works in the production of phthalic acid.

The fixed-bed reactors each had one reaction tube with an internal diameter of 25 mm; a thermocouple shield tube (outside diameter 6 mm) with adjustable temperature measuring position was inserted axially from the top. The depth of the catalyst bed was 160 cm. The reaction tube was surrounded by a salt-bath jacket, in which the salt melt was circulated by means of an airlift pump driven by compressed air. The reaction gas leaving the reactor was washed with dilute sulfuric acid, whereupon an aqueous solution of acrylonitrile was obtained.

### Catalyst Composition

When granular catalysts of homogeneous composition (cf. [4]) were used the reaction was subject to heat build-ups which were difficult to control, to blockages due to catalyst dust, and to formation of large quantities of undesirable by-products (acrolein, oxides of carbon).

[4] Belg. Pat. 571200 (1958).

Since these difficulties were due mainly to poor heat removal from overheated microscopic regions on the catalyst core, we achieved a decisive improvement by the use of catalysts the particles of which consisted of a thermally conducting core and a catalytically active shell. The reaction could be controlled in this way to such an extent that it was possible, by using stoichiometric quantities of oxygen, propylene, and ammonia, to obtain conversions into acrylonitrile of more than 70% under optimal conditions. This process, the results of which represented a considerable improvement over existing data, was patented [5].

If the catalyst core is to possess a high thermal conductance, its crystallinity must be high and its porosity low. The relationship between these properties of the catalyst and the conversion of propylene into acrylonitrile is shown in Table 1, which is based on a series of runs with Bi/Mo/Si oxide shell catalysts.

Table 1. Conversion of propylene into acrylonitrile [mole-%] with various shell catalysts having a Bi/Mo/Si oxide coat 0.05 mm thick; particle size 3 to 4 mm; starting mixture, 1 $C_3H_6$:1 $NH_3$:2 $H_2O$: 8 air; residence time, based on the empty tube, 5 sec; highest temperature measured 470 °C.

| Core material | Porosity [vol-%] | Propylene conversion [mole-%] |
|---|---|---|
| Fused corundum, crushed | 2 | 62 |
| Sintered corundum, crushed | 6 | 60 |
| Granite, crushed | 1 | 64 |
| Quartz, crushed | 1 | 60 |
| Clay clinker, crushed | 8 | 62 |
| Alumina spheres (I) | 12 | 53 |
| Alumina spheres (II) | 25 | 45 |
| Alundum catalyst support | 44 | 31 |
| Aluminum silicate catalyst support | 50 | 30 |
| Glass spheres (amorphous) | 0 | 35 |

Table 2 contains the results of a series of experiments with catalyst systems consisting of two oxide components together with a silica support, coated on fused corundum having a particle size of 3 to 4 mm. The highest propylene conversion in this series was obtained with the binary oxide system $3Bi_2O_3 \cdot 8MoO_3$. The activity of this catalyst can be increased further by structural and chemical modifications.

## Composition of the Original Gas Mixture

The yield of acrylonitrile is strongly influenced, not only by the form of the catalyst, but also by the composition of the original synthesis gas. In addition to the principal components, *i.e.* propylene, ammonia, and air, the mixture must also contain a diluent if the reaction is to proceed smoothly. Water vapor, propane, carbon dioxide, and nitrogen were used in the present work, the best propylene conversion being obtained with water vapor (cf. Table 3).

## Purification of Acrylonitrile

The acrylonitrile produced must be obtained, not only in high yields, but also in a very pure state. For example, the tolerance for interfering impurities (*e.g.* hydrocyanic acid or acrolein) in polymerizations, the principal use of acrylonitrile, is only a few milligrams per kg of pure product. Attempts were made to use a combination of distillation processes, without the addition of foreign substances, for the purification of the crude acrylonitrile containing acetonitrile, hydrocyanic acid, and acrolein as impurities, and at the same time to obtain the by-products as pure substances where this was economically justifiable. The small quantities of acrolein and other carbonyl compounds present are made to

[5] Austrian Pat. 226672 (1962).

Table 2. Conversion of propylene into acrylonitrile [mole-%] in a series of experiments with shell catalysts consisting of silica and oxides of the elements A and B, coated to a thickness of 0.05 mm on fused corundum; particle size 3 to 4 mm; gas composition, $1C_3H_6$:$1NH_3$:$3H_2O$:8 air; residence time, based on the empty tube, 5 sec; highest temperature measured 470 °C; ΔT = difference between maximum temperature and salt-bath temperature.

| A | B | Oxide system with atomic ratio A:B = 1:8 | | Oxide system with atomic ratio A:B = 6:8 | |
|---|---|---|---|---|---|
| | | Conversion [mole-%] | ΔT [°C] | Conversion [mole-%] | ΔT [°C] |
| Be | Mo | 2 | 15 | 3 | 23 |
| Mg | Mo | 2 | 8 | 5 | 14 |
| Ca | Mo | 3 | 20 | 5 | 12 |
| Ba | Mo | 2 | 12 | 3 | 45 [*] |
| Al | Mo | 3 | 10 | 11 | 14 |
| Ti | Mo | 8 | 16 | 15 | 10 |
| Ce | Mo | 2 | 14 | 5 | 8 |
| Th | Mo | 0 | 20 | 0 | >100 |
| Cr | Mo | 0 | 18 | 4 | 13 |
| Mn | Mo | 3 | 20 | 3 | 10 |
| Fe | Mo | 1 | 16 | 0 | 8 |
| Co | Mo | 0 | 20 | 2 | 15 |
| Ni | Mo | 0 | 13 | 8 | 6 |
| Cu | Mo | 0 | 60 | 0 | 5 |
| Ag | Mo | 0 | 15 | 0 | 7 |
| Zn | Mo | 1 | 10 | 2 | 30 |
| Cd | Mo | 2 | 15 | 3 | 10 |
| Sn | Mo | 13 | 30 | 11 | 20 |
| Pb | Mo | 0 | 30 | 1 | 20 |
| Sb | Mo | 0 | 12 | 0 | 6 |
| Bi | Mo | 9 | 20 | 62 | 20 |
| Te | Mo | 10 | 15 | 23 | 18 |
| Al | V | 1 | 34 | 8 | 40 [*] |
| Ti | V | 6 | 38 | 3 | 60 [*] |
| Co | V | 0 | 18 | 9 | 20 |
| Ni | V | 0 | 25 | 8 | 15 |
| Sn | V | 6 | 55 [*] | 9 | 30 |
| Bi | V | 10 | 17 | 19 | 23 |
| Bi | Mn | 0 | 20 | 0 | 25 |
| Bi | W | 4 | 7 | 7 | 10 |

[*] Maximum temperature >470 °C.

Table 3. Propylene conversion into acrylonitrile in experiments with shell catalysts (Bi/Mo/Si oxide on fused corundum having a particle size of 3 to 4 mm) and with various diluents. The molar quantities of the components of the synthesis gas are based on 1 mole of propylene. The molar ratio of ammonia to propylene was 1:1; ΔT = difference between maximum temperature and salt-bath temperature; highest temperature measured: 475 °C; residence time, based on the empty tube, 4 to 6 sec.

| Oxygen (air) [moles] | Diluent [moles] | Conversion [mole-%] | ΔT [°C] |
|---|---|---|---|
| 8 | 0 | 47 | 60 |
| 8 | 0.5 Steam | 58 | 32 |
| 8 | 1.0 Steam | 62 | 28 |
| 8 | 1.5 Steam | 62 | 25 |
| 8 | 1.0 Propane + 1.0 steam | 60 | 26 |
| 8 | 1.0 Propane | 47 | 55 |
| 8 | 4.0 Propane | 47 | 50 |
| 8 | 5.5 Carbon dioxide | 45 | 54 |
| 8 | 5.5 Nitrogen | 44 | 54 |
| 13.5 | 0 | 44 | 57 |

react with the excess hydrocyanic acid to form cyanohydrins which are eliminated by distillation. Acetonitrile is obtained as a pure anhydrous product, without loss of acrylonitrile, by extractive distillation with water as the extracting agent, followed by two fractionations [6].

## Pilot Plant Experiments

### Synthesis

The synthesis was carried out in a tube furnace containing 60 tubes 2 m long and having an internal diameter of 25 mm (Fig. 1). The heat of the reaction was removed

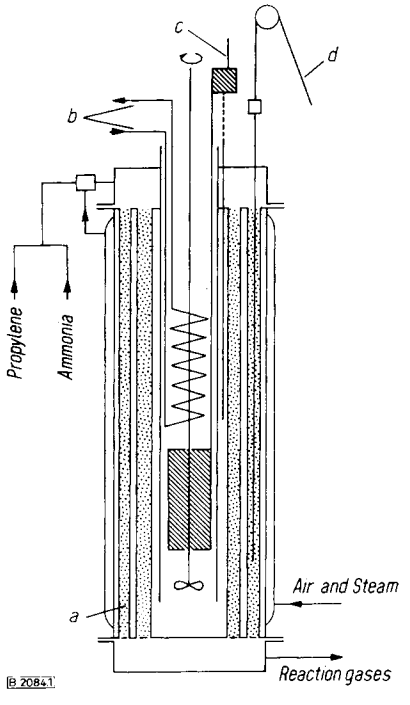


Fig. 1. Experimental reactor for the production of acrylonitrile; *a* catalyst packing, *b* air cooling, *c* electric heater (controlled), *d* temperature measuring position (vertically adjustable).

by a salt bath. The catalyst was arranged in two layers. The gas mixture first passed through a 60 cm bed of a corundum catalyst having a particle size of 3 to 4 mm and a coating thickness of about 0.05 mm, and then through a 100 cm bed having a particle size of 4 to 5 mm and a coating thickness of 0.3 mm. The residence time in the contact zone (based on the empty tube) was about 4 sec. The highest temperature measured in the reaction zone was 480 °C. The temperature of the salt bath used to dissipate the heat of reaction was 455 °C. 1.5 mole of oxygen (as air) and 3 moles of water vapor were used per mole of propylene (95%) and per mole of ammonia.

The gas mixture formed in the reactor was washed at about 80 °C with an aqueous ammonium hydrogen sulfate solution to remove ammonia. The water-soluble components were absorbed in an excess of water. The organic components were concentrated from the aqueous solution by distillation, and were determined mainly by gas chromatography. The exhaust gases from the water wash were determined by gas analysis.

The overall reactions shown in Table 4 were deduced from the analytical results. Some of these reactions are coupled with one another. For example, one molecule of propylene gives one molecule of acetonitrile and one molecule of $CO_2$. Table 4 also shows that about 20% each of propylene and ammonia pass through the reaction zone unchanged.

The proportions of the various reaction products in relation to the starting materials propylene, ammonia, and oxygen are shown graphically in Figure 2.

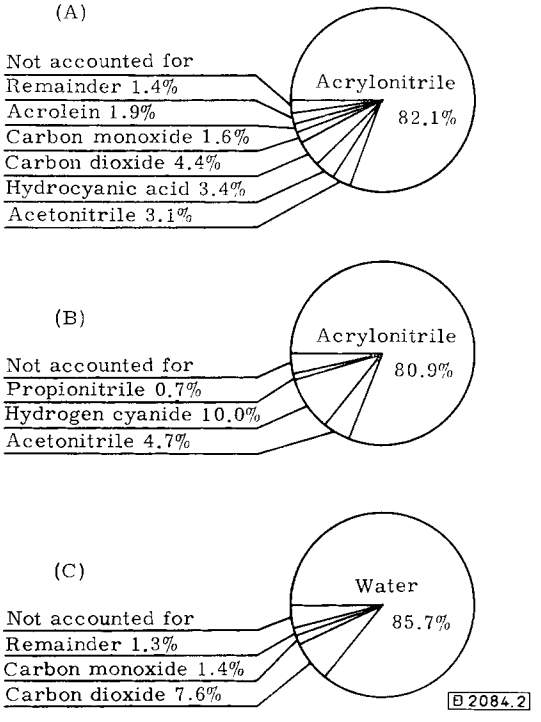


Fig. 2. Proportions of the various reaction products in relation to the consumed reaction gases propylene (A), ammonia (B), and oxygen (C).

Table 4. Reactions occurring in the reactor and the conversion [mole-%] of propylene (C), ammonia (N), and oxygen (O), based on the amounts introduced.

| | Reaction | Conversion [mole-%] | | |
|---|---|---|---|---|
| | | C | N | O |
| I | $C_3H_6 + NH_3 + {}^3/_2O_2 \rightarrow CH_2{=}CH{-}CN + 3\,H_2O$ | 65.6 | 65.6 | 65.6 |
| II | ${}^2/_3C_3H_6 + NH_3 + O_2 \rightarrow CH_3{-}CN + 2\,H_2O$ | 2.5 | 3.8 | 2.5 |
| III | ${}^1/_3C_3H_6 + NH_3 + O_2 \rightarrow HCN + 2\,H_2O$ | 2.7 | 8.1 | 5.4 |
| IV | ${}^1/_3C_3H_6 + {}^3/_2O_2 \rightarrow CO_2 + H_2O$ | 3.5 | — | 10.5 |
| V | ${}^1/_3C_3H_6 + O_2 \rightarrow CO + H_2O$ | 1.3 | — | 2.6 |
| VI | $C_3H_6 + O_2 \rightarrow CH_2{=}CH{-}CHO + H_2O$ | 1.5 | — | 1.0 |
| VII | ${}^2/_3C_3H_6 + {}^1/_2O_2 \rightarrow CH_3{-}CHO$ | 0.4 | — | 0.2 |
| VIII | $C_3H_6 + NH_3 + O_2 \rightarrow CH_3{-}CH_2{-}CN + H_2O$ | 0.2 | 0.19 | 0.1 |
| IX | $C_3H_6 + {}^1/_2O_2 \rightarrow CH_3{-}CO{-}CH_3$ | 0.1 | — | — |
| X | $C_3H_6 + {}^3/_2O_2 \rightarrow CH_2{=}CH{-}COOH + H_2O$ | 0.4 | — | 0.4 |
| XI | ${}^2/_3C_3H_6 + O_2 \rightarrow CH_3{-}NOOH$ | 0.1 | — | 0.1 |
| Sum | | 78.3 | 77.7 | 88.4 |
| Total conversion = C, N, or O consumed | | 79.9 | 81.1 | 92.2 |

The heats of the reactions listed in Table 4 at 460 °C are shown in Table 5. The heat liberated during the synthesis of 1 mole of acrylonitrile at 460 °C is about 170

[6] Austrian Pat. 228188 (1962); 236357 (1964).

Table 5. Heats of reactions I to XI in Table 4 at 460 °C.

| | Product | ΔH [kcal/mole] | ΔH [kcal] per mole of propylene used |
|---|---|---|---|
| I | Acrylonitrile | 122.5 | 80.4 |
| II | Acetonitrile | 86.6 | 3.3 |
| III | Hydrocyanic acid | 75.3 | 6.1 |
| IV | Carbon dioxide | 153.2 | 16.1 |
| V | Carbon monoxide | 85.5 | 3.3 |
| VI | Acrolein | 84.4 | 1.3 |
| VII | Acetaldehyde | 43.1 | 0.3 |
| VIII | Propionitrile | 98.4 | 0.2 |
| IX | Acetone | 56.7 | — |
| X | Acrylic acid | 146.6 | 0.5 |
| XI | Acetic acid | 108.9 | 0.3 |
| | | | 111.8 |

kcal, and the quantity of heat which has to be removed for every kilogram of acrylonitrile formed is about 3200 kcal.

### Isolation and Purification

The various stages in the isolation and purification of the crude acrylonitrile are shown schematically in Figure 3.

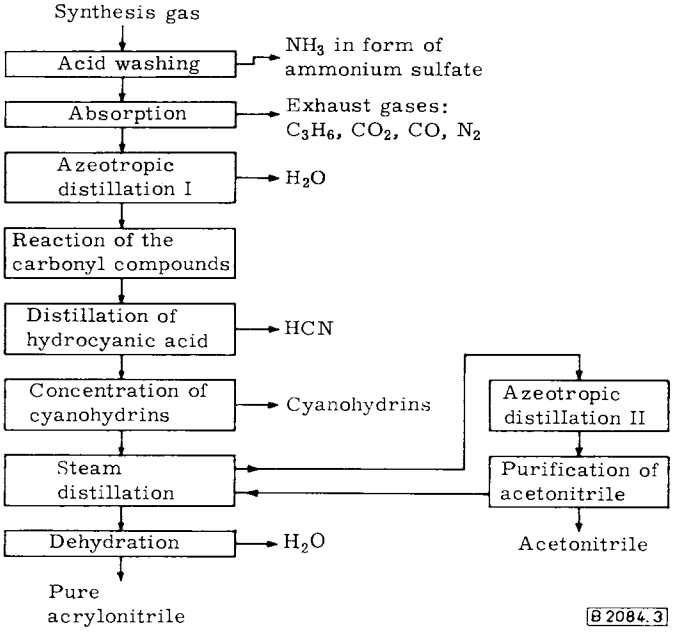


Fig. 3. Scheme of the working-up of the synthesis gas and the purification of the acrylonitrile.

1. The ammonia still present in the reactor gas was removed in a wash column at 80 °C by circulating a large quantity of ammonium hydrogen sulfate solution. The pH of the solution was maintained at 2.5 by continuous addition of sulfuric acid. Practically no loss of acrylonitrile occurred under these conditions.

2. The water-soluble components were absorbed in water in an absorption tower. The concentration of the organic components in the water was 2.5%. Less than 0.1% of the acrylonitrile was retained in the exhaust gases.

3. The organic products were driven off from the aqueous solution in a distillation column. The distillate separated into two layers. The upper layer, which consisted of crude acrylonitrile, was further purified while the lower (aqueous) layer was returned to the column.

4. The carbonyl compounds (acrolein, acetaldehyde, acetone) contained in the crude acrylonitrile were caused to react completely with the hydrocyanic acid present in excess.

5. The free hydrocyanic acid could be distilled out of the resulting mixture without decomposition of the sensitive substances present.

6. The reaction products of the carbonyl compounds with hydrocyanic acid (cyanohydrins) were concentrated by a two-stage vacuum distillation. The residue from the second evaporator stage contained about 70% of cyanohydrin.

7. After removal of the hydrocyanic acid and the carbonyl compounds, the acrylonitrile was subjected to extractive distillation with water as the extracting agent. The head product was water-saturated acrylonitrile containing no acetonitrile, while a very dilute aqueous solution of acetonitrile and acrylonitrile in a ratio of 1:1 was obtained at the bottom of the column. This relatively high proportion of acrylonitrile was left in the mixture to permit the purification of the acetonitrile under favorable conditions.

8. The acrylonitrile was dried to a water content of 0.4% by azeotropic distillation and separation of the water which formed the lower layer in the distillate. A small quantity of the organic distillate is returned to step 4, and traces of low-boiling impurities still present are removed in this way.

9. The acetonitrile/acrylonitrile mixture from the aqueous residue of the extractive distillation was driven off by column distillation (azeotropic distillation II).

10. The head product from the azeotropic distillation II was separated further by distillation. The residue consisted of acetonitrile still containing small quantities of propionitrile; water and acrylonitrile were present only in traces. The head product from this distillation consisted of an acrylonitrile/acetonitrile mixture with a high content of acrylonitrile. This fraction was returned to the extractive distillation, step 7.

With a certain water content in the upper part of the fractionating column, this difficult separation could be achieved without the need for an excessively large number of plates, and with a moderate reflux ratio.

The acrylonitrile obtained by these purification steps was sufficiently pure for use in polymerizations; it contained only about 0.01% of acetonitrile, and the concentration of all other impurities was less than 10 ppm.

### Technical Development

On the basis of the results obtained on the laboratory scale and in the pilot plant, the Lurgi Gesellschaft für Mineralöltechnik mbH, Frankfurt/Main is at present

constructing a plant (production capacity 10000 tons/year) which, in addition to pure acrylonitrile for polymerization, will produce hydrocyanic acid and acetonitrile. In four fixed-bed reactors, acrylonitrile will be synthesized in a one-step process. The crude product from the synthesis will be worked up in eight distillation columns to give the three end-products acrylonitrile, acetonitrile, and hydrocyanic acid. The plant, which is expected to begin operation in 1967, will be automatically controlled and will require a minimum of attention.

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# Alcohols as Petrochemicals

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*Efficient processes have been developed in recent years for the large-scale manufacture of alcohols from petrochemicals. These allow production of aliphatic alcohols both with short and with long alkyl groups more economically than was previously possible by fermentation. In this paper the most important principles and the technical execution of the hydration of olefins, the air oxidation of paraffins, and especially the synthesis reactions (e.g. the catalytic hydroformylation of olefins with carbon monoxide and hydrogen according to Roelen, the Reppe synthesis, and the Ziegler growth reaction with ethylene and triethylaluminum) are described.*

## Introduction

Alcohols are among the most important products of the chemical industry. They are widely used as solvents and anti-freeze agents, and they are important intermediates, *e.g.* for the manufacture of plasticizers, synthetic lubricants, detergents, flotation agents, textile and paint adjuvants, and synthetic fibers. The principal raw materials for the production of alcohols at present are petrochemicals, *i.e.* olefins and paraffins. The reactions used can be grouped into three basic types:

1. *Hydration*, *e.g.* ethylene to ethanol; propene to isopropanol.

2. *Synthesis*, *e.g.* Roelen reaction; Reppe synthesis; Ziegler synthesis.

3. *Oxidations*, *e.g.* preparation of aliphatic or alicyclic alcohols from paraffins or cycloparaffins.

Processes recently developed to the industrial scale include the Ziegler synthesis for the production of unbranched alcohols with an even number of carbon atoms, the oxidation of cyclohexane and cyclododecane, and the Reppe synthesis for the production of n-butanol; the other methods have been in use for a longer time.

The present paper is concerned particularly with the Ziegler synthesis; a survey of the other methods is also included. The production of polyfunctional alcohols such as ethylene glycol and glycerol is not discussed, although these substances are also produced from petrochemicals, *i.e.* from ethylene and propene, respectively.

## Hydration of Olefins

Only lower olefins, particularly ethylene, propene, and butene, are used in the production of alcohols by the hydration of olefins. The hydration may be direct, *i.e.* involving the direct catalytic addition of water in the gas phase (*e.g.* in the preparation of ethanol from ethylene), or indirect, *i.e.* involving the absorption of the olefins in sulfuric acid followed by hydrolysis of the alkyl sulfates (*e.g.* in the production of isopropanol from propene and of sec- and tert-butyl alcohol from butenes).

### Direct Hydration

In the exothermic reaction

$$C_2H_4 + H_2O \rightleftarrows C_2H_5OH; \quad \Delta H = -10.9 \text{ kcal/mole}$$

the equilibrium is displaced towards the right at low temperatures and high pressures. In practice, however, the temperature must not be too low, since the rate of the reaction will otherwise also be too low; moreover, the pressure must not be too high, since some of the water vapor otherwise condenses. On the other hand, low temperatures and relatively low pressures can be used only in the presence of a sufficiently active catalyst [1].

The earliest practical experience of the direct hydration of ethylene was gathered by the Shell Chemical Co., Houston (Texas) [2]. Plants for this process are operated in the German Federal Republic by Hibernia Chemie AG, Wanne-Eickel, and by Erdölchemie, Dormagen.

Ethylene and water vapor in the molar ratio of 0.6:1 are led over phosphoric acid on a Kieselgur support (about 5 × 5 mm). With the aging of the catalyst the temperature is gradually increased from 250 to 270 °C at a constant pressure of 70 atm. The throughput for a con-

[1] *C. R. Nelson* and *M. L. Courter*, Chem. Engng. Progr. *50*, 526 (1954) cf. also Chem.-Ing.-Techn. *27*, 100 (1955) and *P. Sherwood*, Erdöl u. Kohle *8*, 465 (1955). A list of earlier literature is given by *R. Seka* in *G.-M. Schwab*: Handbuch der Katalyse, Vol. VII (2) pp. 44–47. Springer, Vienna 1943.

[2] U.S.-Pat. 2579601 (1951), Shell Development Co., Chem. Abstr. *46*, 6666 h (1952); Brit. Pat. 651275 (1951), Bataafsche Petroleum Mij., Chem. Abstr. *45*, 9074a (1951).

version of 4.5% with respect to ethylene corresponds to about 1800 $Nm^3$ per $m^3$ of catalyst per hour.

The ethylene used is 97% pure, and it is recirculated. To prevent a build-up of inert substances, part of the recirculating gas is drawn off and purified in a Linde plant when the ethylene concentration falls below 85%.

The ethylene and the water vapor are led through a heat exchanger and a furnace into the reactor, where the ethylene is hydrated. The emerging gases pass through the heat exchanger, where part of the alcohol condenses, into a high-pressure trap. After cooling, the gaseous components are washed with water to remove residual alcohol, and the ethylene is returned to the cycle. The condensate from the high-pressure trap and the wash water from the washing column are combined and distilled. The ethanol condensate, which distils first, is hydrogenated over nickel catalysts to eliminate impurities such as acetaldehyde and crotonaldehyde, and the diethyl ether formed as a by-product is distilled off. The product is then concentrated to 95% alcohol in a purifying column. The residue from this column is returned to the purifying plant. The yield is 97%. In addition to diethyl ether, acetaldehyde, and crotonaldehyde, small amounts of olefin polymers, and occasionally t-butyl alcohol, are formed as by products.

The diagram of a plant is shown in Fig. 1.

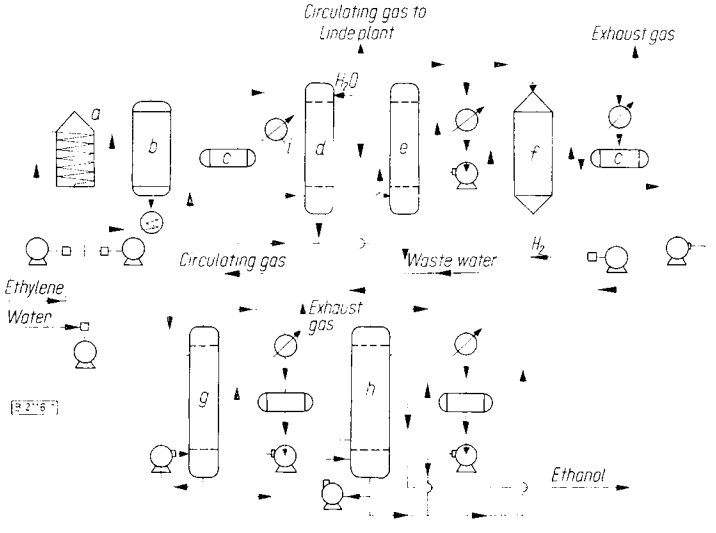



Fig. 1. Scheme of a plant for the production of ethanol by the direct hydration of ethylene [3].

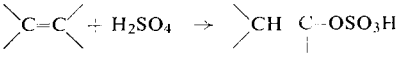
a) preheater, b) reactor, c) settler, d) scrubber, e) concentrating column, f) hydrogenation reactor, g) ether column, h) ethanol column, i) heat exchanger.

The efficiency of the process is illustrated by the following example[*]. The production of 60000 tons of ethanol from natural raw materials by fermentation would require the use of about 660000 tons of grain, *i.e.* a cultivation area of about 275 sq. km. The production of the grain and the processing to make alcohol would require 8800 workers. The synthesis from petrochemicals requires about 45000 tons of ethylene, and the area covered by the plant, which is operated by 35 men, is only about 0.01 sq. km.

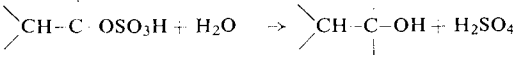
Imperial Chemical Industries, Wilton (England) are using a direct hydration method, probably based on earlier investigations by I.G. Farben-Industrie, for the production of isopropanol from propene. The catalyst used is a molded, so-called blue tungsten oxide having the approximate composition $W_2O_5$, which is prepared by hydrogenation of compressed tungstic acid, *i.e.* hydrated $WO_3$. The reaction is carried out at 270 °C and 250 atm, and the ratio of water to propene is about 5.6:1. Since partial condensation is observed under the conditions of the reaction, the heated mixture is allowed to trickle from the head of the reaction furnace over the catalyst. The contact loading is about 3.3 kg per hour and per liter of catalyst space at conversions of 24% with respect to propene. The product contains about 5.7 wt-% of isopropanol, which is isolated by distillation.

### Indirect Hydration

Olefins are absorbed in sulfuric acid with formation of alkylsulfuric acids or dialkyl sulfates.



The minimum concentration of the acid that gives smooth absorption decreases from ethylene to hexene, and increases again for the higher olefins. Branched olefins are absorbed more readily than the corresponding straight-chain compounds. Hydrolysis of the alkylsulfuric acids or dialkyl sulfates leads to the alcohols.



The sulfuric acid must then be reconcentrated before being used again (strong acid process). On the other hand, the absorption may be carried out under pressure, and in this case a less concentrated acid is required. When the pressure is released, the alkylsulfuric acid is hydrolysed, and the alcohol separates. This is the principle of the so-called weak acid process for the production of isopropanol from propylene[4] (cf. Fig. 2), which is much more economical than the strong acid process.

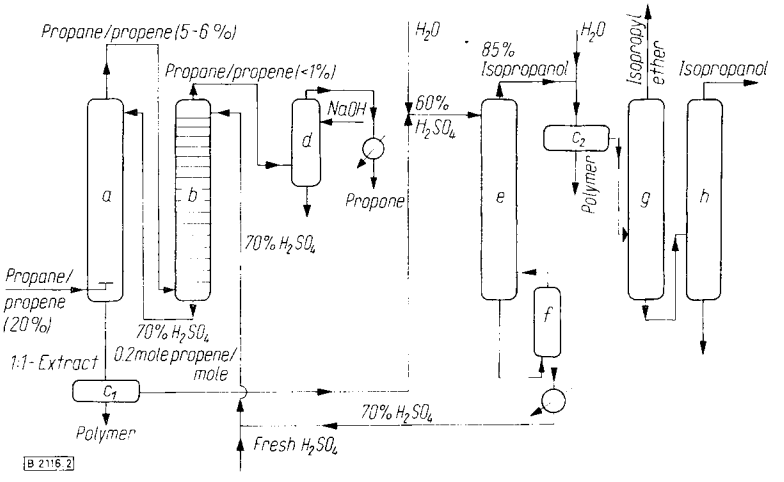



Fig. 2. Scheme of a plant for the production of isopropanol by the indirect hydration of propene.

a) 1st absorption tower, b) 2nd absorption tower (bubble-cap column), $c_1$,$c_2$) sedimentation vessels, d) alkali washer, e) wash column, f) evaporator, g) bubble-cap column, h) 50-plate column.

[*] I am indebted to Dr. *Voß*, Deutsche Benzin und Petroleum AG, Hamburg, for this comparison.

[3] Taken from *M. Sittig*: Organic Chemical Processes, p. 53, Noyes Press, Pearl River 1962.

[4] U.S.-Pat. 2473224 (1949), Standard Oil Development Co., Chem. Abstr. 6645g (1949); U.S.-Pat. 1988611 (1935), Standard Oil of California, Chem. Zbl. *1935* II 2580.

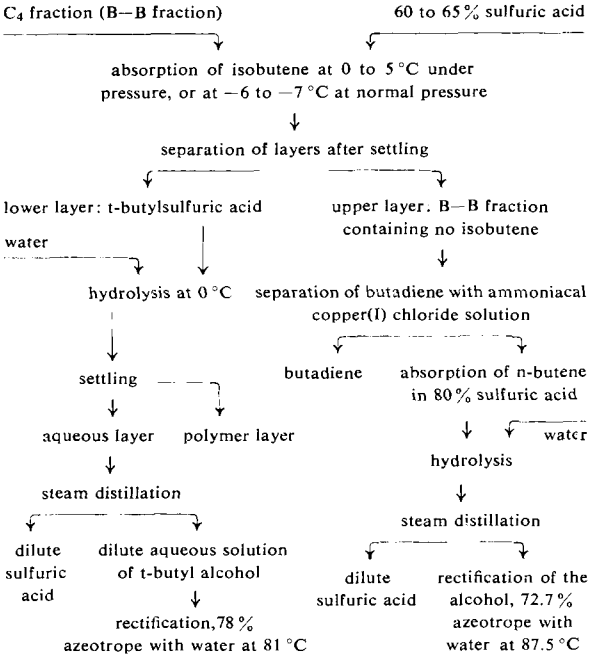
In the weak acid process, propene is absorbed in 70% sulfuric acid at 65 °C and 25 atm. The propane/propene mixture from the cracking plants, which contains about 20–25% of propene, is passed through a gas distributor into an absorption tower. This tower has no plates, and is filled to a height of 14 m with sulfuric acid already containing about 0.2 mole of propene/mole of sulfuric acid. The acid absorbs propene up to a concentration of about 1 mole per mole of sulfuric acid. The exhaust gas still contains about 5 to 6% of propene, which is absorbed (to 99%) in a bubble-cap column in regenerated sulfuric acid from the hydrolysis column. In this column the sulfuric acid absorbs propene to a concentration of about 0.2 mole per mole of sulfuric acid, and is then passed into the first absorption tower.

The 1:1 extract leaving the first absorption tower passes through a relief valve into a sedimentation vessel, where small quantities of polymer settle out. Water is added to give a 60% acid solution, and the mixture is passed into a column in which the isopropanol is distilled as an 85% product. A 70% sulfuric acid accumulates at the base of the column.

The crude alcohol is diluted to 25%, whereupon further polymer settles out after 1 to 2 days. Isopropyl ether is then distilled off in a bubble-cap column (15 plates, reflux ratio 15:1). The residue is concentrated in a 50-plate column to 91% isopropanol. The yields are between 85 and 90%, based on propene converted.

Olefins containing four carbon atoms (B–B fraction) are converted into sec- and tert-butyl alcohols by the strong acid process (cf. Scheme 1). Owing to the strong tendency of the $C_4$ olefins to polymerize, it is particularly important to maintain the correct temperature.

Isobutene is absorbed in 60 to 65% sulfuric acid at 0 to 5 °C and under slight pressure, or at −6 to −7 °C and at normal pressure. t-Butyl alcohol is obtained from the sulfuric acid phase by dilution with water followed by steam distillation.




Scheme 1. The various steps in the production of tertiary and secondary butyl alcohols from the butenes of the B–B fraction [5].

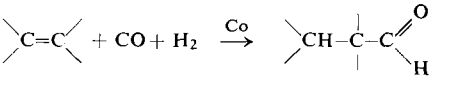
The organic phase is treated with ammoniacal cuprous chloride solution to remove butadiene, and is then absorbed in 80% sulfuric acid at 40 to 50 °C at a low pressure. The n-butylsulfuric acid is hydrolysed by dilution to 30%, and the resulting alcohol is steam distilled. sec-Butyl alcohol is largely converted into methyl ethyl ketone by dehydration. The sulfuric acid can be concentrated, *e.g.* by immersion heaters or by the introduction of air. The presence of coking organic material often leads to pronounced foaming, which frequently interferes with production.

[5] After *F. Asinger*: Chemie und Technologie der Monoolefine, p. 588. Akademie-Verlag, Berlin 1957.

## Syntheses

### Roelen Reaction

In 1938, *O. Roelen* [6] discovered the hydroformylation of olefins with carbon monoxide and hydrogen in the presence of cobalt compounds:




The olefins used nowadays are all obtained from petrochemicals, and the initially formed aldehydes are nearly always converted into the corresponding alcohols by hydrogenation (sometimes in a single reaction step).

The reation is carried out at 150 to 200 °C and about 200 atm; the actual catalyst is the hydrogen tetracarbonylcobaltate $HCo(CO)_4$ formed during the reaction. The raw materials used are generally lower olefins (*e.g.* ethylene, propene, butene), higher α-olefins, or even olefins such as isoheptene or diisobutylene. The alcohols obtained are used as solvents (n-propanol, n-butanol, isobutanol), as esterification components, *e.g.* with phthalic acid or adipic acid for plasticizers, or after sulfation as detergents.

The influence of the structure of the olefin on its reactivity in the hydroformylation and on the structure of the resulting aldehyde and alcohol was studied particularly by *A. I. M. Keulemans et al.* [7]. The following relationships were recognized:

a) Straight-chain olefins, irrespective of the position of the double bond, give a mixture of 40 to 60% of n-alcohols and 60 to 40% of 2-alkyl branched alcohols.

b) The formyl group does not add to a tertiary C atom, and no quaternary C atoms are formed.

c) Addition of a formyl group in the position adjacent to a tertiary C atom takes place only to a small extent.

d) No addition of the formyl group occurs in a position adjacent to a quaternary C atom.

e) The addition of the formyl group is not hindered by an isolated tertiary C atom.

f) The hydroformylation is generally accompanied by migration of the double bond.

The Roelen reaction can be carried out by three basic procedures:

1. Hydroformylation of the olefin, removal of the cobalt catalyst, and hydrogenation of the aldehyde mixture.

2. Hydroformylation of the olefin followed by hydrogenation at a high pressure of hydrogen without removal of the cobalt, which then acts as a heterogeneous hydrogenation catalyst.

[6] *O. Roelen*, Angew. Chem. *60*, 213 (1948); *O. Roelen* in *K. Ziegler*: Präparative org. Chemie I, 157 (1948) (Naturforschung und Medizin in Deutschland 1939/46, Vol. 36).

[7] *A. I. M. Keulemans, A. Kwantes*, and *Th. van Bavel*, Recueil Trav. chim. Pays-Bas *67*, 298 (1948).

3. The aldehyde resulting from the hydroformylation is immediately converted into the alcohol by homogeneously catalysed hydrogenation in the presence of hydrogen tetracarbonylcobaltate.

The fixed-bed process and the mash process, which operate continously, have proved suitable in industry. The fixed-bed process corresponds to the first of the above variants, and the mash process to the second. It should be borne in mind in both cases that the actual catalyst is hydrogen tetracarbonylcobaltate. Thus catalysis in both cases is homogeneous.

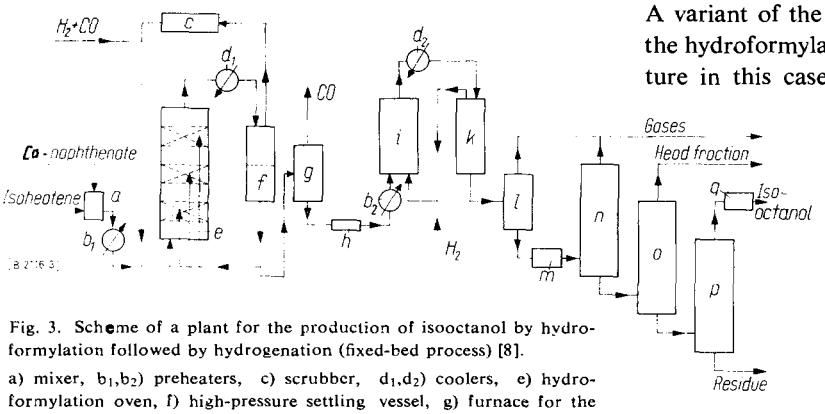



Fig. 3. Scheme of a plant for the production of isooctanol by hydroformylation followed by hydrogenation (fixed-bed process) [8].

a) mixer, $b_1$,$b_2$) preheaters, c) scrubber, $d_1$,$d_2$) coolers, e) hydroformylation oven, f) high-pressure settling vessel, g) furnace for the decomposition of the catalyst, h) filter, i) hydrogenation furnace, k) high-pressure settling vessel, l) low-pressure settling vessel, m) alkali washer, n) stabilizer, o) first runnings column, p) alcohol column.

The fixed-bed process will now be described for the production of isooctanol from isoheptane[8] (cf. Fig. 3). The catalyst is metallic cobalt on pumice or some other support. Losses are compensated by addition of cobalt naphthenate to the fresh olefin. The olefin is made to react at 175 °C and 200 atm; in order to maintain this temperature the product is circulated through a cooler and returned to the reactor at various positions. The ratio of fresh olefin to recirculating liquid is 1:4 to 5, and the residence time is 2.5 hours. Some 400 to 420 $Nm^3$ of water gas are required per 100 *l* of isoheptene; the recirculating system contains approximately 1000 $Nm^3$ of gas.

The catalyst is decomposed at 150 to 160 °C and at a hydrogen pressure of 7 to 10 atm, the metallic cobalt is removed, and the product converted into the alcohol by hydrogenation on nickel catalysts at 200 to 220 °C and 200 atm. The contact loading is 0.6. After working up, isooctanol is obtained in a yield of about 75% with respect to the isoheptene. About 25% of residue remains.

The hydrogenation can also be carried out on sulfide catalysts. This is particularly interesting in that no desulfuration is required, since the hydroformylation is not affected by sulfur.

In the mash process[9], the catalyst (3 to 5%) is slurried in the olefin in the mashing container, and the slurry is forced into the first hydroformylation oven (internal diameter 20 cm, height 8 m), where 70 to 75% of the olefin reacts at 150 to 160 °C and 200 atm (100 atm of CO, 100 atm of $H_2$). The reaction is allowed to continue in a second reactor at 160 to 170 °C. The pressure is released and the product is hydrogenated in two steps at 200 to 220 °C at a hydrogen pressure of 200 atm, the finely divided metallic cobalt formed by the decomposition of the tetracarbonylcobaltate acting as a catalyst. Since the activity of this catalyst is low, relatively long reaction times (about 2 hours) are required. The hydrogen must be essentially free from carbon monoxide (<0.2%), and for this reason a special purification step is included in the gas cycle. When the cobalt has been filtered off, the product is distilled. The filters are periodically back-flushed with fresh olefin to recover the catalyst. A simplified scheme of the process is shown in Figure 4.

In another procedure, the hydrogenation of the aldehyde is carried out under homogenous catalysis with hydrogen tetracarbonylcobaltate[10]. After hydroformylation the temperature is raised to 220 °C, whereupon the hydrogenation begins; the pressure is maintained with the aid of a hydrogen supply.

A variant of the Roelen reaction can also be used for the hydroformylation of alcohols, the reaction temperature in this case being preferably about 200 °C. The product is the next higher homologous alcohol, *e.g.* isoamyl alcohol from t-butyl alcohol or isobutanol from isopropanol[11].

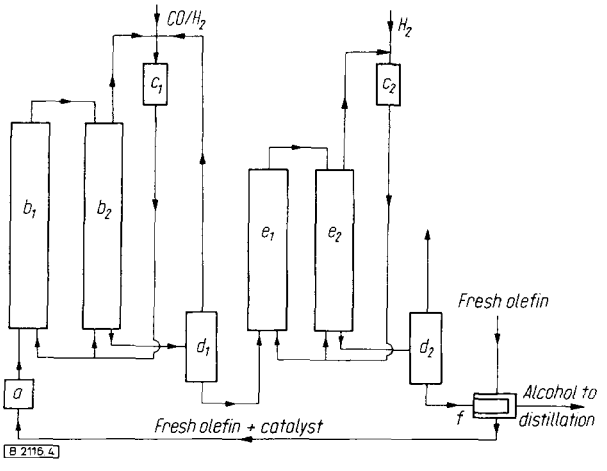



Fig. 4. Simplified scheme of a mash process for the production of alcohols by hydroformylation followed by hydrogenation. a) mashing vessel, $b_1$,$b_2$) hydroformylation furnaces, $c_1$,$c_2$) gas purifiers, $d_1$,$d_2$) decompression vessels, $e_1$,$e_2$) hydrogenation furnaces, f) filter.

## Reppe Synthesis

*W. Reppe et al.*[12] showed that olefins can be converted into alcohols by carbon monoxide/water in the presence of dihydrogen tetracarbonylferrate/tertiary amine at

[8] U.S.-Pat. 2595096 (1952), Standard Oil Development Co., Chem. Abstr. *47*, 141f (1953), U.S.-Pat. 2637796 (1953), Standard Oil Development Co., Chem. Abstr. *48*, 2757d (1954); cf. Chem. Engng. *60*, 346 (1953).

[9] *R. Holroyd*, U.S. Bureau of Mines. Inform. Circ. 7370 (1946).

[10] *J. Wender et al.*, J. Amer. chem. Soc. *71*, 4160 (1949); *72*, 4375, 4842 (1950); *73*, 2656 (1951); *74*, 4079 (1952).

[11] *J. Wender et al.*, J. Amer. chem. Soc. *71*, 4160 (1949); Science (Washington) *113*, 206 (1951).

[12] *W. Reppe* and *H. Vetter*, Liebigs Ann. Chem. *582*, 133 (1953).

temperatures above 100 °C and pressures above 10 atm gage:

$$R\text{-}CH{=}CH{-}R' + 3\,CO + H_2O \rightarrow \begin{matrix} CH_2OH \\ | \\ R{-}CH_2{-}CH{-}R' \end{matrix} \quad \text{and} \quad \begin{matrix} CH_2OH \\ | \\ R{-}CH{-}CH_2{-}R_2 \end{matrix} + 2\,CO_2$$

In contrast to the production of alcohols by hydroformylation and subsequent hydrogenation, the acolhols in this case are produced in a single reaction step at a low pressure and a relatively low temperature.

This process is used by BASF for the production of n-butanol from propene [13]. A plant with an annual capacity of 15000 tons has recently been built in Japan by Nikon, and was put into operation early in 1965. The process is carried out at about 100 °C and about 15 atm gage. The amine used is *N*-butylpyrrolidine, since the pyrrolidine ring is very stable towards transalkylation. The product conatins about 85 % of n-butanol and about 15 % of isobutanol.

Pentacarbonyliron, *N*-butylpyrrolidine, water, and butanol are placed in the reactor. The temperature is raised to 100 °C, and a homogeneous solution of the catalyst, *N*-butylpyrrolidinium hydrogen undecacarbonyltriferrate, is formed within 2 to 4 hours. The formation of butanol begins when the carbon monoxide and propene are introduced (care being taken to ensure intimate mixing). To ensure that the relative concentration of the gases remains constant, only part of the starting materials is allowed to react, and the gases are recycled; otherwise the ratio of pentacarbonyliron to carbonyltriferrate changes, with the result that the reaction is unfavorably affected.

The recirculating gas is first led, at the temperature and pressure of the synthesis, into a bubble-cap column where the *N*-butylpyrrolidine is washed out by material exchange with the refluxing liquid and returned to the reactor. Butanol, water, and pentacarbonyliron are condensed from the head fraction. The remaining gas is pumped back into the reactor, while the gaseous reaction products (carbon dioxide, hydrogen, and propane) are removed in a branch stream by multistage high-pressure scrubbing with water. The condensate flows into a separating vessel, from which the two bottom layers (mainly pentacarbonyliron and water) are returned to the washing column. The third layer (mainly butanol) is introduced into the head of another column, which operates at the pressure used in the synthesis, and fresh carbon monoxide is introduced at the bottom of this column. The pentacarbonyliron is carried to the head of the column by the carbon monoxide, while the crude butanol is drawn off at the bottom.

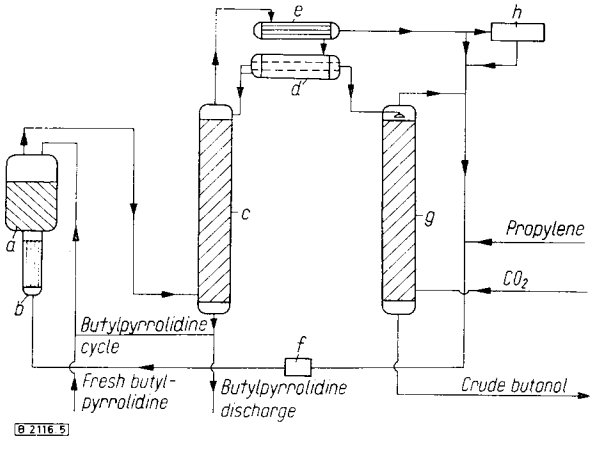



Fig. 5. Scheme of the production of n-butanol by the Reppe process [13]. a) reactor, b) preheater, c) wash column, d) separating vessel, e) cooler, f) gas-recirculating pump, g) pressure column, h) gas washer.

[13] *N. von Kupetow* and *H. Kindler*, Angew. Chem. *72*, 802 (1960).

The crude butanol is washed to remove traces of *N*-butylpyrrolidine, and traces of pentacarbonyliron are destroyed by oxidation. The residual water (about 7 %) is then distilled off, and the mixture of isomers is finally resolved into pure n-butanol and isobutanol. The yield of butanol is about 90 % with respect to propene and carbon monoxide. By-products include propane (about 4 % with respect to propene) and hydrogen (about 6 % with respect to carbon monoxide). Fig. 5 shows a diagram of a plant.

### Ziegler Synthesis

As shown by *K. Ziegler et al.* [14], triethylaluminum reacts with ethylene at high pressures and temperatures to give higher unbranched aluminum trialkyls (growth reaction), which can be converted into aluminum alkoxides by oxidation with oxygen [15]. Hydrolysis of these leads to the corresponding alcohols. Triethylaluminum can be prepared from aluminum and ethylene in a two-step reaction [16].

$$Al + 2\,Al(C_2H_5)_3 + {}^3/_2\,H_2 \rightarrow 3\,AlH(C_2H_5)_2$$

$$3\,AlH(C_2H_5)_2 + 3\,C_2H_4 \rightarrow 3\,Al(C_2H_5)_3$$

$$Al(C_2H_5)_3 + n\,C_2H_4 \rightarrow AlR_3$$

$$AlR_3 + {}^3/_2\,O_2 \rightarrow Al(OR)_3$$

$$Al(OR)_3 + {}^3/_2\,H_2O \rightarrow 3\,ROH + {}^1/_2\,Al_2O_3$$

R = higher unbranched alkyl groups.

The growth reaction gives products in which the chain lengths of the alkyl groups correspond to a Poisson distribution [15], so that the ultimate product consists of a mixture of alcohols (see Fig. 6). These alcohols, known commercially as Alfols®, can be used above all in the plasticizer and detergent fields, depending on their chain length.

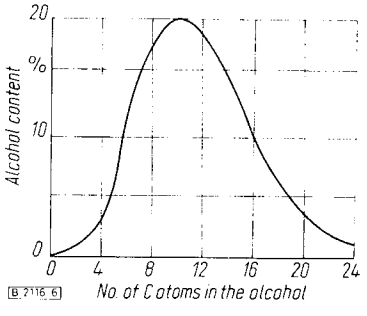



Fig. 6. Composition of the alcohol mixture from the Alfol synthesis for an average chain length of 10 C atoms.

The process has been developed for industrial use by the Continental Oil Company, New York. A plant with an annual output of 50000 tons was put on stream in Lake Charles, Louisiana (USA), around the beginning of 1962 [17]. A plant of similar capacity is being operated in Germany as a joint venture by the Deutsche Erdöl AG, Hamburg, and CONOCO (CONDEA Petrochemie Gesellschaft mbH, Brunsbüttelkoog). The scheme of the plant is shown in Fig. 7.

[14] *K. Ziegler et al.*, Liebigs Ann. Chem. *629*, 121 (1960).
[15] *K. Ziegler et al.*, Liebigs Ann. Chem. *629*, 241 (1960).
[16] *K. Ziegler et al.*, Liebigs Ann. Chem. *629*, 1 (1960).
[17] *P. Lobo et al.*, Chem. Engng. Progr. *58*, 85 (1962).

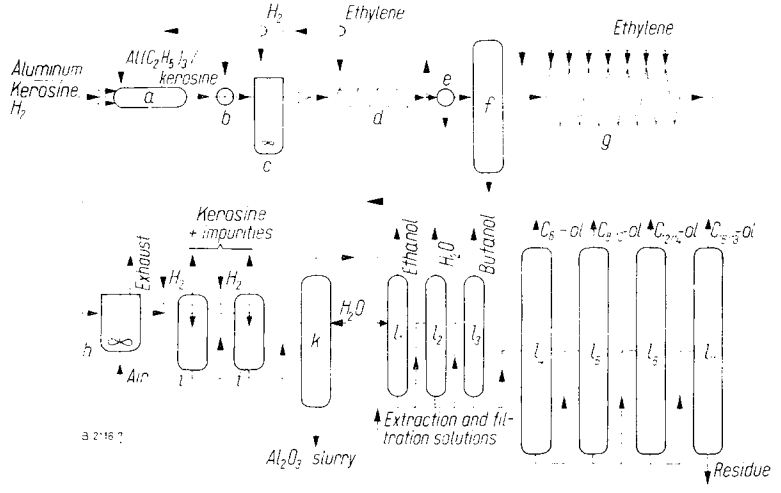



Fig. 7. Scheme of the production of Alfols by the CONDEA Petrochemie process. a) ball mill, b) mixing vessel, c) hydrogenation reactor, d) ethylation reactor, e) centrifuge, f) distillation column for triethylaluminum, g) growth reactor, h) oxidation reactor, i) flash-distillation plant for removal of solvent and purification, k) hydrolysis reactor, $l_1$ to $l_7$) distillation columns.

## Production of Triethylaluminum

The starting material is an aluminum powder obtained from 99.5% aluminum by the addition of a small quantity of a Group IVa metal[18]. The proportion of fine-grain material required depends on the operating conditions: powder grades in with 40–80% <320 mesh are preferred. The aluminum powder is ground in a ball mill for about 4 to 5 hours with kerosine (boiling range 180 to 260 °C) and hydrogen. This "mechanical activation" leads to the exposure of fresh surfaces, but the proportion of fine-grain material decreases. Activation is reinforced by the addition of 5 to 10% of triethylaluminum.

The resulting 30 to 40% aluminum slurry is mixed with the required quantity of triethylaluminum. Diethylaluminum hydride is formed in a hydrogenation reactor at about 120 °C and at a hydrogen pressure of 85 atm. The pressure is then reduced to 25 atm in an air cooler with simultaneous application of ethylene pressure, whereupon the diethylaluminum hydride is ethylated. The temperature rises to about 150 °C; two thirds of the resulting solution of triethylaluminum in kerosine (concentration about 50%), is returned to the hydrogenation step, while the other third is centrifuged and the supernatant is distilled at about 50 mm Hg. This method of purification is much more reliable than filtration, and has the added advantage that not only the unconverted aluminum particles, but also metallic impurities and the alloyed metal are retained. The result is that very pure alumina is obtained as by-product.

## Growth Reaction

The growth reaction is carried out continuously at about 120 °C and at an ethylene pressure of 100 atm[19]; the m value, *i.e.* the average number of ethylene molecules reacting per Al–C bond, can be varied. The process can therefore be adjusted to meet the market requirements, in spite of the difference in the chain lengths of the alcohols. The ethylene used has a purity of about 99%.

The reactor is a steel tube (free from Ni and Cr) which widens towards the end to allow for the increasing volume of the reaction mixture. The ethylene is injected at about 10 to 15 points. The heat-transfer agent is n-heptane at a pressure of about 0.5 atm gage. Settling out of polyethylene is only slight; the polymer can be removed by passing through hot kerosine.

## Oxidation and Purification

The oxidation is carried out with air in stirred reactors having a capacity of about 40 m³, and at 40 °C and 2 atm gage. The reaction is rapid at first, but slows down considerably towards the end, so that the complete oxidation of all the Al–C bonds is not easily possible. Thus in order to minimize side reactions and secondary reactions, the process is carried out to conversions of about 85 to 90%, the end-point being checked by the oxygen content of the exhaust gas.

Before the aluminum alkoxide is hydrolysed, the solvent and the by-products formed during the oxidation (mainly esters) are removed by a two-stage flash distillation at 260 °C and 100 and 50 mm Hg with hydrogen as the stripping gas[20]. Under these conditions the unoxidized Al–C bonds are simultaneously cracked, and the aluminum alkoxide mixture is obtained as the residue. The head product from this distillation can be regenerated and reused as the solvent.

## Hydrolysis

The aluminum alkoxide mixture can be hydrolysed in acidic, as well as in neutral or alkaline media. The simplest method is hydrolysis with sulfuric acid, since only two easily separable phases are obtained in this case. However, CONDEA decided in favor of hydrolysis in a neutral medium, in which aluminum oxide hydrate occurs as a by-product.

The alkoxide mixture and demineralized water (1:1.5) are injected into the reactor (about 15 m³) at about 100 °C. The alcohol mixture formed is removed at the head of the reactor and led to the distillation columns. The aluminum oxide hydrate is taken off at the bottom of the reactor. A two-stage

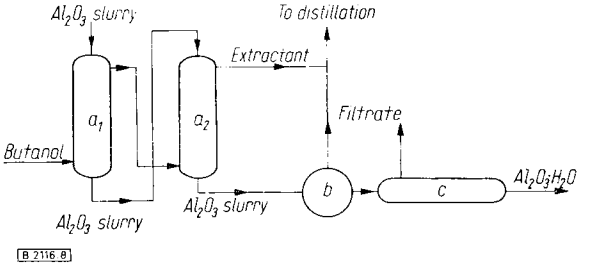



Fig. 8. Scheme of the extraction and processing of the hydrated alumina slurry. $a_1$,$a_2$) extractors, b) filter, c) drier.

[18] U.S.-Pat. 3 104 252 (Feb. 26th, 1960); Continental Oil Co.

[19] Cf. *K. Zosel*, Brennstoff-Chem. *42*, 321 (1960).

[20] U.S.-Pat. 3104251 (July 7th, 1960), Continental Oil Co.

extraction is carried out with butanol saturated with water, followed by filtration at 100 °C and drying. The extracts and the filtrate are led to the distillation plant (Fig. 8).

The aluminum oxide hydrate $Al_2O_3 \cdot H_2O$ obtained has a high purity (*e.g.* $Fe_2O_3$ *ca.* 70 ppm, $SiO_2$ *ca.* 50 ppm, and $Na_2O$ *ca.* 90 ppm).

### Distillation

A multi-stage predistillation is carried out in which first ethanol, then water, and finally butanol are distilled off. The alcohol mixture is resolved in several 30-plate columns about 35 m high. The fractions generally obtained are hexanol, octanol/decanol, dodecanol/tetradecanol, and hexadecanol/octadecanol. The residue (about 10%) is a mixture of higher alcohols, higher esters, and paraffins, which are difficult to separate by distillation.

### Reaction Products

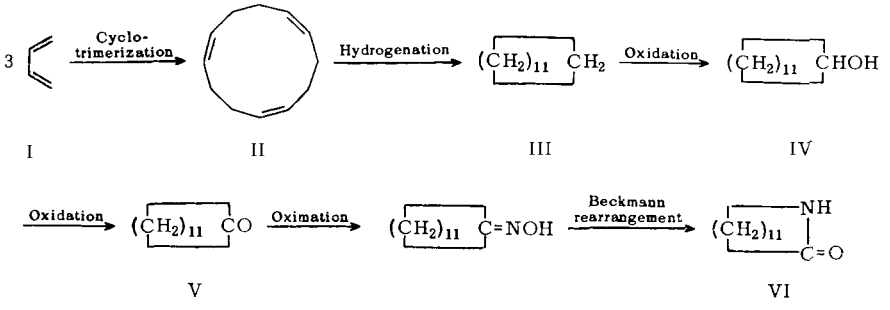
The Alfols obtained are characterized by their freedom from branching and by their low contents of impurities. The lower Alfols (6 to 10 C atoms) can be used for the production of plasticizers for PVC processing; higher Alfols (12 to 18 C atoms) are used, *e.g.* in the form of the sulfates or the products of reaction with ethylene oxide, as biodegradable detergents.

## Alcohols by Oxidation with Air

Air oxidation of unbranched paraffins and cycloparaffins proceeds by random attack on the methylene groups [21,22], *via* the hydroperoxides, to give a mixture of secondary alcohols and ketones. The ketones in particular are subject to further oxidation, and the result is a complex mixture of alcohols, ketones, carboxylic acids, esters, *etc.* In the presence of boric acid, the reaction can be directed predominantly towards the alcohols [23]. Since the alcohols are obtained in this case as esters of boric acid, they are protected against further oxidation. By-products are mainly the corresponding ketones.

The products obtained with straight-chain paraffins are secondary alcohols [24], which can be used as esterifying components for plasticizers, as well as for the preparation of detergents. The straight-chain paraffins can be obtained from petroleum fractions, *e.g.* by the molecular sieve method used by the British Petroleum Company [25], or by the Edeleanu urea-addition method [26].

*F. Broich* and *H. Grasemann* [27] studied the oxidation of cyclododecane III to cyclododecanol IV, which is then converted by a Beckmann rearrangement *via* cyclodecanone and its oxime into ω-laurolactam VI. Cyclododecane can be prepared from butadiene I *via* cyclododecatriene II [28]:




The industrial air oxidation of cyclododecane is carried out at 150 to 160 °C in the presence of about 6% of boric acid. The reaction is carried to a conversion of 20 to 25% (about 9% per hour), and the yield is about 82% of cyclododecanol/cyclododecanone. The ratio of alcohol to ketone is about 6–8:1.

The alcohol is recovered by distilling off unchanged hydrocarbon and hydrolysing the residue. The boric acid is recovered from the aqueous phase. The alcohol/ketone mixture obtained by distillation of the organic phase is dehydrogenated. A simplified scheme of this process is shown in Figure 9.

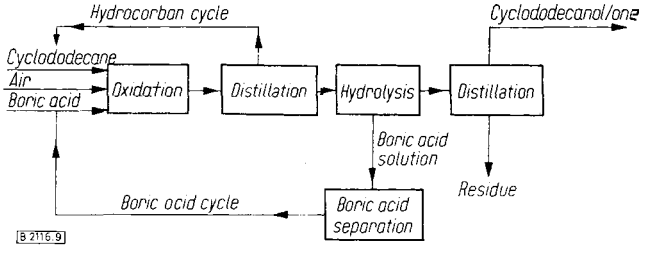



Fig. 9. Simplified scheme for the production of cyclododecanol from cyclododecane.

A plant with an annual output of 5000 tons is being operated by Chemische Werke Hüls AG, Marl (Germany).

Contrary to the procedure described above, no boric acid is present during this oxidation of cyclohexane [29], which is carried out at 140 to 155 °C and 8 to 15 atm; about 50 ppm of a cobalt salt is added as catalyst. Residence times of 10 min to 2 hours give conversions of 6 to 8%. Higher conversions give appreciably lower yields of cyclohexanol/cyclohexanone (1:1). Under the conditions described, the yield is about 60 to 70%. The principal by-products are adipic, glutaric, and succinic acids.

[21] Cf. *W. Pritzkow* and *K. A. Müller*, Liebigs Ann. Chem. *597*, 167 (1956).

[22] *G. Geiseler, F. Asinger*, and *H. Wien*, Chem. Ber. *92*, 958 (1959).

[23] *H. Nobori*, Chem. Abstr. *42*, 6737/38 (1948).

[24] *A. N. Bashkirov et al.*, Chem. Abstr. *1957*, 4027g, 16513e; *1958*, 17087f; *1961*, 3410; J. Petroleum Chem. *1*, 151, 311, 414, 564 (1962), *2*, 83 (1963); VIth World Petroleum Congress (1963), Sect. IV, Paper 38.

[25] *A. A. Yeo, J. Mather, R. J. H. Gilbert*, and *M. Baker*, VIth World Petroleum Congress (1963), Section IV, Paper 15.

[26] Ger. Pat. 128726 (1955), Edeleanu GmbH, Chem. Zbl. *127*, 315 (1956); *A. Hoppe* and *H. Franz*, Erdöl u. Kohle *8*, 411 (1955); cf. also Chem.-Ing.-Techn. *38*, 192 (1966).

[27] *F. Broich* and *H. Grasemann*, Erdöl u. Kohle *18*, 360 (1965).

[28] *G. Wilke*, Angew. Chem. *69*, 397 (1957); *73*, 33 (1961); *75*, 14 (1963).

[29] *W. L. Faith, D. B. Kayes*, and *R. L. Clark*: Industrial Chemicals (New York 1957); cf. also *F. Broich*, Chem.-Ing.-Techn. *34*, 45 (1962).

The alcohol/ketone mixture is dehydrogenated either to cyclohexanone or to phenol or oxidized to adipic acid. The flow sheet of a plant is shown in Figure 10.

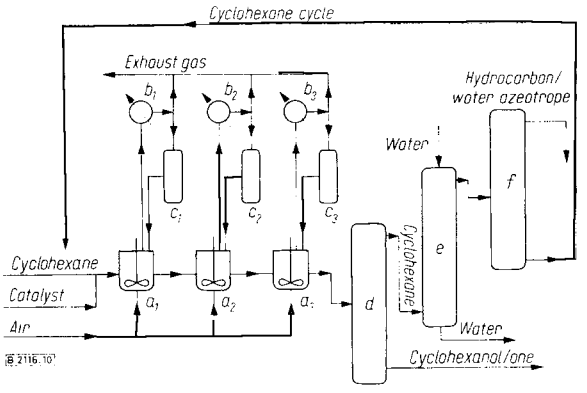
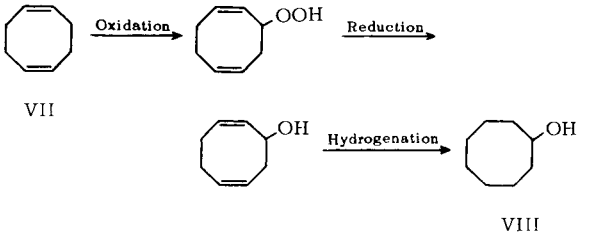



Fig. 10. Scheme of the production of cyclohexanol/cyclohexanone by air oxidation of cyclohexane [30]. $a_1$ to $a_3$) reactors, $b_1$ to $b_3$) coolers (heat exchangers), $c_1$ to $c_3$) settlers, d) cyclohexanol tower, e) wash column, f) cyclohexane tower.

In another procedure proposed by *P. Baumgartner et al*[31] for the production of cyclic alcohols, cyclooctadiene VII and cyclododecatriene, which can be obtained by the cyclodimerization or cyclotrimerization of butadiene[28], are converted into hydroperoxides by oxidation with oxygen at 60 to 65 °C. After reduction, *e.g.* with sodium sulfite, the unchanged hydrocarbons are distilled off and the oxidation products are hydrogenated, *e.g.*:




The yields of cyclooctanol VIII are about 80 to 82%, those of cyclododecanol about 70%.

No industrial application of this process has so far been reported. The cost would probably compare unfavorably with that of the oxidation *e.g.* of cyclododecane in the presence of boric acid, mainly because of the reduction step.

*I am grateful to Dr. Broich, Chemische Werke Hüls AG, and to Dr. Kroeper, Badische Anilin- & Sodafabrik AG, for information supplied.*

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German version: Chem.-Ing.-Techn. *38*, 837 (1966)
Translated by Express Translation Service, London

[30] Taken from *M. Sittig*: Combining Oxygen and Hydrocarbons for Profit, p. 164, Gulf Publishing Co., Houston 1962.

[31] *P. Baumgartner et al.*, VIth World Petroleum Congress (1963), Sect. IV, Paper 6.

# Technology of the Microbiological Preparation of Organic Substances

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*The preparation of organic substances with the aid of the enzyme systems of microorganisms has become competitive as a result of recent progress in the technology of fermentation. The relatively high cost of apparatus and the lower production capacity of microbiological plants in relation to the plants used in purely chemical processes are offset in many cases by the advantages of biological methods (reactions at conventionally inactive positions in the molecule, stereospecific substitutions, coupling of several reactions, mild reaction conditions, possible use of waste products).*

The biochemical capabilities of microorganisms have been utilized in industry for only about 30 years. An exception is the old fermentation industry: empirically discovered methods for production of vinegar, sour milk, and alcoholic beverages, as well as the methods of the indigo-dyeing industry, have been known for centuries. The ability of microorganisms to cause fermentation was discovered by *Pasteur*[1].

Chemically defined products can be produced in two ways by the enzyme systems of microorganisms:

## 1. By Microbiological Transformation of Substrates

A compound is added to the growing or resting cell culture, and after a time in contact with the intracellular or extracellular enzyme, the product is recovered from the culture broth. In this respect glucose and other carbohydrates, which are transformed or broken down to smaller metabolites in the course of the normal respiratory or fermentative metabolism of the cell, may be regarded as substrates.

## 2. By Microbiological Synthesis from Nutrients

The enzyme systems in the cell convert the nutrients into suitable fragments, from which they then synthesize macro-

[1] *L. Pasteur*: Mémoire sur la Fermentation Acétique. J. F. Bergmann, Munich 1864.

molecular metabolites, which are stored in the cell or secreted into the culture broth.

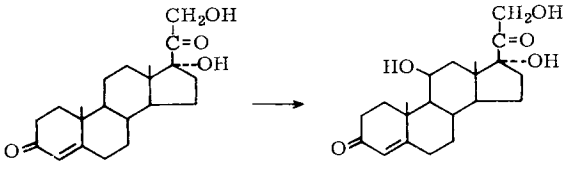
## Microbiological Transformations

The first specific transformations, such as the hydrolysis of starch [2] and the reduction of chloral to trichloroethanol [3], to be discovered after fermentation reactions, were found at the beginning of the 20th century. However, these microbiological reactions were only of academic interest.

It was only in 1934 that the conversion of sorbitol into sorbose [4] attained such importance as an intermediate in the synthesis of vitamin C that it became the first microbiological reaction to be carried out on the industrial scale [5].

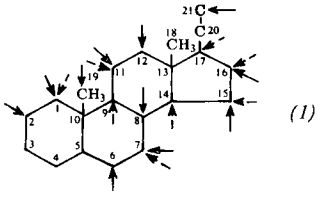
About this time, special fermentation processes were discovered or developed further, with the result that it became possible to produce glycerol, isopropanol, acetone, or butylene glycol economically by microbiological methods. These methods are based on the enzymatic transformation of glucose or of polysaccharides yielding glucose on fermentation. However, some of these fermentation products can now be more advantageously obtained by chemical methods.

Further developments received special impetus as a result of the discovery in 1952 that steroids are hydroxylated in position 11 by some strains of fungi [6].



This discovery formed the basis of an economical method for the production of adrenocortical hormones from other steroids. Many microorganisms were subsequently studied in relation to their action on steroids, and many of the reactions were found to be remarkably stereospecific.

It can be seen from the formula of pregnane *(1)* that α- or β-hydroxylation is possible on almost every carbon atom [7]. The direction of hydroxylation, indicated by arrows, depends on the microorganism used.



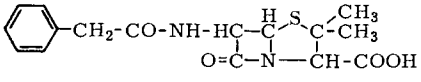
*(1)*

In addition to microbiological hydroxylation, other types of reaction, such as the oxidation of hydroxyl groups, the reduction of keto groups, the hydrolysis of ester groups, and the isomerization and introduction of double bonds, were discovered [8]. Of these reactions, 1,2-dehydrogenation has gained particular industrial importance in the production of prednisolone from hydrocortisone and of prednisone from cortisone.

Many microbiological reactions are known outside the steroid field [9], but few of these have found industrial use. Those that have (cf. Table 1) include the oxidation of naphthalene to salicylic acid, and the cleavage of diaminopimelic acid to lysine and of penicillin to 6α-aminopenicillanic acid [11].

## Microbiological Synthesis [10]

The first isolation of a microbial metabolite on the industrial scale was probably that of ergosterol. However, the special importance of microbial metabolites appeared only with the discovery of penicillin *(2)* [12]. The development of a process for the industrial production of



*(2)*

this, the first antibiotic to be used clinically, was extremely difficult; the problem was solved on the basis of studies by *Chain* and *Florey* [13]. The success of this work was due largely to the switch from the original surface culture to the submerged process, and to the complete exclusion of contaminating organisms. Other important antibiotics including streptomycin, chloramphenicol, erythromycin, tetracyclin, novabiocin, and actinomycin were isolated as microbial metabolites during the 1940's and 1950's [14], and this provided the final drive for the development of the fermentation industry.

## Isolation of Enzymes [15]

The isolation of intracellular enzymes generally involves cytolysis, and is therefore often very expensive. It is possible only in rare cases to extract intracellular enzymes from undamaged cells with solvents. With


[2] *F. Schradinger*, Z. Unters. Nahr. Genußm. *6*, 865 (1903).

[3] *I. Lintner* and *H. Luvers*, Hoppe-Seylers Z. physiol. Chem. *72*, 449 (1911).

[4] *C. Bertrand*, C. R. hebd. Séances Acad. Sci. *122*, 900 (1896).

[5] *T. Reichstein* and *A. Grüssner*, Helv. chim. Acta *17*, 311 (1934).

[6] *D. H. Peterson* and *H. C. Murray*, J. Amer. chem. Soc. *74*, 1871 (1952).

[7] *L. M. Kogan*, Uspekii Khim. *31*, 294 (1962).

[8] *Ch. Tamm*, Angew. Chem. *74*, 225 (1962); Angew. Chem. internat. Edit. *1*, 178 (1962).

[9] *L. L. Wallen, F. H. Stodola, et al.*: Type Reactions in Fermentation Chemistry; Agricultural Research Service, Northern Utilization Research and Development Division, Peoria (Illinois) 1959.

[10] *M. W. Miller*: The Pfizer Handbook of Microbial Metabolites. McGraw-Hill, New York 1961.

[11] *A. M. Walter* and *L. Heilmeyer*: Antibiotika-Fibel. Georg Thieme Verlag, Stuttgart 1965.

[12] *A. Fleming*: Penicillin; its Practical Application. Blakistan, Philadelphia 1946.

[13] *H. W. Florey, E. Chain, et al.*: Antibiotics. Oxford Univ. Press, 1949.

[14] *T. Korzybski* and *W. Kurylowicz*: Antibiotica. VEB Fischer Verlag, Jena 1961.

[15] *F. C. Webb*, Biochemical Engineering Data. van Nostrand, London 1964, p. 605.

Table 1. Microbiological processes used in industry.

1. Microbiological transformations

(a) Miscellaneous substrates

| | | |
|---|---|---|
| D-Sorbitol | → L-Sorbose | *(Acetobacter suboxydans)* |
| Diamino-pimelic acid | → L-Lysine | *(Bacillus sphaericus)* |
| Naphthalene | → Salicylic acid | *(Pseudomonas aeroginosa)* |
| Penicillin | → 6α-Amino-penicillinic acid | *(Bacillus cereus)* |
| Glycerol | → 1,3-Dihydroxyacetone | *(Acetobacter suboxydans)* |
| Reichstein S | → Hydrocortisone | *(Curvularia lunata)* |
| 9α-Fluoro-hydrocortisone | → 16α-Hydroxy-9α-fluorohydro-cortisone | *(Streptomyces roseochromogenes)* |
| Hydrocortisone | → Prednisolone | *(Corynebact. simplex)* |
| Cortisone acetate | → Prednisone | *(Bacillus lentus)* |
| Ethanol | → Acetic acid | *(Acetobacter sp.)* |
| D-Glucose | → D-Gluconic acid | *(Penicillium chrysogenum)* |
| Dextran | → Polydextran | *(Streptococcus sp.)* |

(b) Products of the carbohydrate metabolism of the microorganisms

| | |
|---|---|
| Ethanol | *(Saccharomyces spec.)* |
| Glycerol | *(Saccharomyces spec.* + $NaHSO_3$) |
| Acetone, n-Butanol, Isopropanol | *(Clostridium acetobutylica)* / *(Clostridium butylicum)* |
| Butylene glycol | *(Bacillus polymyxa)* |
| Itaconic acid | *(Aspergillus itaconicus)* |
| Lactic acid | *(Lactobacillus delbrückii)* |
| Fumaric acid | *(Rhizopus nigricans)* |
| Citric acid | *(Aspergillus niger)* |
| Glutamic acid | *(Brevibacterium divaricatum)* |
| Diaminopimelic acid, Tryptophan | *(Escherichia coli)* |

3. Enzyme preparation

| | |
|---|---|
| Proteases | *(Bacillus subtilis)* |
| Amylases | *(Aspergillus oryzae)* |
| Glucose oxidase | (Penicillia) |
| Penicillinase | *(Bacillus cereus)* |
| Invertase | *(Saccharomyces carlsbergensis)* |

(smaller amounts of the following are also manufactured: Cellulases, lipases, catalases, collagenase, pectinase, peroxidases, streptokinase, glutaminate decarboxylase)

2. Microbiological synthesis products

(a) Antibiotics

Penicillin and similar structures

| | |
|---|---|
| Penicillins, α-Aminopenicillanic acid | *(Penicillium chrysogenum)* |
| Cephalosporins | *(Cephalosporium acremonium)* |

Oligosaccharide structures

| | |
|---|---|
| Streptomycin | *(Streptomyces griseus)* |
| Ristocetin B | *(Nocardia lurida)* |
| Paromycin | *(Streptomyces rimosus)* |
| Kanamycin | *(Streptomyces kanamyceticus)* |
| Neomycins | *(Streptomyces fradige)* |

Polypeptide structures

| | |
|---|---|
| Tyrothricin, Gramicidines | *(Bacillus brevis)* |
| Bacitracine | *(Bacillus licheniformis)* |
| Polymyxin | *(Bacillus polymyxa)* |

Macrolide structures

| | |
|---|---|
| Erythromycin | *(Streptomyces erythreus)* |
| Oleandomycin | *(Streptomyces antibioticus)* |
| Spiramycin | *(Streptomyces ambofaciens)* |

Polyene structures

| | |
|---|---|
| Nystatin | *(Streptomyces nursei)* |
| Fumagillin | *(Aspergillus fumigatus)* |
| Trichomycin | *(Streptomyces hachijoensis)* |
| Amphotericin B | *(Streptomyces nodosus)* |

Other structures

| | |
|---|---|
| Tetracyclins | *(Streptomyces spec.)* |
| Griseofulvin | *(Penicillium griseofulvum)* |
| Fusidic acid | *(Fusidum coccineum)* |
| Cycloheximide | *(Streptomyces nursei)* |
| Novobiocin | *(Streptomyces spheroides)* |

(b) Vitamins and provitamins

| | |
|---|---|
| Cyanocobalamin ($B_{12}$) | (Propioni bacteria) |
| Xanthophyll (Lutein) | *(Mycobacterium phlei)* |
| Gibberellin | *(Gibberella fujikuroi)* |
| Ergosterin | *(Saccharomyces sp.)* |
| Carotene | (Penicillia) |
| Riboflavin ($B_6$) | *(Eremothecium ashbyii)* |

*Notes*: 1. Only one microorganism is mentioned for each process, though for some processes several are suitable.

2. In connection with the steroid transformations, only the most important processes are mentioned. The analogous reactions on improved corticoids and the microbiological intermediates in the production of sex hormones are not listed.

3. In connection with the antibiotics listed, it should be noted that the penicillin and tetracyclin groups include several commercial products with structural variants. Some 35 microbiologically produced antibiotics are being marketed at present.

A total of 2100 tons of antibiotics, with a value of $345 million, was produced in the USA in 1963.

extracellular enzymes, on the other hand, the processes involved are simpler, since these enzymes are obtained by separation from the microorganisms by the methods used in the production of antibiotics.

Table 1 shows the enzymes produced in the fermentation industry. An important example is the production of glucoamylase, which degrades starch to dextrose [16]. The yield in this process is reported to be 100 %, whereas that obtained on cleavage with hydrochloric acid is only 86 %.

## Advantages of Microbiological Methods

### 1. Microbiological Transformations

a) Reactions at positions in the molecule at which, owing to insufficient activation, chemical changes can be brought about only by multi-stage processes or not at all.

b) Stereospecific introduction or modification of substituents; it is even possible to obtain optically active structures from optically inactive precursors.

c) Coupling of several reactions with the aid of a microorganism whose enzyme systems catalyse several reaction steps.

d) Mild reaction conditions for substances sensitive to heat, acids, or alkalis, that give unsatisfactory yields in chemical processes, or that require the use of additional reactions in order to protect labile parts of the molecule.

### 2. Microbiological Synthesis

a) The biosynthetic production of complex structures proceeds in most cases as a one-step process.

b) The raw materials are usually cheap substances such as carbohydrates, waste products containing proteins, and inorganic salts.

## Selection and Preparation of Microorganisms

It is of the utmost importance that a suitable strain of bacteria [17] should be chosen for a given process. Un-

[16] *M. Sinclair*, Chem. Engng. *72*, 90, (1965).

fortunately, however, the biological classification of microorganisms gives no information about their enzymatic properties. For this reason new microorganisms are often isolated from soil and water samples. However, this search for strains is frequently expensive. For example, in the examination of 10000 actionomycetes isolated from soil samples, 2500 antibiotically active strains were found, but only ten of these gave new compounds, and only one of these compounds was clinically useful [18].

In many microorganisms that originally give unsatisfactory conversions or metabolite yields, physical or chemical treatment can cause mutations and lead to a marked increase in enzymatic activity.

The enzyme balance of any microorganism can also be controlled within certain limits during fermentation; investigation of this control requires many experiments, owing to the large number of variables involved (composition of the culture medium, temperature, pH, aeration, addition of inhibitors or promoters, age of the culture).

Every fermentation experiment begins with the cultivation and preparation of the inoculum, which is prepared by rinsing down of agar slants or by suspension of lyophilized cultures in physiological saline or nutrient solution. The microorganisms, the quantity of which is still small, are transferred into large Erlenmeyer flasks approximately $^1/_4$-filled with nutrient solution and shaken for a few days. These inoculum cultures are the starting cultures for the industrial fermentation.

## Industrial Fermentation

The production of organic substances by means of microorganisms requires a technology that provides optimal growth conditions on a large scale. It is essential for this growth that suitable nutrient solutions should be available to the organism in a substantially sterile state and at an optimal growth temperature. A sterile air supply must be provided, except in anaerobic processes, which are relatively rarely used in industry. It must also be possible to add starting materials or growth promoters and nutrients during the cultivation. The vessels required for the culture are termed fermenters.

In the processing that follows fermentation, conventional methods such as filtration, extraction, distillation, adsorption, freeze-drying, recrystallization, *etc.*, are used to isolate the products from the culture broth and to purify them.

## Provision of Production Facilities

Low-pressure steam at a maximum pressure of 4 atm gage is adequate for the sterilization of the nutrient solutions. Significantly, however, marked peaks occur in the steam consumption when discontinuous sterilization is used. For heating the nutrient broth to 121 °C in about 1 hour, a 55 m³ fermenter [*] requires 8 to 10 tons of steam. The heating time may be increased, but then poor use is made of the fermenter capacity.

The use of cooling towers for the production of cooling water is generally adequate in Central Europe for growth temperatures of 28 °C or more. In small cooling-water systems, however, the hot water at about 90 °C proceeding from the normal sterilization must not be passed directly into the cooling tower, which is normally not designed for such a high feed temperature. In this case an additional balancing tank is required.

The nutrient solutions are normally prepared with drinking water, the purity of which, even in the biological respect, is constantly supervised. Since disturbances of the biological development, and hence of production, are always to be expected, chemical contamination of the water is very unlikely to be the cause of such disturbances if tap water is used. The chlorine in the mains supply of large towns has not so far been found to interfere, since it escapes during the sterilizing process.

The use of cold water (about 4 °C) for the termination of a reaction is generally unnecessary. With unstable fermentation products, the capital saved on the cooling plant can be much better used to ensure rapid processing.

Modern fermentation plants are protected against explosion. Consequently, fermentative processes can often be stopped by the addition of even a combustible extracting agent. Further, the quantities of solvents required for the addition of starting materials to the culture are generally so large that protection against explosion must be provided in any case.

The oxygen required for the respiration of the microorganisms is introduced as compressed air, the carbon dioxide formed being removed with the exhaust air. In strictly anaerobic processes, the oxygen must be displaced by nitrogen. In the case of facultative anaerobes, the oxygen in and above the liquid is consumed first.

The required pressure of air is determined mainly by the hydrostatic pressure of the column of liquid in the fermenter, the filter resistance, and the pipeline resistance. The pressure drop across a glass-wool filter is about 0.1 to 0.5 atm. No special resistance is normally provided in the air-distributing system of the fermenter. For 50 to 100 m³ fermenters, this gives a preliminary air pressure of 1.5 to 3 atm gage. The turbocompressors used in the yeast industry cannot be used at these relatively high pressures. However, the quantities of air required are not generally as large as in the yeast industry. Consequently screw compressors, which are available in all the required power outputs, are very well suited for the pressure range indicated. These compressors deliver oil-free air, and unlike piston-type compressors, they have no parts that are subject to wear, apart from the ball bearings.

[17] Microorganisms can be obtained from the following collections: 1. American Type Culture Collection (ATCC), Rockville, Maryland (U.S.A.); 2. Agricultural Culture Collection, Northern Utilization Research and Development Div. (NRRL), Peoria, Illinois (USA); 3. Centraalbureau voor Schimmelcultures (CBS), Baarn (Netherlands).

[18] *D. Gröger*, Pharmazie *18*, 728 (1963).

[*] The volumes quoted for fermenters are net volumes (content of liquid). The gross volume is 10 to 15 % higher.

## Production and Sterilization of the Nutrient Solution

The principal components of the nutrient solution are glucose (solid or as syrup), corn steep liquor, yeast extract, malt extract, molasses, soybean meal, inorganic phosphates, inorganic nitrates, and metal salts. The simplest method of preparing and sterilizing the nutrient solution is to fill the fermenter with water, add the nutrient components, and heat at 120 °C for 20 to 40 minutes. Sterile compressed air must be supplied during cooling. Otherwise, non-sterile air is sucked through leaks owing to the decrease in pressure following the condensation of steam. The nutrient solution may be heated (a) by direct injection of steam, in which case the water that condenses is lost as far as the boiler-house is concerned, or (b) by indirect heating with a steam coil, in which case the time required for heating is considerably increased. In case (a), the dilution with condensed water must be taken into account when the fermenter is being charged with water and nutrients.

Continuous sterilization is preferred on the grounds of energy saving. This gives a 70 to 80 % saving in steam and cooling water, and avoids large peaks in consumption. The possibility of continuous sterilization depends on the fact that the sterilization time at 120 °C is about 20 min, whereas at 135 °C only 4 to 8 min are required [19,20]. At the same time, the short-time sterilization should be a very mild treatment to ensure that decomposition is only slight, and hence that the solution obtained will have a particularly high content of thermally labile nutrients.

Figure 1 shows the flow sheet of a continuous sterilization plant. The liquid nutrients are added by weight. The water required to give a nutrient solution having a concentration of 10 to 50 times that used in the transformation is placed in the mixing vessel, and is pumped through a solid elevator by a circulating pump. The liquid or solid nutrients are introduced into the hopper of the solid elevator, and are transported and mixed by the water jet.

Acid or alkali is added so that the pH of the nutrient solution after sterilization favors the development of the microorganisms.

A dosing pump is used to convey the concentrate into the transfer vessel of the sterilization plant, where it is mixed with the required amount of water taken directly from the mains supply. The resulting solution, which is now at the correct concentration, is preheated in the heat exchanger I by the solution that has already been sterilized, the temperature of which is about 135 °C. In the heater, the preheater solution is brought to the sterilization temperature with steam. The solution is kept at the sterilization temperature for a predetermined average time by introduction at a constant rate into a heat reservoir, which consists of a pipe coil of suitable dimensions. The sterile nutrient solution flows through the heat exchanger II and the cooler I, which cools it to the desired final temperature, and it then passes into the fermenter.

The effectiveness of the continuous sterilization process depends on the fact that if the sterilization temperature is not maintained, no non-sterile solution can enter the sterile part of the plant. This is ensured by monitoring the temperature downstream from the heater; if the temperature becomes too low, magnetic valves are operated to prevent the entry of nutrient solution into the heat retainer, with the result that the solution is recirculated. The water supply is then cut off by a float valve and the dosing pump switched off by a maximum-level electrode in the transfer vessel. In this case the passage of the solution through the plant cannot begin again until the correct sterilization temperature has been reached.

The sterilization efficiency of a plant of this type is best checked by filling a large fermenter with sterilized nutrient solution, which is allowed to stand for 40 to 60 hours at about 30 °C without inoculation. If, for example, the sterilization plant leaves one living microorganism per liter, this cannot be detected by the normal sterility controls (tube or plate test). When allowed to stand in the fermenter, however, the remaining microorganisms propagate and can be detected by the usual methods. This also provides a check on the sterility of the fermenter itself.

A third method for the production of the nutrient solution consists in the sterilization of the nutrient concentrate by heat in the fermenter. The water used for sub-

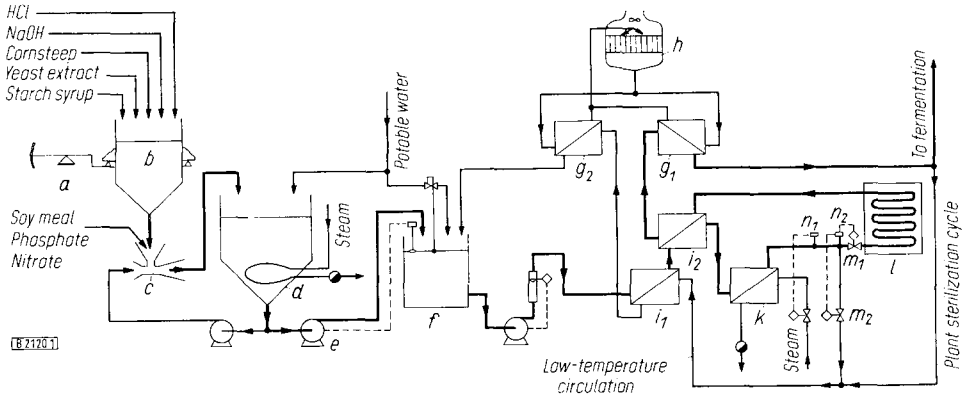



Fig. 1. Flow sheet of a continuous sterilization plant.
*a* balance, *b* measuring vessel, *c* solid elevator, *d* mixing vessel, *e* dosing pump, *f* transfer vessel, $g_1$, $g_2$ coolers I and II, *h* cooling tower, $i_1$, $i_2$ heat exchangers I and II, *k* heater, *l* heat reservoir, $m_1$, $m_2$ magnetic valves, $n_1$, $n_2$ temperature gauge.

[19] *V. F. Pfeifer* and *C. Vojnovich*, Ind. Engng. Chem. *44*, 1940 (1952).

[20] *F. U. Deindoerfer*, Appl. Microbiol. 7, 264 (1959).

sequent dilution is freed from microorganisms by sterile filtration and added to the concentrate. Sterile filters with filtration rates of 20 to 40 $m^3$ of water per hour (filter area 30 to 50 $m^2$) are arranged in series. However, the reliability of the filtration depends on the absence of pores and cracks in the filter layers, for which there is no reliable check method. It must also be borne in mind that all nutrient solutions have a certain limiting concentration beyond which sterilization by heat leads to excessive decomposition, with the result that the growth of the microorganisms is inhibited. Frequently, however, some thermal decomposition is essential for optimal culture conditions [21], and heat sterilization is absolutely necessary in these cases.

In a fourth method of sterilization, 0.05 to 1 % of β-propiolactone is added to the nutrient solution. Even spores are destroyed within 1 to 3 hours. The propiolactone is converted more or less rapidly (depending on the temperature) into harmless propionic acid, so that the solution can then be inoculated. The use of β-propiolactone in large quantities of liquid is costly; it is therefore particularly suitable for smaller quantities of solution where sterilization by heat or by filtration is not possible [21, 22].

## Operation and Construction of the Fermenter

The flow sheet of a fermentation plant is shown in Figure 2. Large production fermenters are linked with seed tanks and second-step seed tanks, the main difference between these being their capacity, cf. Figs. 3 and 4. The inoculum, which is prepared in the laboratory, is introduced under sterile conditions into the seed tank, which has a capacity of 250 to 5000 *l*. After a propagation time of 10 to 80 hours, depending mainly on the microorganism used, this culture broth is pumped, or forced with compressed air, through pipes that have previously been sterilized with steam into the next larger fermenter, which contains sterile nutrient solution. The volume of the preculture is about 10 % of that of the following stage. This procedure leads to a reduction of the proagation time and to optimal utilization of the plant. The growth of mycelium in a 50000 *l* fermenter with and without propagation in seed tanks is shown in Figure 5. The quantity produced in a given time with precultures is about twice as large, since the time required for the cultivation of the microorganisms in the reaction tank is shorter. Similar diagrams are obtained when instead of the weight of fungus the bacteria count per ml is given for bacterial fermentations.

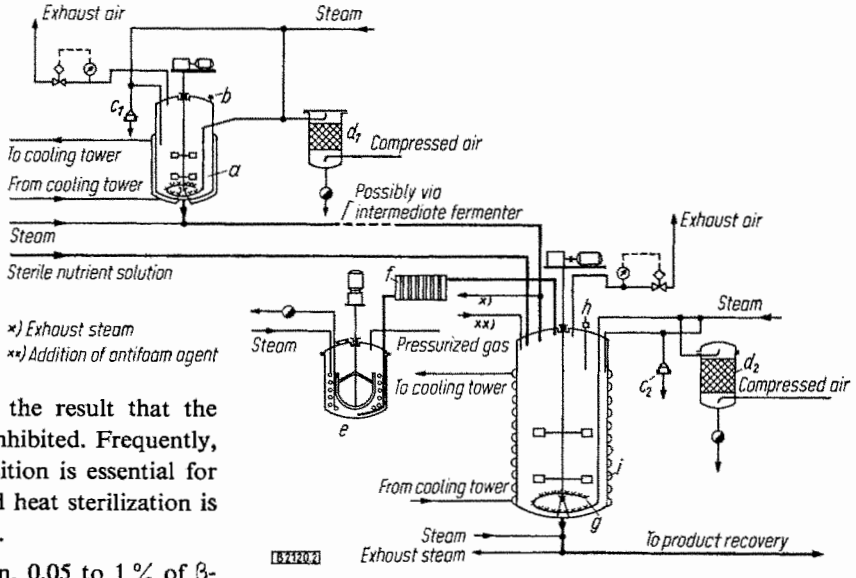



Fig. 2. Flow sheet of a fermentation plant.
*a* seed tank, *b* inoculation port, $c_1$, $c_2$ sampling devices, $d_1$, $d_2$ filters, *e* substrate container, *f* sterile filter, *g* reaction tank, *h* electrode for foam control, *i* cooling coils.

Fig. 3. Seed tank.

The fermenters and cooling coils must be made of chrome-nickel steel, irrespective of their size. Many fermentations must be carried out at relatively low pH. Moreover, when indirect sterilization is used, the cooling coils are corroded by the condensate so severely that they have to be replaced after 5 to 7 years when made of normal steel.

The diameter: height ratio of the fermenter is between 1:2 and 1:5. A slim design leads to a relatively long residence

[21] *P. Himmelfarb, R. B. Read, et al.*, Appl. Microbiol. *9*, 534 (1961).

[22] *C. W. Bruch* and *M. G. Koesterer*, Appl. Microbiol. *10*, 123 (1962).

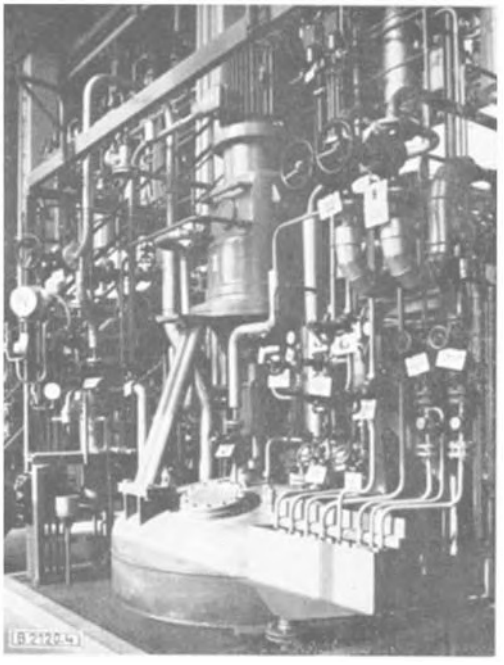


Fig. 4. Reaction tank.

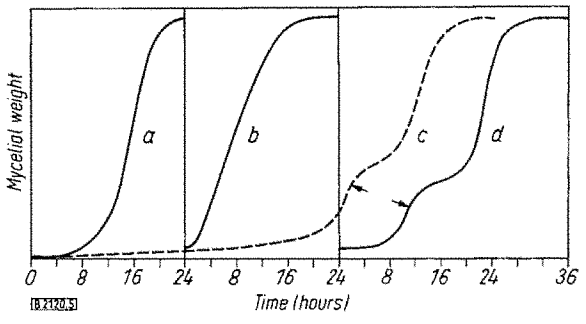



Fig. 5. Biological development in the fermenter as a function of time. The arrows denote the times of substrate addition.

*a* in the 250 *l* seed tank, *b* in the 4000 *l* second-step tank, *c* in the 55000 *l* reaction tank (direct inoculation, mycelial development 72 h), *d* in the 55000 *l* reaction tank (mycelial development using two precultures complete after 32 h).

time of the air in the liquid, and so favors gas exchange. Moreover, in this design the quantity of air passing per unit of surface area is relatively high, so that strong turbulence can be produced, with a consequent saving in stirring. On the other hand, a tall column of liquid requires greater compression work in the production of the compressed air.

The temperature is generally controlled by adjustment of the cooling-water supply, since the heat produced by stirring and by the biological process must be dissipated. It is impossible to specify accurately the cooling surface of a fermenter, since the temperature of the cooling water, the sterilization process, the cultivation temperature, the energy supplied by stirring, and the nature of the microorganisms used can differ widely in the various processes. Fermenters with capacities of up to 500 *l* are normally fitted with a cooling jacket, while internal cooling coils (cf. Fig. 6) or welded half-tubes are used in larger units. Though optimal cooling areas can be obtained with internal cooling coils, these are sometimes undesirable, since they divide the space inside the fermenter. Unfavorable circulation conditions can arise between the cooling coils and the walls of the fermenter, leading to poor aeration and temperature control when fungi are being cultivated without stirring. In yeast fermentations, the heat of reaction can be so great that the culture broth must be pumped through another cooler for additional cooling. A cooling area of 50 to 70 $m^2$ may be taken as an average for a 55 $m^3$ fermenter. With a coolant temperature of 14 °C and a water consumption of 140 to 200 $m^3$ this fermenter can be cooled from 120 °C to a working temperature of 30 °C within 4 to $2^1/_2$ hours without stirring. The consumption of cooling water for the dissipation of the heat of fermentation from a 55 $m^3$ fermenter is 0.5 to 2 $m^3$/hour for bacteria and 2 to 10 $m^3$/hour for fungi.

Fig. 6. Interior of a reaction tank.

Aeration is generally effected with pipe coils fitted at the base of the fermenter, with suitable holes having a diameter of at least 3 mm. The volume of air required per minute is 0.05 to 1.5 times the volume of the nutrient solution, depending on the nature of the fermentation. The air is sterilized by filtration through layers of glass wool or active charcoal, which are themselves sterilized with steam before each run. The air velocity in glass-wool filters should be about 0.3 to 0.8 m/sec [23–26].

The air bubbles can be dispersed by stirring, and the resulting increase in surface area leads to an increase in the oxygen supply to the fermenter. Flat-blade turbine impellers with a peripheral velocity of 2.5 to 4.5 m/sec are often used. Continuous adjustment of the stirrer speed is unnecessary in production fermenters, and reasonable latitude can be achieved by the use of V-belt pulleys of different sizes. Excessive stirring can lead to failures, particularly in fungal fermentations when the mechanical stresses on the mycelium are too great.

Foaming, which is strongly dependent on the nature of the nutrient solution, the microorganism, and the stage of development of the culture, must in most cases be controlled for at least part of the time by the addition of antifoam agents. Otherwise the loss of liquid is high, or the air supply for aeration must be reduced to such an extent that the growth of the microorganisms is inhibited by lack of oxygen. Examples of antifoam agents used are oils (lard oil, soybean oil), fatty acid derivatives, silicones [29], and polypropylene oxide or

[23] *A. E. Humphrey* and *E. L. Gaden*, Ind. Engng. Chem. *47*, 924 (1955).

[24] *E. L. Gaden* and *A. E. Humphrey*, Ind. Engng. Chem. *48*, 2172 (1956).

[25] *E. Humphrey*, Ind. Engng. Chem. *52*, 62 (1960).

[26] *S. Aiba*, J. gen. Microbiol. *8*, 169 (1962).

[27] *G. Zalay*, *I. Gebhardt*, *et al.*, Zbl. Bakteriol., Parasitenkunde, Infektionskrankh. Hyg. I. Abt. Orig. *197*, 114 (1965).

[28] *A. J. C. Olsen*, Chem. and Ind. *1960*, 416; *U. N. Sher*, Chem. and Ind. *1960*, 425.

[29] Chem. Engng. *65*, 11, 54 (1958).

polyethylene oxide derivatives; large quantities of these agents can interfere both with the aeration and with the subsequent isolation of the fermentation products. The foam height is controlled by electrodes which either give a signal to the operator or cause automatic addition of antifoam agent, depending on the frequency of the additions. In some cases the oils added also act as nutrients.

The substrates, *i.e.* the chemical precursors of the desired end products or the special nutrients or growth promoters, are added during the culture time from a substrate container of a suitable size fitted with a stirrer and heating and cooling equipment for the dissolution of the substances. The solution is transferred to the fermenter by means of compressed gas or by pumping. Organic solvents that are frequently used are methanol, ethanol, dimethylformamide, methyl cellosolve, and acetone. The solution is most easily sterilized by passage through a layered filter. If filtration is impossible, *e.g.* in the case of suspensions, other sterilization processes must be used.

The sterility of a fermenter depends primarily on the preculture and on the air filter. However, structural details of the fermenter are also involved. One source of contamination is fine fissures or gaps (*e.g.* flange seals) filled with nutrient solution and microorganisms. If the gaps or flange seals cannot be properly heated during sterilization, it must be expected that the surviving microorganisms will subsequently propagate and grow into the inertior of the fermenter. There is also a danger that the microorganisms in somewhat cooler parts of such gaps may, by exposure to a sterilization temperature that is only slightly too low, become adapted to higher sterilization temperatures and longer times. Further, air-filled cavities can sometimes be formed in these gaps. However, the times and temperatures normally used in the sterilization of fermenters are valid only for an atmosphere of pure steam, and may be increased by up to 200 % in air. Such sources of contamination must be avoided as far as possible in construction. Where flanges are used, additional steaming is sometimes required to ensure sterility. For example, in fermenters having a drain valve in the base, the resulting pocket of liquid cannot normally be brought to the sterilization temperature. This part of the fermenter must therefore be specially heated by the introduction of steam through an open tube that reaches to the lowest point in the pocket; the steam must also be led up to the valve from the outside of the discharge pipe.

Non-sterility can have the following disadvantages, either individually or simultaneously:

1. The normal yield is not obtained.

a) the substance to be transformed by fermentation may be transformed too slowly or only partially, or it may be decomposed.

b) The product formed may be destroyed again.

2. Excessive foaming leads to a need for extra antifoam agent or reduction of the essential aeration.

3. The filtration of the broth before recovering is upset by the formation of slimy substances or by partial decomposition of the mycelia.

4. Extraction is made difficult by formation of an emulsion.

5. The end-products are contaminated with toxins.

The fermentative transformation is controlled analytically. The sterility and the development of the microorganisms are also checked. Since the processes take a long time, the temperature, the pressure or quantity of air, and if necessary the pH are plotted by a pen recorder. The fermentation times range from 8 to 150 hours. No general rules can be given regarding yields and throughputs. In the transformations of steroids, for example, the yields are often around 90 %, and from 10 to 800 kg of pure product are obtained from a 55 $m^3$ fermenter.

The advantages of continuous operation, such as economy of labor, optimal utilization of the fermentation capacity, and faster transformation owing to the fact that the most favorable physiological conditions of the microorganisms are maintained, are subject to the following conditions and disadvantages: The microorganisms must not lose their original enzymatic properties at faster rates of multiplication. However, highly cultivated strains very often degenerate on uninterrupted cultivation. Moreover, the slightest non-sterility causes much greater interference, since this cannot be eliminated. Where several substances are being produced simultaneously it is also more difficult to adapt production to suit the market. Further, owing to the greater research investment required, continuous operation only lends itself to long-term large-scale production. Consequently, continuous fermentation processes are not yet commonly used in industry [30].

## Isolation of the Fermentation Products

Whereas the fermentation scheme can be used for all fermentation processes, only two isolation methods can be outlined in this paper, owing to the wide range of substances that may be involved; however, the processes described include the essential steps. The first process can be used in most steroid transformations and for some antibiotics, such as penicillin. The second method is suitable *e.g.* for the isolation of streptomycin. Sterility is not absolutely essential for the processing, provided that the products are not to be isolated for direct consumption.

### Method I

After fermentation the mycelium is separated by filtration. Filtration rates of 2 to 5 $m^3/h \cdot m^2$ are obtained with a vacuum rotary filter (cf. Fig. 7), which uses a cord take-off in the case of easily filtered mycelium. If the mycelium contains large quantities of slimy matter, so that filter aids (*e.g.* celite) have to be used, the filtration rate is about 0.5 to 2 $m^3/h \cdot m^2$. Depending on the

[30] More comprehensive articles: [28, 31–36].

[31] *J. J. Stefaniak, F. B. Gailey, et al.*, Ind. Engng. Chem. Med. E. *38*, 666 (1946).

[32] *C. G. Heden*, Nordisk Med. *60*, 1090 (1958).

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[36] *W. Saenger*, Pharmazie *2*, 193 (1947).

Fig. 7. Rotary filter plant.

process, the mycelium, the filtrate, or both are then processed further. Figure 8 shows the flow sheet of such a process, in which the product is isolated both from the mycelium and from the culture broth.

out of the mycelium. When the extraction is complete, the mycelium is freed from adhering extraction solvent by distillation.

The desired product is transferred from the culture filtrate, or from the culture broth in the case of bacterial fermentations, into a water-immiscible solvent (*e.g.* methyl isobutyl ketone, amyl or butyl acetate) by countercurrent extraction. This operation is nearly always carried out in multistage centrifugal extractors. The construction of the three principal types is shown in Figure 9. Type I, which has a horizontally rotating drum, has the advantage of considerable latitude with regard to the drum size, owing to its double bearing, so that total throughputs of up to 100 m³/hour are possible with the largest units of this type. The disadvantage that the drum had to be cleaned and inspected through only a few small holes has been eliminated in recent designs. The drum is no longer completely welded together, but is fitted with a screw cover. Type II

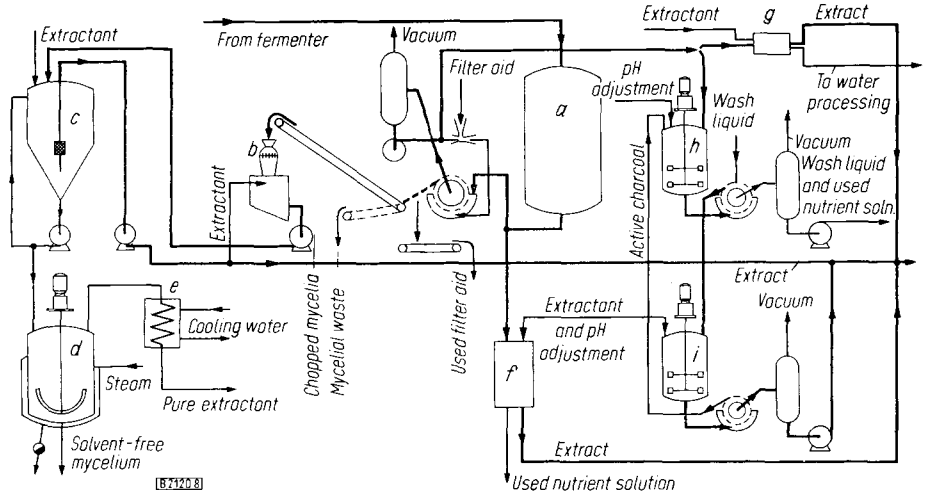


Fig. 8. Flow diagram of a recovery plant for fermentation products from mycelium and culture filtrate.

*a* reservoir for culture broth, *b* chopper for mycelia, *c* extraction tank, *d* distillation vessel, *e* cooler, *f* ion exchanger, *g* centrifugal extractor, *h* adsorption vessel, *i* desorption vessel.

After separation by filtration, the mycelium is chopped and pumped into the extraction tank with the extracting agent. The mycelial extract is filtered through a mesh, and the extraction is repeated. In the isolation of steroids, for example, hot extraction is not recommended, since too many impurities are then dissolved

operates on the same principle but has a vertical axis and is easily dismantled for cleaning. However, the maximum throughput is only 20 m³/hour. Type III is particularly useful when small quantities of solids are to be separated from the culture broth during the extraction. However, the maximum throughput with the largest three-stages type is only 6 to 8 m³/hour.

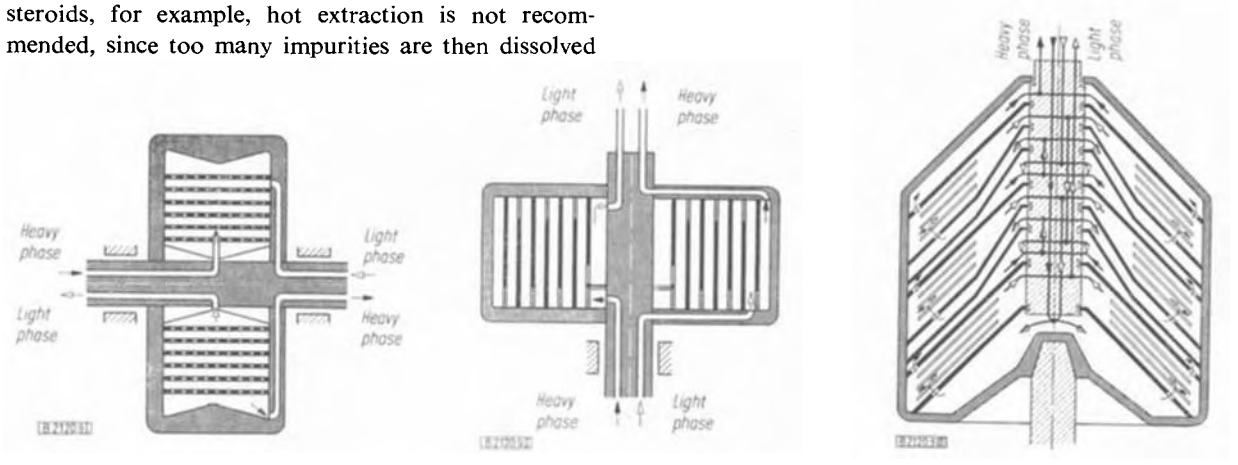


Fig. 9. Centrifugal extractors (Types I to III).

In favorable cases the substance to be isolated can be concentrated by a factor of 15 during the extraction. At the same time, many components of the nutrient solution and many metabolites are retained in the aqueous phase. Penicillin, which contains a carboxyl group, can be obtained pure by repeated pH-controlled partitioning between water and organic solvent, followed preferably by freeze-drying from an aqueous concentrate.

In the case of steroids, the extract obtained is evaporated under moderate vacuum until crystallization occurs. The thin-film evaporators with a rotating wiper system, which have been developed over the past 15 years, are particularly suitable for this purpose. These evaporators have a very high distillation capacity. The substance is heated for only 10 to 30 sec, and the movement of the wipers over the heating surfaces prevents incrustation by crystals that have separated out. The heating surfaces can be satisfactorily cleaned with weighted bronze wipers. The crystal suspension obtained in this way by single-stage or multi-stage evaporation is generally pumped directly into centrifuges without cooling. Depending on the process in question, the resulting crude crystals contain from 40 to 92 % of the desired substance, which is dried if necessary and purified by the usual methods.

### Method II

The microorganisms are removed from the culture broth with or without filtration aids. The pH is adjusted to a predetermined value if necessary, and the filtrate is then treated with active charcoal or ion exchangers. The added solids are filtered off and washed. After readjustment of the pH, the desired substance is desorbed, and the solids removed by subsequent filtration are returned to the process. The end-product is obtained from the extract in more or less pure form by evaporation, spray drying, or precipitation.

At high streptomycin contents, it is possible to dispense with the preliminary filtration, the original culture broth being passed directly through modified ion-exchange columns, where the active substance is absorbed [32].

The relatively large quantities of waste water from the extraction generally still contain some extraction solvent. For example, the solubility of methyl isobutyl ketone in water is 2 wt-%. In this case the solvent can be readily recovered as an azeotropic mixture (b.p. 87.9 °C, 24.3 wt-% of water). The waste water to be purified is passed, with heat exchange, to a single column (cf. Fig. 10), into which enough steam is blown to cause about 5 vol-% to distil over. The distillate separates into two phases in a settling vessel, and the

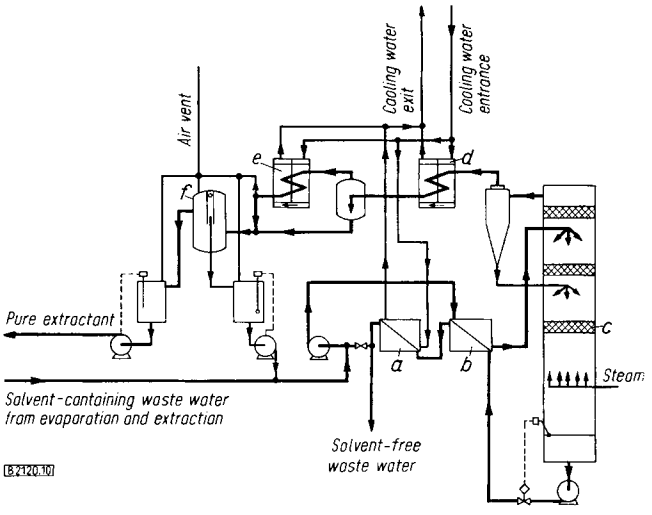


Fig. 10. Diagram of the waste-water treatment.
*a* cooler, *b* heat exchanger, *c* column, *d* condenser, *e* after cooler, *f* separation vessel.

upper phase is returned to the extraction-solvent reservoir. The aqueous phase, which is saturated with methyl isobutyl ketone, is returned to the waste-water distillation unit. The waste water residue from the column is used for heat exchange and is then passed into the sewage system (methyl isobutyl ketone content 0.01 %). With a plant of this type, 20 to 40 $m^3$ of waste water per hour can easily be cleaned, and the value of the solvent recovered far outweighs the cost involved.

The microorganisms obtained as by-products can sometimes be used as feed additives. In most cases, however, they present an appreciable waste and sewage disposal problem, except where large biological sewage farms are available [37].

*The present article is based partly on our own industrial experience. The authors are grateful to Ing. K. Brinkmann and Ing. K. Weber for their substantial design contribution to the construction of fermentation plants.*

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Translated by Express Translation Service, London

[37] More comprehensive articles: [32–36].

## New Synthesis of Derivatives of Isoquinoline and 1,3-Benzothiazin-4-one

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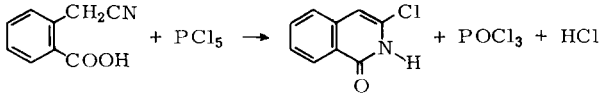
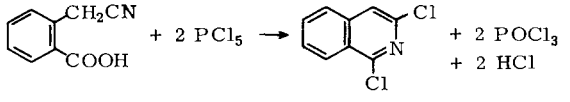
When *o*-cyanomethylbenzoic acid *(1)* is treated with phosphorus pentachloride, 3-chloro-1-isoquinolinol *(2)* is at once obtained. If the reaction is carried out with 2 moles of phosphorus pentachloride in phosphorus oxide chloride as solvent, 1,3-dichloroisoquinoline *(3)* is formed by chlorination of the intermediate *(2)*.

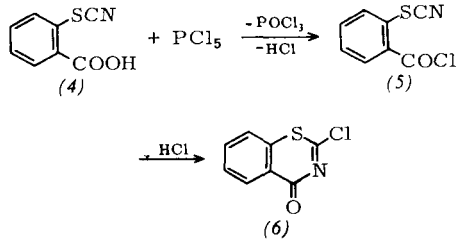


*(1)* *(2)*



*(1)* *(3)*

In order to determine the course of reaction we treated *o*-thiocyanatobenzoic acid *(4)* with phosphorus pentachloride under mild conditions. The *o*-thiocyanatobenzoyl chloride *(5)* [1] first formed then was cyclized to 2-chloro-1,3-benzothiazin-4-one *(6)* in the presence of hydrogen chloride at 60 °C. However, cyclization does not occur in the absence of hydrogen chloride. It seems to follow that cyclization of ω-cyanocarbonyl chlorides depends on acylation of the unstable imide chlorides formed as intermediates [2, 3].



*(4)* *(5)* *(6)*

*3-Chloro-1-isoquinolinol (q)* [4]

6.8 g (0.033 mole) of $PCl_5$ is added to 4.8 g (0.03 mole) of *o*-cyanomethylbenzoic acid in 25 ml of methylene chloride and the mixture is stirred for 2–3 hr first at 0 °C and then at room temperature, then kept overnight. The methylene chloride is distilled off and the residue recrystallized from water. Yield: 5.0 g (94 %), m.p. 218 °C.

*1,3-Dichloroisoquinoline (3)* [4]

A solution of 42.0 g (0.20 mole) of $PCl_5$ in 80 ml of $POCl_3$ is treated slowly with 16.1 g (0.1 mole) of *o*-cyanomethylbenzoic acid. The mixture is stirred for 2 hr at room temperature and 2 hr at the boiling point. The $POCl_3$ is distilled off at atmospheric pressure and the residue recrystallized from alcohol. Yield: 18.5 g (94 %), m.p. 120 °C.

*o-Thiocyanatobenzoyl chloride (5)* [1]

To a slurry of 7.7 g (0.043 mole) of *o*-thiocyanatobenzoic acid in 50 ml of $CCl_4$, is added 9.0 g (0.043 mole) of $PCl_5$ and the mixture is stirred for 2 hr at 0 °C and 6 hr at room temperature. The $CCl_4$ and the $POCl_3$ formed are distilled off in a vacuum, and the solid residue is taken up in benzene and precipitated with light petroleum. Yield: 7.8 g (92 %), m.p. 104–106 °C.

*2-Chloro-1,3-benzothiazin-4-one (6)*

A solution of 0.7 g (0.0035 mole) of *o*-thiocyanatobenzoyl chloride in 3 ml of dibutyl ether is treated with a saturated solution of HCl in diethyl ether. The mixture is heated for 4 hr at 60 °C. The product crystallizes on cooling. Yield: 0.5 g (71 %), m.p. 115–117 °C.

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Publication delayed at the author's request

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[2] *E. Allenstein* and *P. Quis*, Chem. Ber. *97*, 3162 (1964).
[3] *F. Klages* and *W. Grill*, Liebigs Ann. Chem. *594*, 21 (1955).
[4] *S. Gabriel*, Ber. dtsch. chem. Ges. *19*, 2354 (1886).

## Butadienedimethylaluminate Complexes

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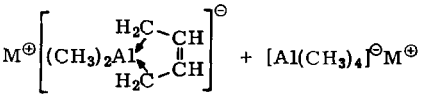
Butadiene and its homologues react with alkali metals (M = Li or Na) with formation of salts $M_2^{\oplus}[C_4H_6]^{2\ominus}$, which immediately add further diolefin stepwise [1]. The butadiene dianion can be trapped as 2-butene by sufficiently acidic reagents, *e.g. N*-methylaniline.

On reaction of butadiene with alkali metal in an ether [$(CH_3)_2O$, THF, $(C_2H_5)_2O$] in the presence of an amount of trimethylaluminum-ether adduct equivalent to the metal, the butadiene dianion $C_4H_6^{2\ominus}$ probably forms an adduct *(1)* with the dimethylaluminum cation present in the dissociation-equilibrium mixture from trimethylaluminum [2, 3]. Suitable reaction conditions are alkali metal: $Al(CH_3)_3$:$C_4H_6$ = 2:2:1, −30 to +20 °C.



*(1)* *(2)*

This complex formation protects the dianion $C_4H_6^{2\ominus}$ from further reaction with butadiene. When the experiment is conducted in tetrahydrofuran with Li or Na, the product *(1)* is precipitated as large colorless crystals and can be purified by recrystallization from a small quantity of THF. The alkali tetramethylaluminate *(2)* formed in equivalent amount can be isolated by distillation of the solvent from the first filtrate, finally at 100 °C/$10^{-3}$ mm. The reaction with butadiene derivatives resembles the formation of alkali metal naphthalenedialkylaluminate and tetraalkylaluminate from alkali metal, naphthalene, and trialkylaluminum in ethers [4].

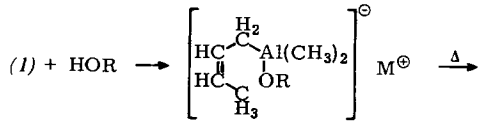
The compound *(1)*·4 THF readily loses 3 moles of THF in vacuum ($10^{-3}$ mm); at 90 °C under the same sonditions all the bound THF is lost. Compound *(1)* is insoluble in aliphatic hydrocarbons and benzene; it decomposes above 150 °C without melting. Its infrared spectrum includes a sharp C=C stretching band at 1580 $cm^{-1}$, this being at longer wavelength than for butadiene (1597 $cm^{-1}$) and indicating a strongly polarized double bond. The $^1$H-NMR spectrum of a solution of *(1)* in THF renders the proposed structure very probable [5]: it contains a well resolved triplet at $\tau$ = 4.86 for the two olefinic protions (a), a moderately split doublet at $\tau$ = 9.46 for the $CH_2$ protons (b) (intensity ratio a:b = 2:3.9), and a singlet at $\tau$ = 11.21 for the $CH_3$ protons (c) (intensity 6.5). For the analogous compounds to *(1)* from 2,3-dimethyl-1,3-butadiene the signal for (b) changes to a singlet at $\tau$ = 9.81 [$Si(CH_3)_4$ as internal standard: $\tau$ = 10].

The bonds[*] between the dianion $C_4H_6^{2\ominus}$ and the $[(CH_3)_2Al]^{\oplus}$ cation are very reactive; on oxidation with dry $O_2$ they are preponderatingly attacked before the Al–$CH_3$ bonds, butadiene being regenerated:

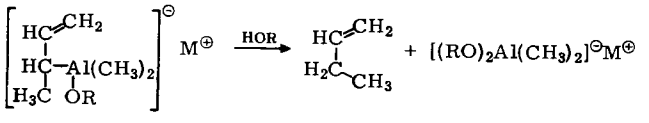
$$(1) + {}^1/_2\,O_2 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + [:\ddot{O}{\rightarrow}Al(CH_3)_2]^{\ominus}Na^{\oplus}$$

(3)

The structure of the oxidation product *(3)* has not been conclusively elucidated. On alcoholysis of the Na compound *(1)*, 1-butene and at most 1 to 4 % of 2-butene are formed alongside methane; the proportion of 2-butene rises to 15 % for the Li compound. *Hoberg*[6] has recently reported an allylic rearrangement of aluminum compounds of the type R'R''Al–$CH_2$–CH=CHR to R'R''Al–CHR–CH=$CH_2$; an apparently analogous rearrangement by way of *(4a)* and *(4b)* evidently occurs on alcoholysis of compounds *(1)*:



(4a)



(4b)

The following considerations are also in favor of a reaction *via (4a)* and *(4b)*:

(a) On the basis of structure *(1)* (which is strongly indicated by the NMR spectra), only 1-butene can be formed if a rearrangement intervenes on hydrolysis. 2-Butene does not rearrange to 1-butene under the reaction conditions.

(b) Hydrolysis of compounds *(1)* with $D_2O$ affords $CH_2{=}CH{-}CHD{-}CH_2D$. The $CH_2D$ group can be identified mass-spectroscopically, and the CHD group infrared-spectroscopically. The NMR spectrum confirms the appearance of [3,4-$D_2$]-1-butene.

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[4] *H. Lehmkuhl*, Angew. Chem. *77*, 623 (1965), Angew. Chem. internat. Edit. *4*, 600 (1965).

[5] We thank Dr. *E. G. Hoffmann* for determining the NMR spectrum.

[*] The ionic structure seems justified because groups R (*e.g.* $CH_3$) that certainly are covalently bound to Al react with insertion of oxygen, yielding >Al–O–R, and, on the other hand, compounds such as naphthalenesodium that are certainly to be formulated as ionic are cleaved by oxygen with regeneration of the original hydrocarbon.

[6] *H. Hoberg*, Angew. Chem. *78*, 492 (1966), Angew. Chem. internat. Edit. *5*, 513 (1966).

## Preparation of Bis(dialkylcarbamoyl)mercury Compounds by Carbonylation in Amines

By Prof. U. Schöllkopf and F. Gerhart

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Although carbamoylmetal compounds containing σ-bonded carbonyl groups may play a decisive role in metal-catalysed carbonylation of amines[1], it has hitherto not been possible to isolate such compounds[2]. We have now found that stable bis(dialkylcarbamoyl)mercury compounds (see table) are formed in accordance with Equation (a) when mercury(II) acetate and a tenfold amount (by weight) of a secondary amine are shaken with carbon monoxide for several days at room temperature. The excess of amine is removed in a vacuum and the residue is crystallized from benzene, ether, or tetrahydrofuran.

| $R^1R^2NH$ | $p_{CO}$ [atm] | $R^1$ | $R^2$ | Yield [%] | M.p. [°C] | $\tilde{\nu}_{CO}$ [$cm^{-1}$] | τ (N–CH–) |
|---|---|---|---|---|---|---|---|
| Dimethylamine | 60 | $CH_3$ | $CH_3$ | 43 | 148–149 | 1555 | 6.72 (s), 6.10 (s) |
| Diethylamine | 1 | $C_2H_5$ | $C_2H_5$ | 64 | 138–139 | 1575 | 6.29, (q), 6.58 (q) |
| Methylbenzylamine | 1 | $CH_3$ | $CH_2C_6H_5$ | 67 | 138 | 1560 | 6.83, 6.98, 7.17, 7.22, 5.12, 5.26, 5.40, 5.43 (each s) |
| Pyrrolidine | 1 | $(CH_2)_4$ | | 45 | 96 | 1530 | 6.20, (t), 6.62 (t) |
| Piperidine | 1 | $(CH_2)_5$ | | 25 | 102 | 1555 | 6.26 (t), 6.47 (t) |
| Morpholine | 1 | $(CH_2)_2{-}O{-}(CH_2)_2$ | | 20.5 | 196 | 1560 | 6.26 (m), 6.38 (m) |

$$R^1R^2NH + Hg(OAc)_2 \xrightarrow{CO} R^1R^2N{-}OC{-}Hg{-}CO{-}NR^1R^2 + 2\,HOAc \qquad (a)$$

The bis(dialkylcarbamoyl) structure and σ-bonded carbon monoxide are indicated by the result of the bromine cleavage (see below), by the carbonyl infrared bands, and by the NMR signals of the N–CH-protons (see table).

The compounds are stable towards concentrated sulfuric acid but decompose in dilute mineral acids:

$$(R^1R^2NCO)_2Hg + 4\,HX \rightarrow 2\,CO + HgX_2 + 2\,R^1R^2\overset{\oplus}{N}H_2 + 2\,X^{\ominus} \qquad (b)$$

The rate of decomposition ($\tau_{1/2}$) depends on the nucleophilicity of the anion. Thus if $R^1{=}R^2{=}C_2H_5$ (0.03 M; pH 4.75), $\tau_{1/2}$ in the presence of 0.56 M $Cl^{\ominus}$, $Br^{\ominus}$, or $I^{\ominus}$ ions amounts to 26, 4.2, and 0.4 min, respectively.

As shown by experiments with bis(dimethylcarbamoyl)mercury and bis(diethylcarbamoyl)mercury, the amino or carbamoyl group can be transferred to other atoms. For instance, with acetyl chloride we obtained *N,N*-diethylacetamide (59 %), with benzyl chloride, *N,N*-dimethylbenzylamine (23 %), and with bromine, *N,N*-diethylcarbamoyl bromide (72 %)[3].

Received: April 26th, 1966 [Z 209 IE]
German version: Angew. Chem. 78, 675 (1966)

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[2] See, however, the synthesis of $R_2NCOFe(CO)_2C_5H_5$ from $NaFe(CO)_2C_5H_5$ and carbamoyl chloride derivatives: *R. B. King*, J. Amer. chem. Soc. *85*, 1918 (1963).

[3] Isolated as tetraethylurea after treatment with diethylamine.

## Synthesis of 6-Deoxy-D-gluco-dialdoheptose and Ring Closure to 8(a),10(a)-Dihydroxy-2,4,6-trioxaadamantane

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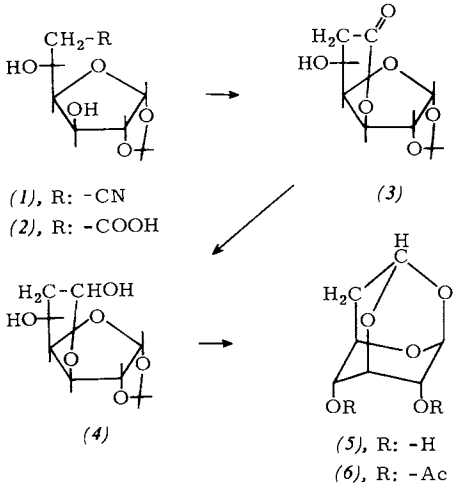
Universität Münster (Germany)

The discovery of a dioxaadamantane system in tetrodotoxin[1] suggested an examination of the cyclization of a correspondingly substituted polyhydroxy compound derived from a natural product. The pyranose ring of β-D-glucose in its 1C conformation carries the hydroxyl groups at C-1 and C-3 and the C-6 hydroxymethyl group in axial positions. A ring closure might therefore be possible after the introduction of a bridgehead atom.

The nitrile *(1)*[2] served as the starting material. Hydrolysis for 1 hour with 0.5 N NaOH at 100 °C gave the labile acid *(2)*, which was isolated in the form of its ammonium salt. This was transformed with a Linde molecular sieve 3 A in refluxing toluene to the lactone *(3)*, m.p. 111–113 °C, $\lambda_{CO}$ = 5.85 and 5.90 μ, in 49 % yield [based on *(1)*]. Reduction of *(3)* with diisobutylaluminum hydride[3] in tetrahydrofuran/toluene (1:2 v/v) afforded the hemiacetal *(4)*, m.p. 157–158 °C, yield 72 %, $[\alpha]_D^{20} = +62.6°$ (c = 1 in water), which exhibits no carbonyl absorption[4]. Careful hydrolysis of *(4)* with the acid form of Amberlite IR 120 in water gave two products: a hygroscopic powder of 6-deoxy-D-*gluco*-dialdoheptose, $[\alpha]_D^{20} = +49.0 \rightarrow +34.0°$ (c = 1 in water), which occurs in a cyclic form of as yet unknown ring size, and a 50 % yield of ether-extractable 8(a),10(a)-dihydroxy-2,4,6-trioxaadamantane *(5)*, m.p. 247–248 °C (slight sublimation), $[\alpha]_D^{20} = +4.1°$ (c = 1 in water) after purification by chromatography[5]; NMR spectrum (ppm in $D_2O$ with tetramethylsilane as external standard]: $>CH_2$, 2.23 (quartet);




*(1)*, R: -CN
*(2)*, R: -COOH
*(3)*
*(4)*
*(5)*, R: -H
*(6)*, R: -Ac

4–O–CH– between 4.02 and 4.52; 2 OH, 4.68; and 2 $\overset{O}{\underset{O}{>}}$CH–, 5.26 (multiplet). Compound *(5)* is not split by periodate. Its diacetyl derivative *(6)* has m.p. 99–100 °C and $[\alpha]_D^{20} = -29.2$ (c = 1 in chloroform).

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German version: Angew. Chem. *78*, 673 (1966)

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[2] *R. Grewe* and *G. Rockstroh*, Chem. Ber. *86*, 536 (1953).

[3] *A. Wettstein* and *J. Schmidlin*, German Published Patent Application 1190450 (April 8th, 1965), CIBA, Basel.

[4] 1,2-*O*-Isopropylidene-α-D-glucofuranuronolactone can be reduced under the same conditions to the hemiacetal of 1,2-*O*-isopropylidene-α-D-*gluco*-hexodialdofuranose, m.p. 124–125 °C, $[\alpha]_D^{20} = +34.8°$ (c = 1 in water).

[5] Chromatography on neutral alumina with chloroform as eluant.

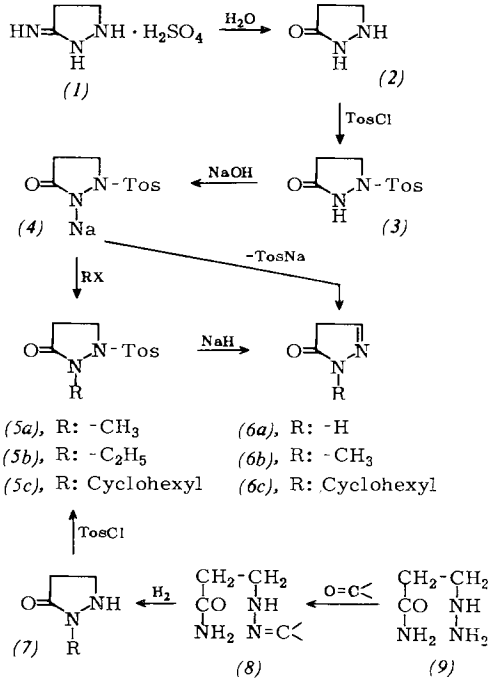
## Synthesis of 5-Pyrazolone and 1-Substituted 5-Pyrazolones [1]

By Dr. H. Dorn, Dr. A. Zubek, and Prof. G. Hilgetag

Institut für Organische Chemie, Deutsche Akademie der Wissenschaften, Berlin-Adlershof (Germany)

The classical syntheses[2] of 5-pyrazolone *(6a)* are unsatisfactory but have not yet been improved. A new, preparatively advantageous route to compound *(6a)* resulted when it was found that 3-iminopyrazolidinium sulfate *(1)*, which has recently become readily accessible[3], is quantitatively converted into the hitherto difficultly accessible compound *(2)* by heating of its aqueous solution. This product can be sulfonylated at one of its two N atoms by arenesulfonyl chlorides at 20 °C in methylene chloride containing 1 mole of pyridine as HCl-acceptor; *e.g.* with *p*-toluenesulfonyl chloride it gives 1-(*p*-toluenesulfonyl)-3-pyrazolidone *(3)*, m.p. 168–169 °C. With alkali hydroxides compound *(3)* gives alkali salts, *e.g.* *(4)*, which when heated in an indifferent solvent, *e.g.* toluene, at 105 °C for a few minutes lose 1 mole of sulfinate and give an excellent yield (90 %) of compound *(6a)*, m.p. 163–164 °C (m.p. of the 4-phenylazo derivative: 195–197 °C).

Sulfinate elimination from 1-substituted 2-tosyl-5-pyrazolidones *(5)* does not occur so easily, but yields of 70–90 % are obtainable by use of sodium hydride in boiling dioxane. This is a synthetic route to the hitherto unknown 1-alkyl-5-pyrazolones, *e.g.* *(6b)*, m.p. 108–100 °C (m.p. of the 4-phenylazo derivative: 115–117 °C), and *(6c)*, m.p. 122 to 123 °C (m.p. of the 4-phenylazo derivative: 98–99 °C). The intermediates *(5a)* [m.p. 128–130 °C, ν(CO) = 1707 $cm^{-1}$, ν($SO_2$ sym) = 1166 $cm^{-1}$, ν($SO_2$ asym) = 1352 $cm^{-1}$], *(5b)* (m.p. 126–127 °C), and *(5c)* (m.p. 118–120 °C) are accessible by alkylation of the alkali salts *(4)* or by treatment of the 1-substituted 5-pyrazolidones *(7)* with arenesulfonyl chlorides in methylene chloride at 20 °C with triethylamine as HCl-acceptor.




The only previously known 1-substituted 5-pyrazolidones *(7)* are those with R = aryl[4]. Representatives with R = alkyl have now been obtained by catalytic hydrogenation (Adams Pt, 20 °C, 200 atm, glacial acetic acid) of hydrazones *(8)* derived from 3-hydrazinopropionamide *(9)* and ketones, *e.g.* 1-cyclohexyl-5-pyrazolidone *(7)*, R = cyclohexyl, m.p. 84.5–85.5 °C (43 % yield).

The position of the tosyl substituent in *(3)* was proved by tosylation of 1-methyl-3-pyrazolidone to an isomer of *(5a)*, *i.e.* 2-(*p*-toluenesulfonyl)-1-methyl-3-pyrazolidone, m.p. 111 to 113 °C, ν(CO) = 1744 $cm^{-1}$, ν($SO_2$ sym) = 1159, 1175 $cm^{-1}$, ν($SO_2$ asym) = 1359 $cm^{-1}$.

Received: May 9th, 1966 [Z 232 IE]
German version: Angew. Chem. *78*, 676 (1966)

[1] Part 7 of Redox Cleavage of Sulfonamides. – Part 6: *H. Dorn, G. Hilgetag*, and *A. Zubek*, Chem. Ber. *99*, 183 (1966).

[2] *S. Ruhemann* and *K. J. P. Orton*, J. chem. Soc. (London) *1895*, 1002; *L. Knorr*, Ber. dtsch. chem. Ges. *29*, 253 (1896).

[3] *H. Dorn* and *A. Zubek*, Z. Chem. *5*, 457 (1965).

[4] *F. Stolz*, Ber. dtsch. chem. Ges. *28*, 630 (1895); *H. Dorn, A. Zubek*, and *G. Hilgetag*, Chem. Ber. *98*, 3377 (1965).

## Inner Phosphonium and Ammonium Dithiophosphonates

By Doz. E. Fluck[1] and H. Binder

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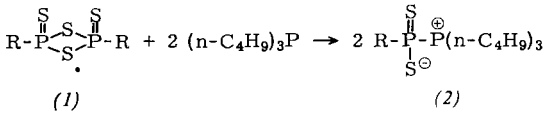
Universität Heidelberg (Germany)

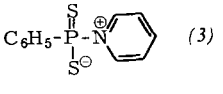
If a suspension of a perthiophosphonic anhydride in benzene, boiling in an $N_2$-stream, is treated with 2 moles of tri-n-butylphosphine (*e.g.* 5 g of $[C_6H_5PS_2]_2$ *(1)*, 5.9 g of $(n\text{-}C_4H_9)_3P$, and 50 ml of benzene), complete solution occurs in *ca.* 5 minutes. When the solution is cooled, or if necessary concentrated, colorless crystals separate which can be obtained analytically pure by washing with a little benzene. The resulting compounds *(2)* are to be considered as inner phosphonium salts stabilized by resonance. They are stable in air, and cryoscopic molecular-weight determinations in benzene, bromoform, and nitrobenzene indicate that they are monomeric. Their $^{31}P$-NMR spectra include two doublets with coupling constants characteristic of P–P linkages.



*(1)* *(2)*

| *(2)*, R = | M.p. (°C) | δ (ppm) | J (cps) |
|---|---|---|---|
| $C_6H_5$– | 97–98 | – 60.0; – 6.8 | 118 |
| *p*-$CH_3O$–$C_6H_4$– | 87 | – 60.0; – 7.4 | 109 |
| *p*-$C_2H_5O$–$C_6H_4$– | 85–87 | – 60.9; – 6.8 | 108 |

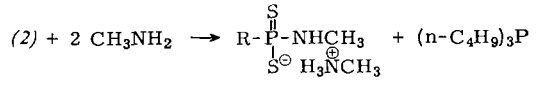
Strongly basic tertiary amines react like phosphines with perthiophosphonic anhydrides, giving inner ammonium salts. If, for instance, phenylperthiophosphonic anhydride is boiled for 1 hour with 10 moles of pyridine and the cooled solution is treated with benzene to turbidity, the crystalline pyridine *N*-phenyldithiophosphonic betaine *(3)* separates (m.p. 122–125 °C; $\delta_P$ = 82.2 ± 1.0 ppm; yield 80–85 %).



*(3)*

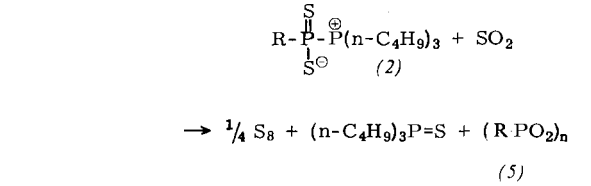
This compound reacts with tributylphosphine with elimination of pyridine and formation of compound *(2)*.

The inner phosphonium salts *(2)* react with primary and secondary aliphatic amines (spontaneously at room temperature in a pressure tube) with fission of the P–P bond, yielding ammonium phosphonoamidodithioates *(4)* and tributylphosphine.



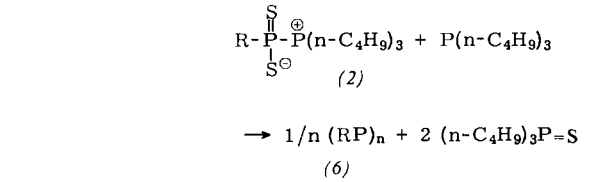
*(4)*

With liquid sulfur dioxide the compounds *(2)* yield tributylphosphine sulfide, sulfur, and the corresponding phosphonic anhydride *(5)* [2], whereas with an excess of tributylphosphine



*(5)*

(15 hr at 80 °C in benzene) they give arylcyclophosphines *(6)* and tributylphosphine sulfide.



*(6)*

Investigation of the reaction of amines and phosphines with phosphonic anhydrides are in progress.

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German version: Angew. Chem. *78*, 677 (1966)

[1] We thank the Landesgewerbeamt Baden-Württemberg for financial support.

[2] *E. Fluck* and *H. Binder*, Angew. Chem. *77*, 381 (1965); Angew. Chem. internat. Edit. *4*, 359 (1965).

## Novel Purine Syntheses

By Prof. W. Pfleiderer and H.-U. Blank

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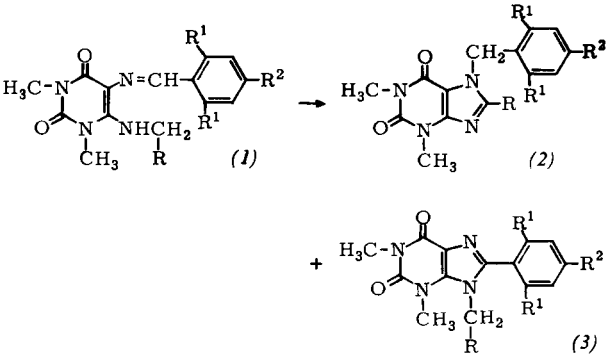
Technische Hochschule Stuttgart (Germany)

In the dehydrogenating cyclization of 4-amino-5-benzylideneamino-1,3-dimethyluracil to 8-phenyltheophylline *Traube*[1] found a synthesis of imidazole derivatives which was later used mainly for preparation of benzimidazoles[2]. If $N^4$-alkyl-5-benzylideneamino-1,3-dimethyluracil-4-amines are chosen as starting materials and cyclized in nitrobenzene, the main products are not 9-alkyl-8-phenyltheophyllines, but instead 7-benzyltheophylline or its 8-alkyl derivatives, in analogy with the cyclization of 3-substituted or 1,3-disubstituted 6-alkylamino-5-nitrosouracils[3].



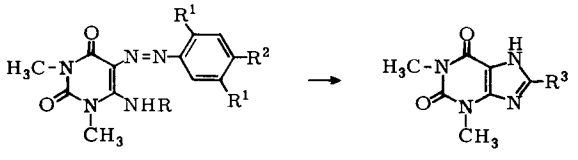
*(1)* *(2)* *(3)*

| R | $R^1$ | $R^2$ | Yield (%) of *(2)* | Yield (%) of *(3)* |
|---|---|---|---|---|
| *(a)* H | H | $NO_2$ | 40 | 12 |
| *(b)* H | H | H | 48 | |
| *(c)* H | Cl | H | 51 | |
| *(d)* $C_6H_5$ | H | H | 50 | |

However, many side reactions occur, in contrast to the cyclization of nitrosouracils. When, for instance, a solution of 4-methylamino-5-*p*-nitrobenzylideneaminouracil *(1a)* in nitrobenzene is refluxed for only a short time (2–5 min), fractional crystallization of the product leads to a 40 % yield of 7-*p*-nitrobenzyltheophylline *(2a)* and a 12 % yield of 8-*p*-nitrophenylisocaffeine *(3a)*. Since the Schiff bases *(1b)–(1d)* also afford 7-benzyltheophyllines *(2b)–(2d)* as main products in yields around 50 %, the reaction must proceed by attack of the alkyl substituent on the 4-amino group onto the azomethine portion of the molecule. This is thus a new type of imidazole ring closure.

Cyclization in *Traube*'s sense can be achieved by the use of aqueous alcohol in presence of Cu(II) ions as solvent, instead of nitrobenzene. Compound *(3a)* is formed from *(1a)* in 61 % yield after only 5 minutes' boiling. The reaction-determining factor is probably complex formation between the Cu and the azomethine group.

A novel purine ring closure was also found in the cyclization of 4-alkylamino-1,3-dimethyl-5-phenylazouracil *(4)*. If the derivative *(4a)* is boiled in nitrobenzene for about 4 hr under reflux, theophylline *(5a)* is obtained in 50 % yield; heating of the compound *(4b)* alone above its melting point gives 8-methyltheophylline. In both cases the α-C atom of the substituent on the 4-amino group enters into reaction and appears as C-8 in the purine derivative.



*(4a)*, R: $-CH_3$, $R^1$: -Cl, $R^2$: -H
*(4b)*, R: $-CH(CH_3)-CO_2C_2H_5$, $R^1$: -H, $R^2$: -Cl

*(5a)*, $R^3$: -H (50%)
*(5b)*, $R^3$: $-CH_3$

Received: May 18th, 1966 [Z 237 IE]
German version: Angew. Chem. *78*, 679 (1966)

[1] *W. Traube* and *W. Nithak*, Ber. dtsch. chem. Ges. *39*, 227 (1906).

[2] *R. Weidenhagen*, Ber. dtsch. chem. Ges. *69*, 2263 (1936); *D. Jerchel, H. Fischer*, and *M. Kracht*, Liebigs Ann. Chem. *575*, 162 (1952); *D. Jerchel, M. Kracht*, and *K. Krucker*, *ibid. 590*, 232 (1954).

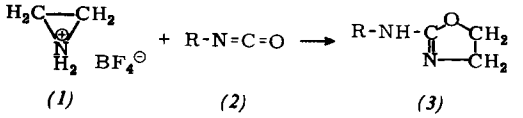
[3] *H. Goldner, G. Dietz*, and *E. Carstens*, Naturwissenschaften *51*, 137 (1964); Z. Chem. *4*, 454 (1964); Liebigs Ann. Chem. *691*, 142 (1966); *E. Bühler* and *W. Pfleiderer*, Angew. Chem. *77*, 129 (1965); Angew. Chem. internat. Edit. *4*, 146 (1965).

## Synthesis of 2-Oxazoline-2-amines and 2-Thiazoline-2-amines by Reaction of Aziridinium Tetrafluoroborate with Isocyanates and Isothiocyanates

By Prof. E. Pfeil and K. Milzner

Chemisches Institut, Universität Marburg (Germany)

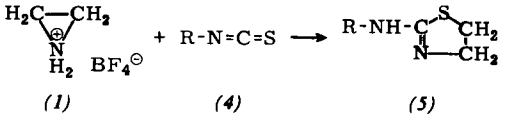
Aziridinium tetrafluoroborate *(1)* [1] adds to
(a) isocyanates *(2)* with formation of 2-oxazoline-2-amines *(3)*:



*(1)* *(2)* *(3)*

| *(3)*, R | M.p. [°C] | Yield [%] |
|---|---|---|
| $C_6H_5$ | 117–119 | 89.6 |
| $C_6H_{11}$ | 131 | 44.3 |

and (b) to isothiocyanates *(4)* with formation of 2-thiazoline-2-amines *(5)*.



*(1)* *(4)* *(5)*

*(5)*, R = $C_6H_5$, m.p. 160–161 °C, yield 47.2 %.

Equivalent amounts of compounds *(1)* and *(2)* or *(4)* are mixed and kept at a bath temperature of 130 °C for (a) 22 hr and (b) 3 hr, respectively. After cooling, the unchanged isocyanate or isothiocyanate is extracted with ether, and the 2-oxazoline-2-amine or 2-thiazoline-2-amine is liberated from the residue with sodium methoxide/methanol. After removal of the methanol the product is extracted with diisopropyl ether and recrystallized from the same solvent. The structures of the products are proved by mixed melting points, IR and NMR spectra, and elementary analysis.

Received: May 13th, 1966 [Z 239 IE]
German version: Angew. Chem. *78*, 677 (1966)

[1] Preparation: *E. Pfeil* and *U. Harder*, Chem. Ber. *97*, 510 (1964).

## cis-Selective Olefin Syntheses

By Dr. M. Schlosser, G. Müller, and Dr. K. F. Christmann

Organisch-Chemisches Institut,
Universität Heidelberg (Germany)

In many examples reaction of phosphorus ylides with aldehydes affords preferentially the thermodynamically less stable *cis*-olefin [1]. There are various interpretations as to whether and how the lithium salt present influences the stereochemistry of the carbonyl olefination [1c, 1d, 2].

We have found that alkylidenetriphenylphosphoranes tend in general towards *cis*-olefination. Here the proportion of *cis*-olefin in the isomer mixture is highest when the ylide is prepared in "salt-free" form [3]. Lithium salts favor the formation of *trans*-isomers, the more so the larger the radius of the anion. For example, salt-free alkylidenetriphenylphosphorane and benzaldehyde in benzene/light petroleum (4:1) at 0 °C [4] give *cis*- and *trans*-1-phenyl-1-butene in the ratio 96:4; the *cis*/*trans* ratio becomes 90:10, 86:14, 83:17, and 52:48 if the reaction is carried out in the presence of an equivalent amount of lithium chloride, bromide, iodide, or tetraphenylborate, respectively. Benzylidenetriphenylphosphorane and other ylides with α-substituents capable of resonance are not suitable for *cis*-selective olefination.

$(C_6H_5)_3P{=}CH{-}R + R'{-}CHO \rightarrow (C_6H_5)_3PO + R'{-}CH{=}CH{-}R$

| R′ | R′–CH=CH–R<br>Yields and *cis*/*trans* ratio | | | |
|---|---|---|---|---|
| | R = $CH_3$ | R = $C_2H_5$ | R = $C_3H_7$ | R = $C_6H_5$ |
| $C_2H_5$ | – | 70 %; 97:3 | – | 61 %; 25:75 |
| $C_3H_7$ | – | 49 %; 95:5 | 78 %; 95:5 | – |
| $C_5H_{11}$ | 66 %; 91:9 | – | – | – |
| *trans*-styryl | 77 %; 87:13 | – | – | – |
| *p*-$CH_3O{-}C_6H_4$ | 78 %; 90:10 | 95 %; 92:8 | 80 %; >90:10 | 76 %; 19:81 |
| *p*-$CH_3{-}C_6H_4$ | 88 %; 89:11 | 59 %; 95:5 | 71 %; 92:8 | 88 %; 36:64 |
| $C_6H_5$ | 98 %; 87:13 | 88 %; 96:4 | 66 %; 94:6 | 100 %; 44:56 |
| *p*-$Cl{-}C_6H_4$ | 77 %; 82:18 | 54 %; >99:1 | 64 %; >99:1 | 72 %; <30:70 |

*Experimental*:

Liquid ammonia (200 ml) is distilled from sodium under nitrogen and condensed through a dry ice-cooled condenser into a three-necked flask. After dissolution of 2 g of solid sodamide with stirring by a magnetic stirrer, 50 mmole of

alkyltriphenylphosphonium bromide is added. The mixture is refluxed for 1 hr, whereafter the ammonia is evaporated through a mercury seal. The residue is boiled for 1 hr with 200 ml of anhydrous benzene. The benzene solution is cooled and allowed to flow with vigorous stirring into a mixture of 20 mmole of aldehyde and 50 ml of benzene/light petroleum (1:1) cooled to 0 °C. After 1 hour's stirring the *cis-trans* ratio of the olefin produced is determined by gas chromatography; the olefin is then isolated by distillation.

The structures of the products were determined by C–H analysis, IR spectra, and comparison with authentic samples.

Received: May 17th, 1966 [Z 240 IE]
German version: Angew. Chem. 78, 677 (1966)

[1] Examples: a) *P. C. Wailes*, Chem. and Ind. *1958*, 1086, and literature cited there; b) *H. Pommer*, Angew. Chem. *72*, 817 (1960); c) *L. D. Bergelson* and *M. M. Shemyakin*, Tetrahedron *19*, 149 (1963); d) *L. D. Bergelson, V. A. Vaver, L. I. Barsukov*, and *M. M. Shemyakin*, Tetrahedron Letters *1964*, 2669; e) *P. A. Chopard, R. F. Hudson*, and *R. J. G. Searle*, Tetrahedron Letters *1965*, 2357.

[2] *H. O. House, V. K. Jones*, and *G. A. Frank*, J. org. Chemistry *29*, 3327 (1964).

[3] *G. Wittig, H. Eggers*, and *P. Duffner*, Liebigs Ann. Chem. *619*, 10 (1958); cf. *H. J. Bestmann*, Angew. Chem. *77*, 613 (1965); Angew. Chem. internat. Edit. *4*, 587 (1965).

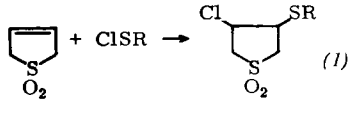
[4] Under these conditions betaine formation in this system is irreversible (*M. Schlosser* and *K. F. Christmann*, unpublished work).

## Synthesis of 2-Alkylthio- and 2-Arylthio-1,3-butadienes

By Prof. K.-D. Gundermann and P. Holtmann [1]

Organisch-Chemisches Institut, Bergakademie-Technische Hochschule, Clausthal-Zellerfeld (Germany)

We have found that alkanesulfenyl chlorides and benzenesulfenyl chloride add smoothly to $\Delta^3$-thiolene 1,1-dioxides in tetrahydrofuran at 0 to 5 °C, yielding 3-alkylthio- or 3-arylthio-4-chlorothiolane 1,1-dioxides *(1)* (cf. Table).



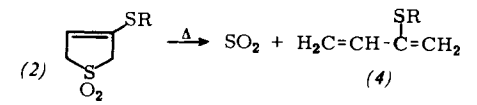
*(1)*

| R | Yield of *(1)* [%] | M.p. of *(1)* (C °) |
|---|---|---|
| $CH_3$ | 88 | 52–53 |
| $C_2H_5$ | 80 | 25 |
| $C_6H_5$ | 87 | 81 |

When the products *(1)* are warmed with an equivalent amount of triethylamine in dimethyl sulfoxide for 2 hr at 90 °C, they give 3-alkylthio- or 3-arylthio-$\Delta^3$-thiolene 1,1-dioxides *(2)* (yields 60–90 %), respectively, whose structures follow from the NMR spectra [2].

*(2)* *(3)*

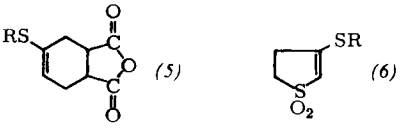
If the alkylthiochloro compounds *(1)* are left with triethylamine in benzene solution für 15 hr, the alkylthio-2-thiolene 1,1-dioxides *(3)* are formed in *ca.* 80 % yield. These products isomerize to the 3-thiolenes *(2)* when heated for 1 hr with triethylamine in dimethyl sulfoxide at 90 °. Only the 3-thiolenes *(2)* are cleaved by heating at 105–110 °C in presence of t-butylpyrocatechol as polymerization inhibitor, losing $SO_2$ and giving the butadienes *(4)* (see table).



*(2)* *(4)*

| *(4)*, R | Yield (%) | B.p. (°C/mm) | $n_D^{20}$ | *(5)*, M.p. (°C) |
|---|---|---|---|---|
| $CH_3$ | 79 | 62/90 | 1.5241 | 117 |
| $C_2H_5$ | 55 | 67/70 | 1.5123 | 104 |
| $C_6H_5$ | 64 | 65/0.3 | 1.5922 | 87 |

Analytical data and infrared and NMR spectra confirm the structures of compounds *(4)*, which are stable for weeks when kept at 0 °C under nitrogen. Warming them for 1 hr with maleic anhydride in boiling benzene affords 63–80 % yields of the Diels-Alder adducts of type *(5)*. When the butadienes are heated at 90 °C for 5 hr without a solvent, dimers are formed which on desulfuration with Raney nickel in methanol at 50 °C give ethylcyclohexane with small amounts of *trans*-1,2-diethylcyclobutane and cyclooctadiene.



*(5)* *(6)*

Two hours' warming in 1 % sodium methoxide solution rearranges the thiolenes *(2)* and *(3)* to 3-alkylthio-2-thiolene 1,1-dioxides *(6)*, whose infrared spectrum is characterized by a particularly intense C–C band at 1565 $cm^{-1}$.

Received: May 17th, 1966 [Z 241 IE]
German version: Angew. Chem. 78, 678 (1966)

[1] *P. Holtmann*, Lecture at the Nordwestdeutsche Chemiedozententagung, Clausthal-Zellerfeld, on June 12th, 1966; *K.-D. Gundermann*, Second Organic Sulphur Symposium, Gromingen 1966, Abstracts p. 21.

[2] *E. N. Prilezhayeva* recently obtained thiolenes of the type *(2)* from 3-chloro-$\Delta^3$-thiolene1,1-dioxide (personal communication, May 9th, 1966).

## Stereospecific Synthesis and Hydrolysis of Optically Active *O*-Ethyl Ethylphosphonobromidothioate

By Prof. J. Michalski, Dr. M. Mikołajczyk, and Dr. B. Pliszka-Krawiecka

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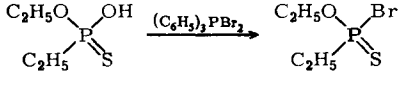
Optically active *O*-ethyl ethylphosphonochloridothioates are obtained from the antipodes of *O*-ethyl hydrogen ethylphosphonothioate *(1)* and phosphorus(V) chloride [1].

We have found a simple route to the optically active bromides *(2)* in treatment of the acid *(1)* with triphenylphosphine dibromide, $(C_6H_5)_3PBr_2$.



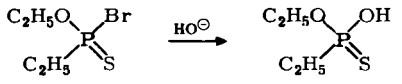
*(1)*, $[\alpha]_D^{23} = +13.90°$ *(2)*, $[\alpha]_D^{23} = +140.4°$

The (+)-thiophosphonic acid *(1)* in ether is dropped into an ethereal solution of an equimolar amount of triphenylphosphine dibromide obtained *in situ* from triphenylphosphine and bromine [2]. The mixture is stirred for 8.5 hr at room temperature and then filtered. The residue remaining

after removal of the ether is vacuum-distilled, yielding the (+)-bromide *(2)* as a colorless, optically stable liquid, b.p. 23–24 °C/0.1 mm, $n_D^{23} = 1.5235$, in 53 % yield.

A similar reaction in boiling ether (6.5 hr) gives a 50 % yield of a (+)-bromide with $[\alpha]_D^{23} = +135.3°$ [*].

For determination of its optical purity and relative configuration the (+)-bromide *(2)*, $[\alpha]_D^{23} = +140.4°$, was hydrolysed by 2.85 N KOH in dioxane-water (4:7 v/v) at °C to the (+)-thiophosphonic acid *(1)*, $[\alpha]^{23} = +13.0°$ (yield 80 % in $2^1/_2$ hr).



*(2)*, $[\alpha]_D^{23} = +140.4°$ *(1)*, $[\alpha]_D^{23} = +13.0°$

Comparison of the rotation of the acid obtained by alkaline hydrolysis with that of the starting material showed that the (+)-bromide *(2)* had an optical purity of at least 94 %. If we assume that the alkaline hydrolysis occurs with inversion [3] then the thiophosphonic acid *(1)* reacts with $(C_6H_5)_3PBr_2$ also with inversion. It is remarkable that the reactions of the acid *(1)* with $PCl_5$ and $(C_6H_5)_3PBr_2$ occur in stereochemically identical ways.

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[*] Rotations were measured for the neat liquids.

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[3] *M. Green* and *R. F. Hudson*, J. chem. Soc. (London) *1963* 3883; *J. Michalski, M. Mikołajczyk*, and *J. Omelańczuk*, Tetrahedron Letters *1965*, 1779; *M. Mikołajczyk*, Tetrahedron, in press.

## One-Stage Synthesis of Hexamethyl-Dewar-Benzene from 2-Butyne [1]

By Dr. Wolfgang Schäfer

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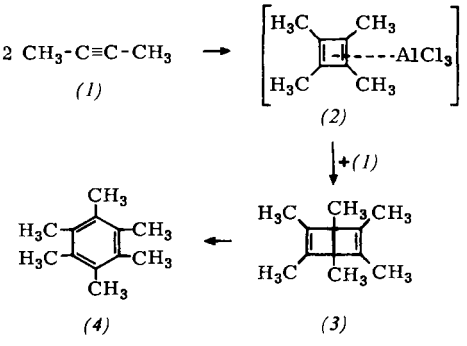
Hexamethylbicyclo[2.2.0]hexa-2,5-diene (hexamethyl-Dewar-benzene) *(3)* can be prepared by trimerization of 2-butyne *(1)* with anhydrous aluminum chloride as catalyst at 20 to 35 °C. Benzene may be used as solvent. Compound *(3)* was not previously known [2].

The trimerization of 2-butyne *(1)* may occur by way of a complex *(2)* of $AlCl_3$ with the tetramethylcyclobutadiene, which does not exist in the free form.



*(1)* *(2)* *(4)* *(3)*

The compound *(3)* is quantitatively isomerized to hexamethylbenzene *(4)* in the presence of catalysts at room temperature (enthalpy of rearrangement: $\Delta H = -62.4 \pm 0.4$ kcal/mole).

If 2-butyne *(1)* is trimerized above 50 °C the benzene derivative *(4)* is formed predominantly and only a small amount of the bicyclic compound *(3)* can be isolated. Trimerization in boiling benzene gives hexamethylbenzene *(4)* in 80 to 90 % yield, and a mixture of oils. Some of these oils are dimerization products of tetramethylcyclobutadiene previously obtained in a different way [3].

1 kg of 2-butyne [4] is dropped, with stirring, during 2.5 hr into a suspension of 50 g of freshly sublimed $AlCl_5$ in 1 *l* of benzene (dried over sodium), care being taken, by water-cooling, that the temperature does not exceed 35 °C. For completion of the reaction the mixture is stirred for a further 4 hr at 35 °C. (At 20 °C the reaction time is approximately 20 hr.) Then the mixture is cooled to 0 °C and the catalyst is decomposed by adding dropwise 50 to 100 ml of water, until the initially brown mixture turns pale yellow. Unchanged 2-butyne is removed with some benzene by distillation at room temperature and 200 mm, being collected in two successive receivers cooled by dry ice/methanol. Fractionation of the condensate allows recovery of *ca.* 200 g of 2-butyne.

The butyne-free benzene solution is washed with water until neutral and fractionated in vacuum, yielding a first fraction of benzene and then 490 to 510 g of a colorless liquid *(3)*, b.p. 43–45 °C/15 mm, $n_D^{20} = 1.4479$, m.p. 7 °C. After cooling, the distillation residue affords 150–165 g of hexamethylbenzene. Compound *(3)* can be kept for months in a refrigerator and for a long time even at room temperature protected from light.

The NMR spectrum of the bicyclic compound *(3)* in $CCl_4$ (with tetramethylsilane as internal standard) contains two singlets at 8.4 and 8.9 τ, of relative areas 2:1. The signal at 8.4 τ is assigned to the $CH_3$ groups attached to the doubly bound C atoms, and that at 8.9 τ to the methyl groups attached to tertiary C atoms. The NMR spectrum of hexamethylbenzene *(4)* contains only one signal at 7.85 τ.

In the IR spectrum of the bicyclic compound *(3)* there is a weak band at 1680 $cm^{-1}$ (C=C in strained ring systems), also bands at 1370 $cm^{-1}$ ($-CH_3$) and 1060 $cm^{-1}$ ($CH_3$-C=C), as well as at 1280, 1220, 735, and 660 $cm^{-1}$.

This synthesis enables a Dewar-benzene derivative to be prepared on a technical scale for the first time [5].

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[1] The scope of the reaction and the transformations of *(3)* are being studied.

[2] *C. E. Berkoff, R. C. Cookson, J. Hudec*, and *R. O. Williams*, Proc. chem. Soc. (London) *1961*, 312, merely presumed that formation of *(4)* in 20 % yield on dehalogenation of 3,4-dichlorotetramethylcyclobutene by activated zinc dust in the presence of *(1)* proceeded by way of *(3)*; see also J. chem. Soc. (London) *1965*, 194.

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[4] Dried over sodium; according to gas chromatography it contained 92.7 % of *(1)*.

[5] 2-Butyne is obtained, *e.g.*, as by-product on dehydrogenation of butane to 1,3-butadiene by *Houdry*'s procedure.

## Synthesis and Formula of Biological and Mineral Carbonate-apatite

By Prof. E. Hayek, Dr. H. Konetschny, and Dr. E. Schnell

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The designation carbonate-apatites is given to minerals (dahllite, staffelite, kollophane) that are analogous to apatite $Ca_5(PO_4)_3(F,OH,Cl)$ in crystal structure but contain also carbonate. Carbonate-apatites also form the mineral substance of bones and teeth. All carbonate-apatites contain calcium phosphate and carbonate (the latter in amounts

corresponding to only a few percent of $CO_2$), together with smaller amounts of other cations and anions.

We have found that the reaction between calcium hydrogen phosphate and calcium carbonate in an aqueous slurry can be used to prepare the basic substance of mineral as well as of biological apatites. Passing air (purified by KOH) through an aqueous suspension of $CaHPO_4 \cdot 2H_2O$ and $CaCO_3$ (molar ratio 3:2) at 37 °C for some days, and subsequent filtration and washing with water, gives preparations in which about a third of the carbonate used is incorporated homogeneously.

Of the infrared bands of the calcite used, only those at 1430 $cm^{-1}$ (strong) and at 880 $cm^{-1}$ (weak) are found in the spectrum of the new preparation. In other respects its IR spectrum is the same as that of octacalcium phosphate $Ca_4H(PO_4)_3 \cdot 2H_2O$, and agrees completely with that of the mineral substance of bones. Its X-ray diagram shows none of the reflections characteristic of the $CaCO_3$ used and coincides in general with those of octacalcium phosphate and of the mineral substance of bones.

These facts and analysis of the product lead to the following formulation of the reaction (water of crystallization being neglected):

$$3\ CaHPO_4 + 2\ CaCO_3 = 5/4\ [Ca_4(PO_4)_2(HPO_4)_{0.4}(CO_3)_{0.6}] + 5/4\ H_2O + 5/4\ CO_2$$

The ratio 6.67:1 of Ca:$CO_2$ corresponding to this formula is somewhat exceeded in the synthetic product, as also in biological apatite, owing to side reactions that do not incorporate carbonate (formation of octacalcium phosphate and hydroxyapatite). In the electron microscope the synthetic product shows a leaflet structure resembling that of the bone substance but being more pronounced.

The above formula is in keeping with the chemical and structural properties of the principal component of biological carbonate-apatite. The octacalcium phosphate thus not only acts as nucleus for the hard tissues[1], but also as its major component after partial replacement of $HPO_4^{2-}$ by $CO_3^{2-}$. Complete conversion of $HPO_4^{2-}$ into $PO_4^{3-}$ leads to $Ca_4(PO_4)_{2.4}CO_{3)0.4} = Ca_5(PO_4)_3(CO_3)_{0.5}$. If the reactants are boiled for 10 hr the carbonate-containing product gives a very sharp X-ray diagram which is identical with that of pure hydroxy-apatite[2] except for intensity differences and minimal changes of position. Once again there are no calcium carbonate interferences. The IR spectrum is also analogous to that of hydroxy-apatite, but the bands at 3850 and 635 $cm^{-1}$ characteristic of OH groups are, at most, weak and of the carbonate bands only those at 1430 and 880 $cm^{-1}$ appear. Here again there are variations in the carbonate content, but the above composition is almost reached and the product thus to a great extent resembles mineral carbonate-apatites with not too high fluorine contents. In the electron microscope needles are seen (some longer than 1 μ) similar to those in crystalline hydroxy-apatite[3].

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## Synthesis of Tetramethyl Cyclopentadiene-1,2,3,4-tetracarboxylate

By Dr. G. Seitz

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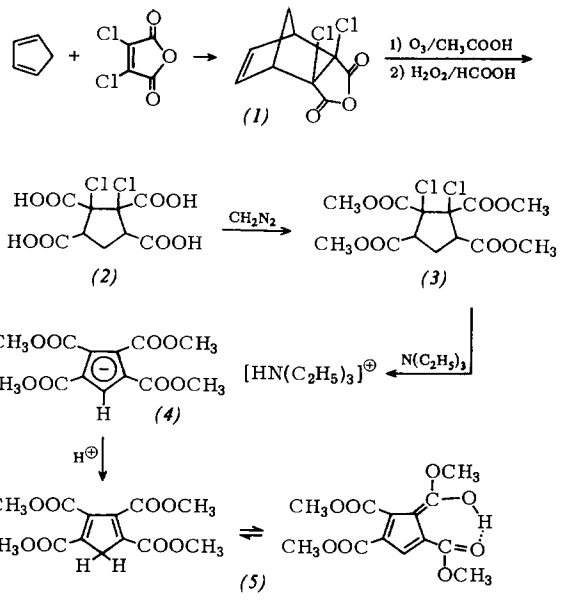
*Webster*[1] and *Friedrich*[2] recently described syntheses of cyano-substituted cyclopentadienes. We have prepared tetramethyl cyclopentadiene-1,2,3,4-tetracarboxylate *(5)* by the route shown in the scheme below.




Cyclopentadiene and dichloromaleic anhydride in benzene give the Diels-Alder adduct *(1)*, m.p. 192 °C[3], which was ozonized in 95 % acetic acid at room temperature. The crystalline ozonide (decomp. 125 °C) can be oxidized by hydrogen peroxide in formic acid to crystalline 3,4-dichloro-cyclopentane-1,2,3,4-tetracarboxylic acid *(2)*. This acid decomposes readily and is immediately converted by etheral diazomethane into its tetramethyl ester *(3)*, m.p. 110 °C. Removal of two molecules of hydrogen chloride with triethylamine leads to *(4)*, the resonance-stabilized, water-soluble triethylammonium salt of *(5)*. Acidification of the aqueous solution of *(4)* with HCl precipitates the crystalline compound *(5)*, which is obtained in analytically pure, yellowish crystals from methanol. This ester *(5)* does not melt sharply. When heated above 130 °C it slowly decomposes, assuming an intense red color. Like all cyano- and carbonyl-substituted cyclopentadienes[4–6], compound *(5)* is strongly acidic. As in the case of cyclopentadienetricarbaldehyde[6] the NMR and IR spectra can be unambiguously interpreted only by ascribing to compound *(5)* a tautomeric fulvene structure with an intramolecular O···H–O hydrogen bond. Thus the NMR spectrum (measured in $CDCl_3$ with tetramethylsilane as internal standard) shows four singlets for the twelve methoxy protons, close together but distinctly differentiable, of intensity 3 at 3.82 ppm, 3.98 ppm, 4.05 ppm, and 4.09 ppm. The ring proton at position 5 gives rise to a sharp singlet at 7.63 ppm of intensity 1, whereas there is no recognizable signal for the acidic proton (up to 32 ppm). The IR spectrum in $CCl_4$ and in KBr shows two sharp bands at 1739 $cm^{-1}$ and 1715 $cm^{-1}$ which can be assigned to the differently conjugated ester carbonyl groups. The broad, intense band at 1600 $cm^{-1}$ must originate from a delocalized C=O and C=C double bond, as is typical of carbonyl-substituted fulvenes with intramolecular hydrogen bonds[6]. Equally characteristic of the fulvene system is a strong band at 1330 $cm^{-1}$[7,8], while a somewhat weaker band at 1445 $cm^{-1}$ arises from the $CH_3$ deformation vibration. It appears with equal intensity in the IR spectrum of the chloro-ester *(3)*. No free hydroxyl group can be recognized. The O···H-O chelate band, which is usually broad, probably occurs in the region of the C–H stretching vibrations at about 3050 $cm^{-1}$ to 2650 $cm^{-1}$, which would explain why all the bands in that region appear diffuse. Only after deuteration (by shaking of the solution with $D_2O$) can sharp bands be obtained for the C–H stretching vibrations (3060 $cm^{-1}$, 3020 $cm^{-1}$, 2960 $cm^{-1}$); there is, however, no band near 2000 $cm^{-1}$ that would be produced by a deuterated hydrogen bond.

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[4] *O. Diels*, Chem. Ber. *75*, 1452 (1942).

[5] *E. LeGoff* and *R. B. LaCount*, J. org. Chemistry *29*, 423 (1964).

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## Synthesis of Pyrimidine-5-carbaldehyde

By Prof. H. Bredereck, Dr. G. Simchen, Dr. A. Santos, and H. Wagner

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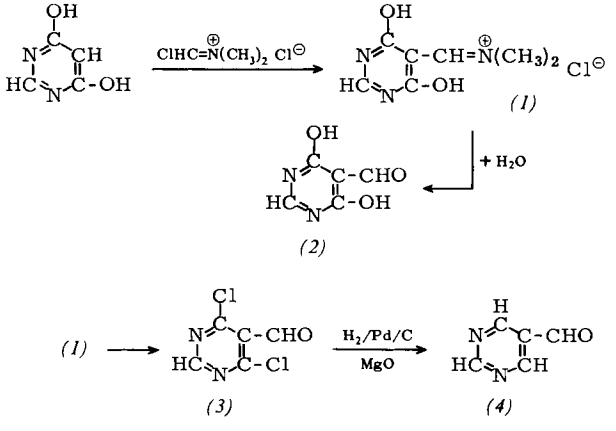
Technische Hochschule Stuttgart (Germany)

In the course of our studies on the nucleophilicity of the 5-position of substituted pyrimidines we obtained 4,6-dihydroxypyrimidine-5-carbaldehyde *(2)*[1] by reaction in chloroform at 0 to 20 °C of 4,6-dihydroxypyrimidine (prepared from malondiamide and formamide) with the reaction product of dimethylformamide and phosgene[2]. The formylation was exothermic with a yield of 93 % after 2 to 3 hr.

Chlorination of the quaternary salt *(1)* with phosphorus oxychloride/dimethylaniline, or of *(1)* in dimethylformamide with phosgene/dimethylaniline (10 hr at 110 °C) and subsequent removal of the solvent, treatment of the residue with ice, and extraction with chloroform afforded 4,6-dichloropyrimidine-5-carbaldehyde *(3)* in 63 % yield[1,3].

The formylation and chlorination can be carried out in one experiment: after the reaction with the dimethylformamide-phosgene product the chloroform is removed and replaced by dimethylformamide, and phosgene is passed into the mixture for 10 hr at 110 °C.

Hydrogenation of the chloro-aldehyde *(3)* with hydrogen and palladium-charcoal in methanol containing an excess of magnesium oxide (to remove the HCl) at room temperature and pressure and subsequent filtration, distillation of the methanol, and extraction of the residue with methylene chloride yielded the new compound pyrimidine-5-carbaldehyde, m.p. 38–41 °C, in 79 % yield (40 % calculated on malondiamide).

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[2] *Z. Arnold*, Coll. czechoslov. chem. Commun. *24*, 4048 (1959).

[3] *H. Wagner*, Diploma Thesis, Technische Hochschule Stuttgart, 1966.

## On the Secondary Structure of Serine-Specific Transfer Ribonucleic Acid [1]

By H. Doepner, Dr. H. Seidel, and Prof. F. Cramer

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Göttingen (Germany)

Recently we described a relation[2] between the thermal hyperchromicity of variously pre-treated s-RNA's[3] of different origins and the extent of their base-pairing as determined by *N*-oxidation.

We have now examined ser-t-RNA from brewer's yeast, whose nucleotide sequence has been elucidated by *Zachau et al.*[4]. The figure shows the change in absorption on thermal denaturation of this t-RNA.

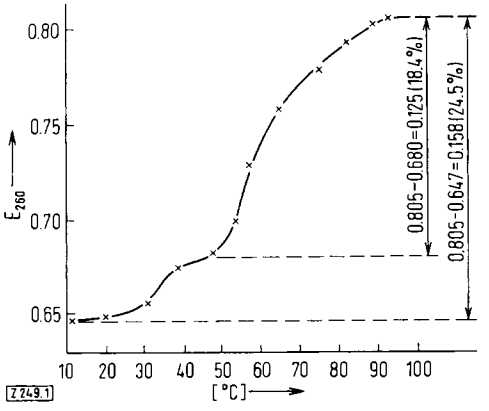


Fig. 1. Change of extinction at 260 mμ ($E_{260}$) on thermal denaturation of ser-t-RNA in 0.4 M phosphate buffer (pH 7.0) without $Mg^{2+}$.

The denaturation curve exhibits two steps. The first stage in the denaturation (between 30 and 45 °C) accounts for only a small part of the total hyperchromicity (breakdown of tertiary structure?)[5,6]. The second stage may correspond to destruction of the secondary structure (helix-coil transition).

As seen from the figure, the total hyperchromicity amounts to 24.5 %, which according to our previous relationship[2] corresponds to about 27 base pairs per molecule of ser-t-RNA. The hyperchromicity in the second stage is 18.4 %, corresponding[2] to 24 to 25 base pairs per molecule of ser-t-RNA.

This result agrees well with the optimal amount of base-pairing attainable by arrangement of the nucleotide sequence in five helical regions as proposed by *Zachau et al.*[4] for ser-t-RNA.

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[1] We thank Prof. *H. G. Zachau* for a sample of ser-t-RNA.

[2] *H. Doepner*, *H. Seidel*, and *F. Cramer*, Angew. Chem. *78*, 601 (1966); Angew. Chem. internat. Edit. *5*, 591 (1966).

[3] The following abbreviations are used: s-RNA = soluble ribonucleic acid; ser-t-RNA = serine-specific transfer-ribonucleic acid; hyperchromicity = increase in the extinction at 260 mμ on increase in temperature.

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[6] *D. D. Henley*, *T. Lindahl*, and *J. R. Fresco*, Proc. nat. Acad. Sci. U.S.A. *55*, 191 (1966).

## Synthesis of Oligodeoxynucleotides with Terminal 5'-Phosphate Groups

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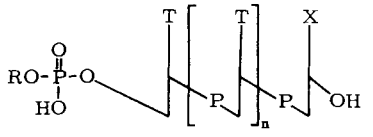
Unless enzymatically obtained, all the oligodeoxynucleotides larger than the dinucleotide synthesized through a dinucleotide intermediate have a hydroxyl group at the 5'-end[1].

We have now achieved a stepwise synthesis of oligodeoxynucleotides with a terminal 5′-phosphate group.

Condensation of thymidine-5′-(2,2,2-trichloroethyl hydrogen phosphate) *(1)* [2] with 3′-*O*-acetylthymidine-5′-phosphoric acid *(2)* by means of dicyclohexylcarbodiimide in pyridine and subsequent removal of the acetyl group and separation on a DEAE-cellulose column give the dinucleotide *(3a)*. This can be converted by condensation with *(2)* into the trinucleotide *(3b)*. We have carried out this condensation up to the tetranucleotide *(3c)*. $N^6$,3′-*O*-Diacetyldeoxycytidine-5′-phosphoric acid *(4)* can be used in place of *(2)* in the last condensation, and then the oligonucleotides *(5a)* to *(5c)* are obtained.

After conversion of these compounds into the pyridine salts, the 2,2,2-trichloroethyl group can be removed from all of them with activated Cu/Zn [3] in dimethylformamide (50 °C, 1 hr) [2]. The yields of oligonucleotide in these processes amount to 85–90% for *(3a)*–*(3c)*, 65% for *(5a)* and *(5c)*, and 90% for *(5b)*.



*(3)*, X = Thymyl
*(5)*, X = Cytosyl

After conversion into the ammonium salts the oligonucleotides can be cleaved to mononucleotides by snake-venom phosphodiesterase.

| | R | n | Yield (%) [a] | $R_f$ in system [b] A | B | C |
|---|---|---|---|---|---|---|
| *(3a)* | $CCl_3$–$CH_2$ | 0 | 53 | 0.57 | 0.61 | |
| *(3b)* | $CCl_3$–$CH_2$ | 1 | 56 | 0.39 | 0.57 | |
| *(3c)* | $CCl_3$–$CH_2$ | 2 | 43 | 0.20 | 0.42 | |
| *(3d)* | H | 0 | | | | 0.35 |
| *(3e)* | H | 1 | | | | 0.25 |
| *(3f)* | H | 2 | | | | 0.19 |
| *(5a)* | $CCl_3$–$CH_2$ | 0 | 42 | 0.53 | 0.66 | |
| *(5b)* | $CCl_3$–$CH_2$ | 1 | 40 | 0.31 | 0.55 | |
| *(5c)* | $CCl_3$–$CH_2$ | 2 | 43 | 0.18 | 0.45 | |
| *(5d)* | H | 0 | | | | 0.33 |
| *(5e)* | H | 1 | | | | 0.27 |
| *(5f)* | H | 2 | | | | 0.23 |

[a] Calculated on the total oligonucleotide used.

[b] A: Ethanol/1 M ammonium acetate (7:3).
B: 2-Propanol/conc. $NH_3$/water (7:1:2).
C: 1-Propanol/conc. $NH_3$/water (55:10:35).

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## Osazone Formation by D-Glucosamine

By Prof. F. Micheel and H. Dallmann

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Universität Münster (Germany)

The literature and textbooks express the view, based on experiments by *F. Tiemann* [1], that D-glucosamine gives D-phenylglucosazone analogously to D-glucose. As there is a close relation between the mechanism of the Amadori rearrangement and formation of osazones by aldose we have re-examined the behavior of D-glucosamine towards phenylhydrazine.

We have established that on complete exclusion of atmospheric oxygen D-glucosamine does not form D-glucosazone, but only a phenylhydrazone (m.p. 118–120 °C, $[\alpha]_D^{25} = -13.2°$ (after 10 min) → −72.3 ° ($c = 1$, water)]. This hitherto unknown substance was separated by way of the *N*-tosyl derivative. It can be obtained from the components in good yield without addition of acid. The *N*-formyl, *N*-acetyl, *N*-benzyloxycarbonyl, and *N*-tosyl derivatives of D-glucosamine also form the phenylhydrazone, with loss of the acyl group attached to the N atom. From the *N*-tosyl derivative, *N*-tosyl-D-glucosamine phenylhydrazone can be isolated as intermediate.

In the presence of atmospheric oxygen, however, D-glucosazone is formed, the yield depending on the amount of oxygen admitted. Our maximal yield was 61%. Clearly a dehydrogenation by the oxygen, and probably also loss of ammonia from an imino group, must occur before entry of the second phenylhydrazine residue.

The fact that D-glucosamine does not form an osazone in the absence of oxygen is in agreement with the behavior of its *N*-glycosyl derivatives. In no case is it possible to induce the *N*-glycosyl derivative to undergo the Amadori rearrangement [2]. Since osazone formation is preceded by an Amadori rearrangement it is understandable that there can be no osazone formation from D-glucosamine in the absence of oxygen.

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German version: Angew. Chem. *78*, 681 (1966)

[1] *F. Tiemann*, Ber. dtsch. chem. Ges. *19*, 50 (1886).

[2] *K. H. Heinemann*, Dissertation, Universität Münster, 1966; *K. H. Schwieger*, Diploma Thesis, Universität Münster, 1959.

## Reactions of N-Alkyl- and N-Aryl-S-chloroisothiocarbamoyl Chlorides with Isocyanates; Synthesis of 1,2,4-Thiadiazolidine-3,5-diones [1]

By Dr. G. Ottmann and H. Hooks, Jr.

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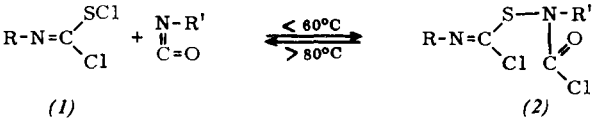
*N*-Alkyl and *N*-aryl-*S*-chloroisothiocarbamoyl chlorides *(1)* [2] react with aliphatic and aromatic isocyanates to form *S*-(chlorocarbonylamino)isothiocarbamoyl chlorides *(2)*. The weakly exothermic reaction proceeds quantitatively below 60 °C according to IR-spectroscopy, but is reversible at elevated temperatures.

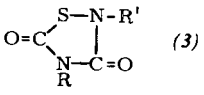


*(1)* *(2)*

| *(2)*, R | R′ | M.p. [°C] | Yield [%] |
|---|---|---|---|
| $C_2H_5$ | n-$C_8H_{17}$ | 132–133 | 77 |
| n-$C_4H_9$ | n-$C_4H_9$ | 133–134 | 85 |
| n-$C_4H_9$ | n-$C_8H_{17}$ | 114 | 65 |
| $C_6H_5$ | $C_2H_5$ | 108–109 | 90 |
| $C_6H_5$ | i-$C_3H_7$ | 101–102 | 78 |
| $C_6H_5$ | n-$C_4H_9$ | 97–99 | 86 |
| $C_6H_5$ | n-$C_8H_{17}$ | 92–93 | 68 |
| $C_6H_5$ | $C_6H_5$ | 79–80 | 97 |
| $C_6H_5$ | $CH_3$·$C_6H_4$ | 95–96 | 91 |
| $C_6H_5$ | *p*-Cl·$C_6H_4$ | 72–73 | 95 |
| $C_6H_5$ | *p*-$CH_3OC_6H_4$ | 85–92 | 98 |
| $C_6H_{11}$ | i-$C_3H_7$ | 131–132 | 55 |

The structure of the products *(2)* is supported by elemental analysis, molecular-weight determination, IR spectra, and their reactions. The infrared spectrum is void of the characteristic isocyanate absorption around 2270 $cm^{-1}$ but features absorptions at 1760 $cm^{-1}$ and 1670 $cm^{-1}$, which indicate the presence of a C=O group and a C=N linkage.

*S*-(Chlorocarbonylamino)isothiocarbamoyl chlorides *(2)* are exceptionally reactive, white solids, which fume heavily in moist air. With water and particularly with aqueous alcohols a vigorous, highly exothermic reaction ensues, accompanied by evolution of HCl and precipitation of the previously unknown 1,2,4-thiadiazolidine-3,5-diones *(3)* as white, crystalline solids.



*(3)*

| *(3)*, R | R′ | M.p. [°C] | B.p. [°C/mm Hg] | $n_D^{25}$ | Yield [%] |
|---|---|---|---|---|---|
| $C_2H_5$ | n-$C_8H_{17}$ | | 134/0.6 | 1.4920 | 76 |
| n-$C_4H_9$ | n-$C_4H_9$ | | 111/0.6 | 1.4960 | 77 |
| n-$C_4H_9$ | n-$C_8H_{17}$ | | 142/0.25 | 1.4890 | 71 |
| $C_6H_5$ | $C_2H_5$ | 94–95 | | | 91 |
| $C_6H_5$ | iso-$C_3H_7$ | 112–113 | | | 95 |
| $C_6H_5$ | n-$C_4H_9$ | 81–82 | | | 90 |
| $C_6H_5$ | n-$C_8H_{17}$ | 70–71 | | | 86 |
| $C_6H_5$ | $C_6H_5$ | 114–115 | | | 84 |
| $C_6H_5$ | *p*-$CH_3$–$C_6H_4$ | 136–137 | | | 76 |
| $C_6H_5$ | *p*-$CH_3O$–$C_6H_4$ | 157–158 | | | 85 |
| $C_6H_5$ | *p*-Cl–$C_6H_4$ | 170.5–171 | | | 91 |

Structure *(3)* was assigned because reduction of the hydrolysis products of *(2)* with lithium aluminum hydride in tetrahydrofuran renders 1,3-disubstituted ureas in up to 65% yield. Structure *(3)* is also verified by elemental analysis, infrared and mass spectroscopy, and by the fact that the compounds do not form hydrochlorides. The infrared spectra display two carbonyl absorptions at about 1735 $cm^{-1}$ and 1665 $cm^{-1}$. A weak absorption at about 1700 $cm^{-1}$ is noted with R = aryl. The formation of the 1,2,4-thiadiazolidine-3,5-diones *(3)* suggests that the imidoyl chloride portion of structure *(2)* and not the carbamoyl chloride group is the primary center of the nucleophilic attack.

*Synthesis Example*:

A solution of 412 g of *N*-phenyl-*S*-chloroisothiocarbamoyl chloride in 150 ml of dry pentane is added to a stirred solution of 307 g of 4-chlorophenyl isocyanate in 1000 ml of dry pentane at such a rate that a reaction temperature of 20–25 °C is easily maintained (external cooling bath at 10–15 °C). The mixture is allowed to stand for 12–15 hours, and the white precipitate is separated in a dry $N_2$ atmosphere by suction filtration and washed with fresh pentane.

The product of the first reaction step is added portionwise with stirring to 1500 ml of water, thereby maintaining a temperature of 60–70 °C. The mixture is filtered after cooling to room temperature; the filter cake is washed with water until the filtrate is free of chloride ions, and then with cold alcohol. The product may be recrystallized from methanol.

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German version: Angew. Chem. *78*, 681 (1966)

[1] Chlorination of Isothiocyanates, 4th Communication. – 3rd Communication: *G. Ottmann* and *H. Hooks, Jr.*, Angew. Chem. *78*, 210 (1966); Angew. Chem. internat. Edit. *5*, 250 (1966).

[2] *G. Ottmann* and *H. Hooks, Jr.*, Angew. Chem. *77*, 427 (1965); Angew. Chem. internat. Edit. *4*, 432 (1965); J. org. Chemistry *31*, 838 (1966).

## Preparation of Di-2-naphthyltrisulfane 2-Oxide

By Prof. P. W. Schenk, Dr. R. Steudel, and J. Bilal

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We have prepared di-2-naphthyltrisulfane oxide *(1)*, the first stable substituted sulfane oxide. The compound is formed in about 10% yield, alongside $(C_{10}H_2)_2S_2$, when 2-thionaphthol is condensed with thionyl chloride (molar ratio 2:1) in anhydrous ether at −20 °C:

$$2\ RSH + SOCl_2 \rightarrow RS{-}SO{-}SR + 2\ HCl \qquad R: 2\text{-Naphthyl}$$
*(1)*

It is a yellow, crystalline powder of m.p. 115–118 °C (decomp.), insoluble in ether. The formula given is confirmed by elemental analysis and cryoscopic molecular-weight determination in benzene.

A strong band at 1118 $cm^{-1}$ in the infrared spectrum (in KBr) indicates the SO stretching vibration of the thionyl group attached to two sulfur atoms.

The compound is reduced quantitatively by anhydrous hydrogen iodide at 20 °C:

$$R_2S_3O + 2\ HI \rightarrow R_2S_3 + I_2 + H_2O$$

The trisulfane formed was identified by IR spectroscopy. Di-2-naphthyltrisulfane 2-oxide decomposes quantitatively at 130 °C:

$$2\ R_2S_3O \rightarrow 2\ R_2S_2 + S(\text{solid}) + SO_2$$

It is stable for several days at room temperature. We ascribe its relative stability, compared with that of polysulfur oxides and other polysulfane oxides, to steric hindrance of disproportionation by the large substituents.

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## Synthetic Steroids with Moulting Hormone Activity [1]

By Dr. P. Hocks, Dr. A. Jäger, Dr. U. Kerb, and Dr. R. Wiechert

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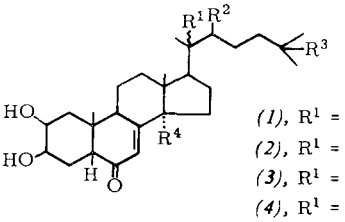
and Dr. A. Furlenmeier, Dr. A. Fürst, Dr. A. Langemann, and Dr. G. Waldvogel

Chemische Forschungsabteilung, F. Hoffmann La-Roche und Co. A.-G., Basel (Switzerland)

During our work [2] on the synthesis of the insect moulting hormone ecdysone we have obtained, *inter alia*, the ecdysone homologues *(1)*–*(3)* which differ from the natural hormone *(4)* only in lack of one, two, and three hydroxyl groups, respectively.

These compounds showed 1/80, 1/50, and 1/15, respectively, of the activity of ecdysone in the Calliphora test. They are thus the first non-natural steroids with moulting hormone activity.

Recently we isolated a 20-ξ-hydroxyecdysone *(5)* [1] from the dried pupae of the silkworm (*Bombyx mori*); it has been found to be 1.25 times as active as ecdysone in insect metamorphosis [3].



*(1)*, $R^1 = R^2 = R^3 = R^4 = H$
*(2)*, $R^1 = R^2 = R^3 = H$; $R^4 = OH$
*(3)*, $R^1 = R^4 = H$; $R^2 = R^3 = OH$
*(4)*, $R^1 = H$; $R^2 = R^3 = R^4 = OH$
*(5)*, $R^1 = R^2 = R^3 = R^4 = OH$

Received: May 24th, 1966 [Z 245 IE]
German version: Angew. Chem. *78*, 680 (1966)

[1] Part VI of Insect Hormones. – Part V: *P. Hocks* and *R. Wiechert*, Tetrahedron Letters, *1966*, 2989.

[2] *U. Kerb, P. Hocks, R. Wiechert, A. Furlenmeier, A. Fürst, A. Langemann*, and *G. Waldvogel*, Tetrahedron Letters *1966*, 1387; Helv. chim. Acta, in press.

[3] *P. Karlson*, Vitamine and Hormone *14*, 227 (1956).

## S-Amination of Thioureas and Thiourethanes

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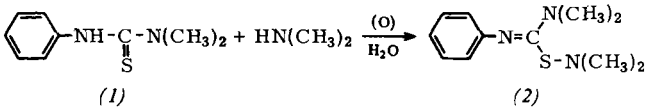
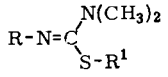
der Farbenfabriken Bayer AG., Leverkusen (Germany)

*Dedicated to Professor A. Lüttringhaus on his 60th birthday*

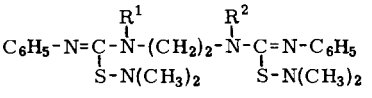
Oxidation of di- and tri-substituted thioureas, such as *(1)*, with aqueous alkali hypochlorite in the presence of secondary or cyclic primary amines leads to *S*-aminoisothioureas *(2)*, generally in very good yields.



*(1)* *(2)*

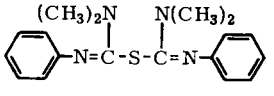


| R | $R^1$ | Reaction in | Yield [%] | Appearance, m.p. [°C] |
|---|---|---|---|---|
| Phenyl | Morpholino | $CH_3OH/H_2O$ | 85 | Yellow, undistill. oil |
| Phenyl | Cyclohexylamino | $CH_3OH/H_2O$ | 90 | Yellow, undistill. oil |
| 2,5-Dichlorophenyl | Dimethylamino | $CH_3OH/H_2O$ | 77 | Colorless cryst., 74—75 |
| *p*-Nitrophenyl | Dimethylamino | $DMF/H_2O$ | 90 | Green-yellow cryst., 107 |
| *p*-Tolyl | Cyclohexylamino | $CH_3OH/DMF/H_2O$ | 47 | Colorless cryst., 60 |
| *p*-Phenetyl | Cyclohexylamino | $CH_3OH/H_2O$ | 90 | Colorless cryst., 51 |
| Cyclohexyl | Dimethylamino | $CH_3OH/H_2$ | 82 | Pale yellow cryst., 64 |



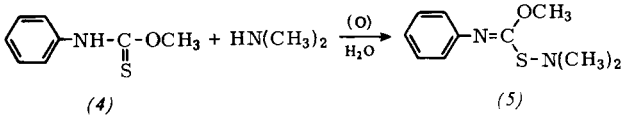
| $R^1$ | $R^2$ | Reaction in | Yield [%] | Appearance, m.p. [°C] |
|---|---|---|---|---|
| Methyl | Methyl | $DMF/H_2O$ | 90 | Pale yellow, undistill. oil |
| $-CH_2-CH_2-$ | | $DMF/H_2O$ | 29 | Pale yellow cryst., 114 |

Action of acids on *(2)* gives the sulfide *(3)* with loss of sulfur and amine.

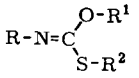


*(3)*

Thiourethanes, *e.g. (4)*, are oxidized to *S*-aminoisothiourethanes *(5)*.



*(4)* *(5)*



| R | $R^1$ | $R^2$ | Reaction in | Yield [%] | Appearance, m.p. [°C] |
|---|---|---|---|---|---|
| Phenyl | Ethyl | Dimethylamino | $CH_3OH/H_2O$ | 75 | Colorless cryst., 48 |
| Phenyl | Isopropyl | Dimethylamino | $CH_3OH/H_2O$ | 76 | Colorless cryst., 53 |
| *p*-Chlorophenyl | Methyl | Dimethylamino | $CH_3OH/H_2O$ | 90 | Yellow undistill. liquid |
| *p*-Nitrophenyl | Methyl | Morpholino | $DMF/H_2O$ | 33 | Pale yellow cryst., 115—116 |
| Cyclohexyl | Methyl | Cyclohexylamino | $CH_3OH/H_2O$ | 54 | Yellow undistill. oil |

The reactions were carried out in aqueous suspensions or water-miscible solvents.

Only the compounds containing short-chain amine groups can be distilled in a high vacuum without decomposition.

Some of the compounds have herbicidal properties.

*Examples:*

1. *S*-Dimethylamino-*N,N*-dimethyl-*N'*-phenylisothiourea:

180 g (1 mole) of *N,N*-dimethyl-*N'*-phenylthiourea are suspended in 500 ml of 40 % aqueous dimethylamine, and 650 ml of 12 % sodium hypochlorite are added during an hour, with stirring, the temperature being kept between 30 and 35 °C by cooling. The mixture is then stirred for three hours at this temperature and the oil that separates is collected, washed with water, dried over sodium sulfate, and distilled in a high vacuum. 190 g (= 81 %) of a pale yellow oil of b.p. 88–90 °C/0.015 mm are obtained.

2. *S*-Dimethylamino-*O*-methyl-*N*-phenylisothiourethane:

200 g (1.3 moles) of *O*-methyl-*N*-phenylthiourethane are suspended in 500 ml of water and 300 ml of 40 % aqueous dimethylamine, and then oxidized as in example 1. The resulting oil is distilled in a high vacuum, yielding 206 g (= 82 %) of a pale yellow liquid of b.p. 94–95 °C/0.12 mm.

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Publication delayed at the authors' request

## Preparation and Properties of Imidazole-2-carbaldehyde

By Prof. H. Schubert and H.-D. Rudorf

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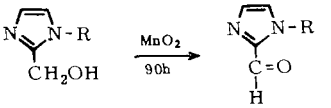
Universität Halle (Germany)

*Dedicated to Professor A. Lüttringhaus on his 60th Birthday*

Of the two imidazolecarbaldehydes the 4-aldehyde has long been known [1]. Anomalies in its behavior (failure to undergo the benzoin or Cannizzaro reaction) make its comparison with the 2-aldehyde desirable.

Attempted oxidation of 2-methylimidazole by $SeO_2$ in dioxane or xylene does not proceed beyond formation of an adduct; if the mixture of the reactants is heated above the melting point of the base, the imidazole ring is largely destroyed. Methods of oxidation that yield imidazole-4-carbaldehyde from 4-imidazolemethanol cannot be transferred to the 2-imidazolemethanols *(1a)* and *(1b)*; only by use of $N_2O_4$ or potassium peroxodisulfate [2] could we achieve dehydration and then in very small amounts that were preparatively useless.

We found, however, that treatment of the bases *(1a)* and *(1b)* with a six-fold amount of activated manganese dioxide B [3] in anhydrous ether, acetone, or $CCl_4$ at room temperature afforded the imidazole-2-carbaldehyde.



*(1)* *(2)*

*(a)*, R: -H
*(b)*, R: $-CH_2-C_6H_5$

Imidazole-2-carbaldehyde *(2a)* is precipitated in crystalline form on removal of the solvent by distillation, the yield being 70 %. Purification is effected by sublimation in a vacuum or by recrystallization from water, yielding colorless crystals of m.p. 204 °C (sealed tube), $\tilde{\nu}_{CO}$ = 1700 $cm^{-1}$, $\lambda_{max}$ =

285 mμ, ε = 12,500 (in alcohol); the aldehyde gives a 2,4-dinitrophenylhydrazone perchlorate, m.p. = 319 °C (from 50 % acetic acid). As with the 4-aldehyde, it does not undergo the benzoin or Cannizzaro reaction, giving instead intractable brown, tarry products.

1-Benzylimidazole-2-carbaldehyde *(2b)* (b.p. 128 °C/4 mm Hg), prepared similarly, gives the usual carbonyl reactions, affording an oxime, m.p. 167 °C (from alcohol), semicarbazone, m.p. 196 °C (from dilute alcohol), phenylhydrazone, m.p. 169 °C (from alcohol), 2,4-dinitrophenylhydrazone perchlorate, m.p. 228 °C (from alcohol), and hydrochloride, m.p. 142 °C (from dilute HCl). The benzoin condensation occurs smoothly in alcoholic solution, giving pale yellow 1,1′-dibenzyl-2,2′-imidazoloin, m.p. 140 °C, whose IR spectrum confirms the ene-diol structure expected by analogy with pyridoin[4]. The imidazoloin is oxidized in boiling dioxane by a current of air to the almost colorless diketone 1,1′-dibenzyl-2,2-oxalyldiimidazole, m.p. 148 °C.

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German version: Angew. Chem. *78*, 715 (1966)

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[2] *Z. Horii, K. Sakurai, K. Tomino*, and *T. Konishi*, J. pharmac. Soc. Japan *76*, 1102 (1956); Chem. Abstr. *51*, 3553b (1957).

[3] *M. Harfenist, A. Bavley*, and *W. A. Lazier*, J. org. Chemistry *19*, 1608 (1954).

[4] *H. R. Hensel*, Angew. Chem. *65*, 491 (1953).

## An Unusual Diazo-Coupling Reaction

By Dr. W. Kullick

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Farbenfabriken Bayer AG., Leverkusen (Germany)

*Dedicated to Prof. A. Lüttringhaus on his 60th birthday*

On diazotization of anthranilamides whose amide group is not fully substituted, benzo-1,2,3-triazin-4-ones *(1)*[1] are formed, which do not undergo diazo coupling in an aqueous medium.

Opening of the triazinone ring and coupling to yield azo dyes can, however, be achieved by heating *(1)* with 3-hydroxy-2-naphthamides *(2)* or acetoacetamides in polar organic solvents (*e.g. o*-dichlorobenzene or nitrobenzene) at 100–150 °C. The solution, initially clear and colorless, soon becomes colored and the dye *(3)* usually crystallizes during the reaction.

This reaction is of interest for preparation of azo dyes containing only partially substituted carboxamide groups adjacent to the azo group, since such dyes are not accessible by normal diazotization and coupling.

The structures of the products were proved by degradation.

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German version: Angew. Chem. *78*, 673 (1966)

[1] *A. Weddige* and *H. Finger*, J. prakt. Chem. *35*, 262 (1887).

## Alkylations by Dialkoxycarbonium Salts

By Dr. S. Kabuß

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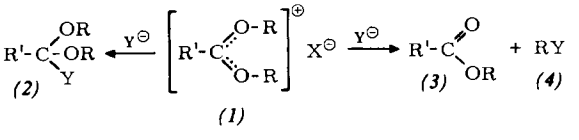
*Dedicated to Prof. A. Lüttringhaus on his 60th Birthday*

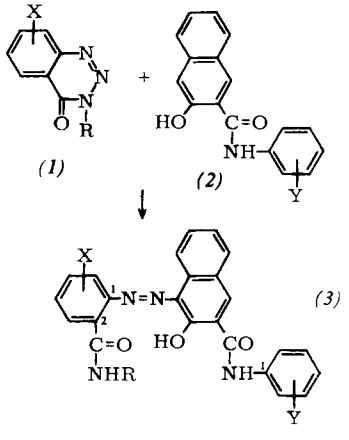
Dialkoxycarbonium ions [as in *(1)*][1] are typical ambident cations[2] which, according to the reaction conditions, react with nucleophiles either in a kinetically controlled reaction to give orthoacid derivatives *(2)* or in a thermodynamically controlled reaction with dealkylation to give carboxylic esters *(3)*.



*(1)*

*(1a)* R′ = H, R = $C_2H_5$, X = $SbCl_6$
*(1b)* R′ = $CH_3$, R = $C_2H_5$, X = $SbCl_6$

In alkylation reactions *(1)* → *(4)* the ester molecule *(3)* is the leaving group. Since replacement reactions occur the easier the more weakly basic is the leaving group, we should expect that dialkoxycarbonium salts *(1)*, like trialkyloxonium salts, would be very strong alkylating agents, able to react by transalkylation with even weak nucleophiles.



*(1)* *(2)* *(3)*

| Carbonium salt | Nucleophile | Alkylation product $X^+SbCl_6^-$; $X^+$ = | M.p. (°C) | Yield (%) |
|---|---|---|---|---|
| *(1a)* | $C_6H_5-CO-N(C_2H_5)_2$ | *(5)* $[C_6H_5-C(=OC_2H_5)-N(C_2H_5)_2]^+$ | 131–132 | 95 |
| *(1b)* | | | | 91 |
| *(1a)* | $CH_3-CO-N(C_6H_5)_2$ | *(6)* $[CH_3-C(=OC_2H_5)-N(C_6H_5)_2]^+$ | 166–168 | 97 |
| *(1a)* | $(C_6H_5)_2S=O$ | *(7)* $[(C_6H_5)_2S=OC_2H_5]^+$ | 123–125 | 92 |
| *(1a)* | $C_6H_5-C\equiv N$ | *(8)* $[C_6H_5-C\equiv NC_2H_5]^+$ | 72–74 | 90 |
| *(1b)* | | | | 61 |
| *(1a)* | $O(C_2H_5)_2$ | *(9)* $[O(C_2H_5)_3]^+$ | 129 [a] | 87 |
| *(1a)* | $(C_6H_5)_2C=O$ | *(10)* $[(C_6H_5)_2C=OC_2H_5]^+$ | 122 [a] | 90 |
| *(1a)* | $(CH_3)(C_6H_5)C=O$ | *(11)* $[CH_3-C(=OC_2H_5)-C_6H_5]^+$ | 133 [a] | 91 |
| *(1a)* | $C_6H_5-CHO$ | *(12)* $[C_6H_5-CH=OC_2H_5]^+$ | 130 [a] | 91 |
| *(1a)* | $C_6H_5-CH_2-CO_2C_2H_5$ | *(13)* $[C_6H_5-CH_2-C(=OC_2H_5)-OC_2H_5]^+$ | 65–68 | 92 |
| *(1a)* | $(CH_3)_2CH-CO_2C_2H_5$ | *(14)* $[(CH_3)_2CH-C(=OC_2H_5)-OC_2H_5]^+$ | 72–75 | 62 |

[a] With decomposition.

| R | X | Y | *(3)*, M.p. (°C) |
|---|---|---|---|
| H | H | 2-$CH_3$ | 287–289[a] |
| $C_6H_5$ | H | 2-$OCH_3$ | 257–258[a] |
| 2-$CH_3$-4-NHAc-$C_6H_3$ | H | 5-Cl-2,4-$(OCH_3)_2$ | 242–244[a] |
| 2-$CH_3$-4-Cl-$C_6H_3$ | H | 2-$CH_3$ | 294–296 |
| $C_6H_5$ | 5-CONH-$C_6H_5$ | 2-$OCH_3$ | 271–274[a] |
| $C_6H_5$ | 5-Cl | 2-$OCH_3$ | 266–268[a] |
| $C_6H_5$ | 4,6-$Cl_2$ | 4-Cl | 245–247[a] |
| *o*-$CH_3$-$C_6H_4$ | 5,6-CO-$C_6H_4$-*o*-CO- | 2-$OCH_3$ | 310–312 |

[a] With decomposition.

Experiment confirmed this expectation. Dialkylamides, sulfoxides, ethers, aldehydes, and ketones are alkylated to the corresponding salts by dialkoxycarbonium salts, the reactions being quantitative and often very fast[3]. Even esters of higher carboxylic acids can be alkylated in good yield if they are added in excess and if the lower-boiling ester is removed from the equilibrium mixture.

Dialkoxycarbonium salts are among the strongest alkylating agents known, being even stronger than trialkyloxonium salts.

For instance, the salts *(10)–(14)* cannot be obtained by reaction of nucleophiles with trialkyloxonium salts[4].

The reaction is best carried out by using the unsubstituted dialkoxycarbonium salts that are readily accessible from orthoformic esters[3], and it is convenient to use these as the well-crystalline hexachloroantimonates, *e.g. (1a)*. The substance to be alkylated is added in slight excess to a solution of this salt in $CH_2Cl_2$. The products crystallize immediately [*e.g. (11)* and *(12)*] or overnight [*e.g. (7)* and *(8)*] or can be precipitated by $CCl_4$.

Dialkoxycarbonium salts derived from higher carboxylic esters react appreciably more slowly, *e.g. (1b)*, and often give poorer yields and less pure products[5].

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German version: Angew. Chem. *78*, 714 (1966)

[1] *H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert,* and *K. Wunderlich*, Liebigs Ann. Chem. *632*, 38 (1960).

[2] *S. Hünig*, Angew. Chem. *76*, 400 (1964); Angew. Chem. internat. Edit. *3*, 548 (1964).

[3] The alkylation of ethers was already observed by *H. Meerwein*, Angew. Chem. *72*, 927 (1960); cf. also [4], p. 341.

[4] *H. Meerwein* in *Houben-Weyl*: Methoden der organischen Chemie. Thieme Verlag, Stuttgart 1965, Vol. VI/3, p. 329.

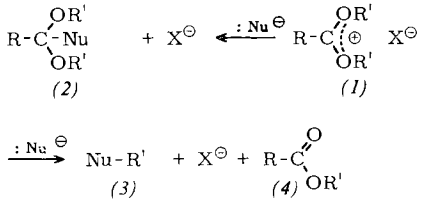
[5] Aryl-substituted dialkoxycarbonium salts also have alkylating properties: Angew. Chem. *78*, 714 (1966); Angew. Chem. internat. Edit *5*, 676 (1966).

## Aryl-Substituted Dialkoxycarbonium Ions as Alkylating Agents

By Prof. K. Dimroth and P. Heinrich

Institut für Organische Chemie, Universität Marburg (Germany)

Dialkoxycarbonium ions *(1)* can react with nucleophiles (:Nu) either by addition, to give saturated 1,1-dialkoxy compounds *(2)*, or by alkylation of the nucleophile, to give compounds *(3)* and carboxylic esters *(4)*[1,1a].



*(2)* *(1)*



*(3)* *(4)*

*(a)*, R : H; R' : $CH_3$, $C_2H_5$; $X^{\ominus}$ : $SbCl_6^{\ominus}$

*(b)*, R : $CH_3$; R' : $CH_3$, $C_2H_5$; $X^{\ominus}$ : $SbCl_6^{\ominus}$

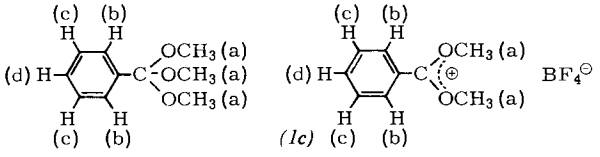
*(c)*, R : $C_6H_5$; R' : $CH_3$; $X^{\ominus}$ : $BF_4^{\ominus}$

*(d)*, R : 2,4,6-$(CH_3)_3C_6H_2$; R' : $CH_3$; $X^{\ominus}$ : $BF_4^{\ominus}$

Independently of *Kabuss*[2], who worked with *(1a)* and *(1b)*, we have found that the aryl-substituted dimethoxycarbonium salts *(1c)* (m.p. 88–90 °C[1a]) and *(1d)* (m.p. 89–91 °C) are powerful alkylating agents. For instance, on addition of 2,6-dimethyl-4-pyrone to a solution of the salt *(1c)* or *(1d)* in $C_2H_4Cl_2$ at room temperature, 4-methoxy-2,6-dimethylpyrylium fluoroborate is at once precipitated in *ca.* 60% yield.

However, under the same conditions pyrocatechol gives no detectable amount of its mono- or di-methyl ether with the salt *(1c)* but instead adds to it; the product, which is at once precipitated, yields *o*-hydroxyphenyl benzoate on addition of water. If it is desired to add both OH groups of pyrocatechol to *(1c)*, giving methyl *o*-phenylene orthobenzoate, then it is necessary to treat pyrocatechol with trimethyl orthobenzoate and a catalytic amount of a strong acid, such as 2-hydroxy-5-sulfobenzoic acid, the reaction then occurring *via (1c)*[3]. The salt *(1d)* is readily obtained crystalline from trimethyl 2,4,6-trimethylorthobenzoate and anhydrous $HBF_4$ in ether (93% yield); for steric reasons the cation thereof no longer gives addition reactions but merely methylates the pyrocatechol to guaiacol (83% yield).

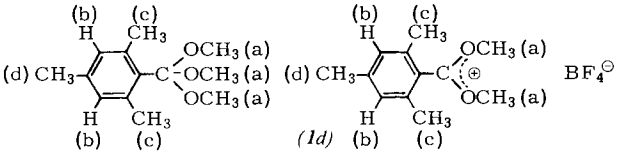
Compound *(1c)* is the first containing a reactive ambident cation for which the normally favored kinetically controlled addition is linked, owing to the high activation energy due to steric hindrance, with a thermodynamically favored alkylation[4].



*(1c)*

a: 2.52ppm (S)
b + c + d: 6.96ppm (M)

a: 4.23ppm (S)
b + c + d: 7.48ppm (M)



*(1d)*

a: 2.62ppm (S)
b: 6.39ppm (S)
c: 2.02ppm (S)
d: 1.77ppm (S)

a: 4.23ppm (S)
b: 6.71ppm (S)
c, d: 1.88ppm (S)

NMR spectra of *(1c)* and *(1d)* in liquid $SO_2$ at −10 °C (TMS as external standard) show equal chemical shifts for the $OCH_3$ protons in *(1c)* and *(1d)*; the polarization of the $OCH_3$ groups should therefore also be about equal. Studies with *para*-substituted cations analogous to *(1c)* are in progress.

Received: June 20th, 1966 [Z 271 IE]
German version: Angew. Chem. *78*, 715 (1966)

[1] *H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt,* and *J. Spille*, Chem. Ber. *89*, 2060 (1956); *H. Meerwein* in Houben-Weyl: Methoden der organischen Chemie. 4th Ed., Thieme, Stuttgart 1965, Vol. VI/3, pp. 299, 329.

[1a] *H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert,* and *K. Wunderlich*, Liebigs Ann. Chem. *632*, 38 (1960).

[2] *S. Kabuss*, Angew. Chem. *78*, 714 (1966); Angew. Chem. internat. Edit. *5*, 675 (1966).

[3] *K. Dimroth, P. Heinrich,* and *K. Schromm*, Angew. Chem. *77*, 863 (1965); Angew. Chem. internat. Edit. *4*, 873 (1965).

[4] *S. Hünig*, Angew. Chem. *76*, 400 (1964); Angew. Chem. internat. Edit. *3*, 548 (1964).

# Modern Methods of Analysis

The section *Analytische Chemie* of the *Gesellschaft Deutscher Chemiker*, the *Österreichische Gesellschaft für Mikrochemie*, and the *Schweizerische Gesellschaft für Analytische Chemie und Angewandte Chemie* held a symposium from the 13th to the 16th April 1966 in Lindau (Germany).

From the lectures:

## The Importance of Ultramicroanalysis of Streak Samples for Trace Analysis

*H. Ballczo*, Vienna (Austria)

Ultramicroanalysis of streak samples has become possible by use of the corundum rod, a small sintered rod of pure alumina [1]. It is now possible to isolate minute amounts of inclusions (inhomogeneities) in, *e.g.*, minerals and to subject them to complete microanalysis. In this method, not only are the difficulties of sampling (comminution) and of working up (choice of material for the containing vessel) overcome, but the concomitant advantages (better distribution, use of up to 2000 μg) make it possible to subject the sample to evaporation analysis and thus to determine also traces. When it is to be heated (for sublimation) the rod is placed in a small quartz cylinder, inclined so that the streak is at the top, covered with a small quartz tube that is somewhat narrowed in the middle, and heated at the lower end.

If, *e.g.*, a molybdenite contains arsenopyrites, wolframite, and zinc blende as impurities, the volatile oxides are collected one after the other (*e.g.*, $SeO_2$ from 316 °C, $As_2O_3$ from 321 °C, $MoO_3$ from 800 °C) and, if the cover tube is changed, can be investigated separately in turn; the difficultly volatile impurities such as $WO_3$, $Bi_2O_3$, $Sb_2O_3$, ZnO, and $SnO_2$ remain behind and they too can be further separated. For example, evaporation with HCl converts ZnO into the volatile (from 732 °C) $ZnCl_2$. Further, the quartz test tube can be subjected to reducing conditions (*e.g.*, heating with sodium azide at 275 °C or with sodium formate at 440 °C), which results in sublimation of the metals Cd (from 260 °C), Zn (from 360 °C), and simultaneously also Pb, Ag, and Ga; or by means of the hydrogen chloride evolved from $ZnCl_2$ (from 365 °C) $SO_3$ can be driven out of sulfates and $H_2S$ out of sulfides, as shown by *F. Feigl*. The sulfide formed during the reduction can be removed by cautious heating with ammonium chloride (evolution of HCl at 135 °C). The detection of $H_2S$ has been improved by more than two powers of ten (5 ng instead of 2 μg) by a development process (CdS → $Ag_2S$ → Ag). The solubilizing medium is conveniently sprayed on in aqueous or alcoholic solution ($ZnCl_2$). However, very small amounts of water or OH groups (OH-apatite, *etc.*) or free sulfur (in sulfides) can also be determined – for the first time – in a streak (in a melt with KSCN or benzoin by *F. Feigl*'s method).

## An Oscillometric Analytical Procedure with Continuous Recording

*R. Bertram*, Clausthal-Zellerfeld (Germany)

In oscillometry chemical processes are followed by measuring the electrical properties of the reaction mixture. Generally changes in conductivity and dielectric constant are determined. For the procedure in question the measuring cell containing the mixture is placed in a special circuit element coupled to the rest of the circuit so that the resulting frequency is an unambiguous measure of the changes occurring in the cell. The resulting frequencies (50 c/s to 1 Mc/s), are measured by a receiver, and an attached high-speed recorder ensures instantaneous and complete recording. The process is applicable over the whole ionic conductivity range for cells with or without direct electrode contact. Among other reactions, the rapid hydrolysis of phenyl trifluoroacetate and the slow adsorption of sodium hydroxide on quartz powder has been investigated; finally, a new mode of dissolution of molten lead in a cadmium chloride melt has been discovered. Drying processes have been recorded for solids in platelet form down to water contents of $10^{-2}$ wt.-%. Even though recording is instantaneous a relative accuracy of $10^{-3}$ % is obtained, which is beyond that of any other conductivity method.

[1] Degussit Al 24, from DEGUSSA, Frankfurt/M. (Germany).

## Determination of Traces of Arsine in Inert-Gas Mixtures in Presence of a Large Excess of Stibine. Influence of Precipitation Conditions on the Enrichment of Arsenate during Coprecipitation with Phosphate

*W. Gann*, Hagen (Germany)

Arsine and stibine are removed from the gas mixture to be analysed by absorption in a perchloric acid solution of sodium triiodide. Antimony is determined in an aliquot of the absorbing solution by reduction with hypophosphite and photometric determination of the resulting iodoantimonate-(III). Traces of arsenate are enriched from the absorbing solution by addition of sodium phosphate and then of calcium chloride at pH ≥ 12, causing coprecipitation with calcium phosphate. The phosphate precipitate is dissolved in a little hydrochloric acid, and after a reduction with hypophosphite the arsenic is determined in this solution photometrically as brown arsenic sol. The range of applicability is 20 μg to the mg region per 50 ml of absorbing solution for stibine, and 5 μg to 60 μg per 50 ml for arsine. There is no interference with the determination of arsine unless more than 10 mg of antimony is present in the absorbing solution.

## Interpretation of Potentiometric and Photometric Titration Curves Obtained on Recording Apparatus

*E. Greuter*, Herisau (Switzerland)

Automatically recorded titration curves have the advantage of showing the complete course of the titration, so that anomalies can be recognized immediately. A potential-volume curve is produced. For its generation the advance of the paper and the addition of the reagent must be accurately proportional. The equivalence point is preferably determined graphically from the curve; parallel tangents to the curve are drawn in front of and behind the equivalence point; a parallel line drawn midway between these two tangents cuts the curve at the equivalence point.

Tests have been made to determine what faults can arise on use of automatically recording analytical apparatus. The errors observed are caused by the recording itself and during measurement along the volume axis of the potentiogram. Titrations of hydrochloric and acetic acid with sodium hydroxide, with various experimental programs, gave deviations of +3.3 %, +1.8 %, −2.0 %, and +1.9 % in the results relative to the standard values.

Unsymmetrical curves are harder to evaluate; no mathematically sound method is known for this purpose.

Electrical differentiation of the potentials arising during the titration with respect to the time, and recording of the derivatives against volume, are often advantageous. End-points close to each other often give only one potential jump on the integral curve, whereas the derivative curve often shows the two equivalence points separated. The simplest method of electrical differentiation is by means of a capacitance-resistance circuit.

Photometric titration curves can be recorded by coupling a potentiograph to a spectrophotometer. Acid-base titrations give symmetric curves if the pK of the indicator equals that of the acid (or base) to be titrated. The photometric titration curve can be obtained by graphical addition of a potentiometric titration curve to the curve showing the change in extinction of the indicator in relation to pH.

## Micromethod for Analytical Determination of Lower Oxidation States

*R. Gruehn*, Münster (Germany)

A new method permits determination of lower oxidation states in substances that react in a KOH melt with evolution of $H_2$. 0.5–15 mg samples, including single crystals, are added to a degassed KOH melt in a vacuum; all the substance dissolves in its highest oxidation state, while an equivalent amount of hydrogen is set free. The hydrogen is pumped off, compressed in a Töpler pump, and measured in a Hg buret; it can be identified by combustion over CuO. For instance, the compositions of six $NbO_x$ phases have been accurately determined, giving the following values of x: 2.417 ± 0.003 (2 modifications); x = 2.454 ± 0.002; x = 2.462 ± 0.002 to x = 2.467 ± 0.001 (phase range); x = 2.467 ± 0.001 to 2.479 ± 0.001 (phase range); x = 2.483 ± 0.001. Moreover, the lower phase limit of the H modification of niobium pentoxide has x = 2.489 ± 0.001. Other lower oxides, oxide halides, and halides of Mo, W, Nb, Ta, and Ti have been investigated. The oxidation states of the compounds $NbCl_{2.33}$, $Ta_6Cl_{14}{\cdot}8H_2O$, and $Ta_6Br_{14}{\cdot}8H_2O$ have been confirmed by this method.

## Direct UV-Spectrophotometric Evaluation of Thin-Layer Chromatograms

*H. Jork*, Saarbrücken (Germany)

In thin-layer chromatography one obtains discrete zones, for the localization, identification, and/or quantitative analysis of which spectrophotometric methods can be used. By use of the Zeiss chromatogram-spectrophotometer, reflection fluorescence and absorption spectra can be obtained directly from the chromatogram layer, both for the visible and the ultraviolet region.

For localization of invisible, absorbing zones the whole chromatogram is examined at a wavelength specific for the compound in question. Then differences in the amount of reflection are found for various parts of the layer.

The reflection spectrum of a zone that has thus been located is best taken with a slit width corresponding approximately to the radius of the spot. It usually corresponds exactly to the absorption spectrum measured in solution (*e.g.* for *p*-ethoxyacetanilide and trimethylxanthine). If this is not the case, as for 2,3-dimethyl-4-dimethylamino-1-phenylpyrazol-5-one or acetylsalicyclic acid, then these medium effects, *e.g.*, that of Kieselgel G as a layer, can be used for characterization of the substance present. The sensitivity obtained by taking the spectrum directly is at least ten times greater than for measurement in the usual cells. For absorption spectra at least 3 μg of substance is required, for fluorescence spectra only 30 to 50 ng.

Direct quantitative evaluation of thin-layer chromatograms is possible with the Kubelka-Munk function (relative deviation ± 3 %).

## Analytical Use of Infrared Spectroscopy with Gratings. Quantitative Analysis of Gas Traces

*G. Kemmner, G. Nonnenmacher*, and *W. Wehling*
Überlingen (Germany)

The sensitivity and detection limits of the quantitative infrared-spectroscopic analysis of gas traces depend on the cell length and on factors related to the apparatus: resolving power, signal-to-noise ratio, and the scale of the ordinate. The cell thickness can be varied independently of the instrument; the recording parameters, on the other hand, are connected with the design of the instrument, and are essentially determined by energy relationships.

The influence of the apparatus parameters on the quantitative analysis of $C_2H_2$, $N_2O$, and CO has been tested on dilution series of these gases in nitrogen. Concentrations between 100 ppm and close to the detection limit (see below) were determined by means of two grating instruments and one NaCl-prism instrument in a 1 m gas cell and at various scanning conditions.

According to the distance between their rotational lines the investigated absorption bands show varying dependence on the spectral slit width ΔS. The effect is slight in the case of $N_2O$. CO and $C_2H_2$ exhibit increasingly resolved fine structure with decreasing ΔS; the molar extinction coefficients of the analytical lines increase by a factor of 4 to 6 when ΔS is reduced from 4 to 0.6 $cm^{-1}$ in the case of $C_2H_2$, and from 18 to 0.5 $cm^{-1}$ in the case of CO.

The high dispersion of grating instruments gives flexibility in the adjustment of the recording parameters under the conditions of the quantitative analysis: narrow slits for the highly sensitive measurement of larger concentrations, and wide slits for a favorable signal/noise ratio with relatively good resolving power for measurements in the lower ppm range with ordinate scale expansion.

The smaller the spectral slit width and the greater the signal/noise ratio, the lower are the detection limits. For an optical path of 1 m, the detection limits in the most favorable case (Perkin-Elmer 225 with a 50-fold expansion of the ordinate) were found to be 2.5 ppm for CO, 0.4 ppm for $N_2O$, and 0.1 ppm for $C_2H_2$. These values lie in a range that, without ordinate scale expansion, is analytically attainable only by the use of a 10 m gas cell.

## Element-Specific Determination of Gas-Chromatographically Separated Metal Compounds by Use of Atomic Absorption Spectroscopy; Determination of Lead Alkyls in Gasoline

*B. Kolb, G. Kemmner, Fr. H. Schleser*, and *E. Wiedeking*
Überlingen (Germany)

Atomic absorption spectroscopy can be used for determination of the concentration, in a sample, of an element amenable to this method. Since, however, a given element may occur as various compounds, these must be separated when it is necessary to differentiate between them. For volatile compounds this is most simply done by gas chromatography, the column being connected directly to the burner of an atomic absorption spectrophotometer. The recorder draws a chromatogram in which, of all the components separated, only the compounds to be analysed appear as peaks. The combination of gas chromatography with atomic absorption spectroscopy is particularly suitable for analysis of traces of volatile metal compounds in complex mixtures. Since the process is specific to an element no compound-specific response factor is required.

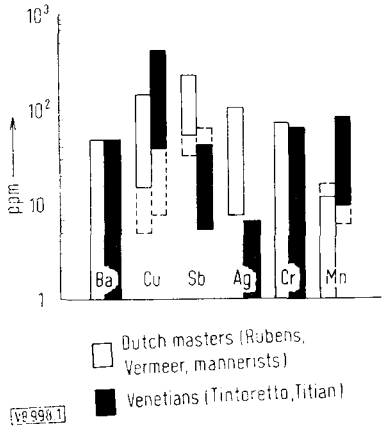
In the determination of tetramethyl- and tetraethyl-lead in gasoline, use of the 217 mμ line of a lead hollow-cathode lamp gave a detection limit of $4\times10^{-11}$ g-atom of Pb per sec, which under the given working conditions and a sample size of 5 μl corresponds to a concentration of 32 mg $Pb(CH_3)_4$ and 85 mg $Pb(C_2H_5)_4$ per liter of gasoline, respectively.

## Use of Activation Analysis for Determination of Traces in the White Lead of Paintings

*F. Lux* and *L. Braunstein*, Munich (Germany)

In collaboration with the Dörner Institut of the Bavarian State Collection of Paintings a study has been begun of the use of activation analysis for determining the content of trace components in the white lead of paintings. Its object is to test the possibility of dating pictures and of ascribing them to various schools on the basis of the trace components in the white lead,the chief pigment all paintings.This can be achieved only by activation analysis since only microgram samples are available from a painting and the content of trace material often amounts to only a few ppm, so that the amounts of the trace ingredient will sometimes lie in the range $10^{-11}$ to $10^{-10}$ g. In similar studies of the white lead of paintings by Dutch artists, *Houtman* and *Turkstra*[2] concluded that the trace content decreased after about 1850.

In our work the content of Ag, Ba, Cr, Cu, Mn, and Sb in the white lead was determined. The samples were taken from undoubtedly white parts of the pictures, *e.g.* white spots. Each sample was subdivided into one for short irradiation (irradiation time 4 hr; $^{139}$Ba, $^{64}$Cu, $^{56}$Mn) and another for long irradiation (irradiation time 300 hr; $^{110m}$Ag, $^{51}$Cr, $^{122}$Sb). The samples were irradiated in the research reactor at Munich (FRM) with a flux of $5\times10^{12}$ or $3\times10^{13}$ neutrons $cm^{-2}$ $sec^{-1}$. The individual nuclides were determined by a combination of radiochemical separation and gamma-spectrometric measurement. A 1600 channel pulse-height analyser was used for this measurement. Counting times for the longer-lived nuclides were up to 800 min. The limits of detection were $5\times10^{-10}$ g for Ba, $2\times10^{-10}$ g for Cr, $10^{-10}$ g for Ag and Cu, and $10^{-11}$ g for Mn and Sb. Samples of white lead were taken on the one hand from paintings by Dutch masters of the 16th and 17th century, namely *Rubens*, *Vermeer*, and the mannerists *Hemessen*, *Janssens*, and *Roymerswaele*, and on the other from paintings of the Venetians *Titian* and *Tintoretto*. The results are given in Fig. 1.




They show that the Dutch and the Venetian white leads differ in Ag, Sb, and Mn content. It is thus proved in principle that there is a characteristic distribution pattern for the trace ingredients in white lead of paintings of about the same age.

As regards the recognition of imitations, our studies and the conclusions reached by *Houtman et al.*[2] show that modern white lead differs from the old material in a distinctly lower copper content (<1 ppm) and sometimes in the very marked occurrence of a single trace ingredient, to the extent of some tenths of a percent (*e.g.*, Ba in our work or Zn[2]).

[2] *J. P. W. Houtman* and *J. Turkstra*: Radiochemical Methods of Analysis. Vol. I, Conf. Proc. Salzburg 1964, IAEA Vienna 1965, p. 85.

## Spectrochemical Determination of Impurities in Very Pure Aluminum after Removal of the Matrix by Distillation as Organometallic Compound

*K. H. Neeb*, Erlangen (Germany)

Metallic aluminum reacts with ethyl bromide with formation of triethylaluminum tribromide, which can be vacuum-distilled without decomposition, leaving some important impurities as a nonvolatile residue. This simple method of separation can be utilized to determine traces of other elements in very pure aluminum. For evaluation of the behavior of ppm amounts of impurities, control mixtures containing radioactive isotopes were studied; the distillation residue was analysed spectrographically. Recoveries in the residue and the lower limits of determination (for 1 g of aluminum) are shown in the table.

| Impurity | Fe | Cu | Pb | Ag | Cr | Mn | Co | Ni |
|---|---|---|---|---|---|---|---|---|
| Recovery (%) | 99 | 99 | 99 | 99 | 95 | 94 | 98 | 102 |
| Lower lim. of detn. (ppm) | 0.3 | 0.02 | 0.5 | 0.02 | 0.1 | 0.07 | 0.05 | 0.4 |

Low background values were obtained by confining the reagents used to low-boiling liquids such as ethyl bromide, bromine, and nitric acid that are easy to purify by distillation. The process is not limited to final use of spectroscopic determination.

## A Novel Pulse Process with Digital Readout for Automatic Titration

*F. Oehme*, Glattbrugg-Zurich (Switzerland)

Except where the reagent is generated coulometrically, almost all accurate automatic titrators involve use of syringe burets. Induction motors used for control of the buret have the disadvantage, due to inertia of the control mechanism, that the volume added does not correspond to the duration of the dosage command when the latter is short; a further result of the inertia is that a small excess may be added when the cut-off is very sudden.

Step motors do not suffer from these disadvantages. Single impulses delivered as signals by a pulse generator are passed on as defined rotations of the buret control mechanism even if the pulse duration is only $^1/_{100}$ sec. For example, a step motor rotates about 18° per pulse. The motor stops at once when the current stops and remains magnetically arrested.

The step-motor drive and the pulse generator on which it is based have the following advantages:

(a) The volume added is shown directly by counting the pulses, *e.g.* by a mechanical counter.

(b) Very great resolution of the volume used can be achieved by a simple program. For instance, 1 ml can be added in 1000 separate portions.

(c) If the recorder used for drawing a titration curve includes a step-motor drive for advancing the paper, the two motors can be actuated by a single, common pulse generator. A cable connection (impulse conductor) can be used for synchronization of control of the buret and movement of the paper.

(d) The impulse feeder mentioned in (c) can be as long as desired, which opens obvious possibilities for remote control.

(e) The frequency of the impulse generator can be so related to the signal from the servo-generator of a potentiometer recorder that the rate of addition can be related to the steepness of the titration curve.

## Use of Thin-layer Chromatography and Infrared Spectroscopy for Elucidation of the Thermolysis Products of Triphenylphosphine

*H. Schindlbauer* and *F. Mitterhofer*,
Vienna (Austria)

Phosphines and phosphine sulfides can be readily separated on thin-layer chromatograms run on silica gel layers with weakly or moderately polar solvents. The $R_F$ values increase rapidly in the order tertiary > secondary > primary phosphines. Positional isomers of phosphines (*e.g.* the three tritolylphosphines) are best separated on basic alumina with hexane/benzene (5:1 v/v) as solvent; the $R_F$ values increase in the order *p-* > *m-* > *o-*. Phosphine oxides are well separated by use of ether/ethyl acetate. Replacement of a phenyl group by methyl greatly decreases the $R_F$ value of all organophosphorus compounds.

Phosphines can be oxidized to phosphine oxides on the plate before running by spotting with iodine in $CCl_4$; similarly they can be converted with methyl iodide into phosphonium salts, which run in their dissociated form in acetone/HCl but in their undissociated form in acetone/$NH_3$. Phosphines are best made visible by iodine in $CCl_4$ (yellow spots), whereas compounds of quadrivalent phosphorus are well disclosed by permanganate-sulfuric acid (white on pink). The two-dimensional technique and the wedge method make separation of organophosphorus compounds possible.

The decomposition products (66 hr at 400 °C under $N_2$) of triphenylphosphine have been identified by this technique. All the products were also studied by infrared spectroscopy. When no reference sample was available for thin-layer chromatography, the spots of the unknown were isolated on a preparative scale and analysed infrared-spectroscopically, and the assumed product was then synthesized.

The decomposition products of triphenylphosphine were proved to contain substantial amounts of phosphorus, benzene, biphenyl, and *p*-biphenylyldiphenylphosphine,with smaller amounts of *o-*, *m-*, and *p*-terphenyl, *p*-phenylenebis-(diphenylphosphine), *m*-biphenylyldiphenylphosphine, and diphenylphosphine, with only traces of 9-phenyl-9-phosphafluorene detectable.

## New Analytical Separations of Traces of Material on Dextran Gel

*H. Spitzy*, Graz (Austria)

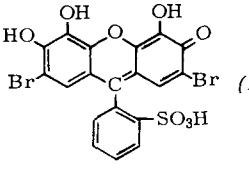
Dextran gels can be used for other analytical purposes besides gel filtration. Reversible adsorption of aromatic and heterocyclic compounds is the basis for a separation of thyroid hormones from blood serum [3].

A further use of dextran gels arises from the fact that the strength of adsorption of solvents varies in accord with their polarities. This effect (known also for ion-exchange resins) has the result that with methanol/water mixtures the water is enriched in the gel phase compared with the mobile outer phase. During passage through a column filled with Sephadex swollen in methanol/water a mixture of alkali chlorides is separated by virtue of the different solubilities of these chlorides in methanol/water mixtures (more correctly, in methanol/water mixtures of different compositions). Under suitable conditions (methanol concentration, 75 vol.-%; column dimensions, 42×1 cm; gel type, Sephadex G-25 fine; rate of addition, 4.40 ml $hr^{-1}$ $cm^{-2}$) all the alkali chlorides can be separated quantitatively at concentrations of $10^{-4}$ M downwards. For an addition of 0.5 ml this corresponds to 340 ng of Li to 6.3 μg of Cs. Yields are 95–100 %. Microgram quantities of Li and K are separated quantitatively from a more than 1000-fold excess of sodium (1600 μg) on a 7.5×1.5 cm column. For Li, Na, and K it is a matter of pure distribution chromatography, but for Cs and Rb adsorption phenomena enter, so that quantitative elution is adversely affected at concentrations below $10^{-4}$ M.

## Photometric Determination of Small Amounts of Tin with Bromopyrogallol Red

*D. Thierig* and *F. Umland*, Münster (Germany)

The 1:1 complex formed by Bromopyrogallol Red *(1)* with Sn(II) or Sn(IV) in acetate-buffered solution of pH 3 is suitable for photometric determination of tin. Direct analysis can be effected in presence of at least a 100-fold molar excess of alkalis, alkaline earths, lead, and mercury(II); interference



*(1)*

by most of the heavy-metal ions can be avoided by separation of the tin as $SnI_4$ before the determination; then there is no interference by 1000-fold excesses of Be, As, Bi, Ti(IV), V(V), Cr(III), Mn(II), Fe(II), Fe(III), Cu, Zn, Ce(III), or W(VI). Only Sb causes a too high and Ag a too low extinction. The extinction coefficient was determined as $\varepsilon = 18000$ *l* $mole^{-1}$ $cm^{-1}$ at 515 mμ. The most favorable concentration limits are 6–90 μg of tin in 25 ml of solution. [VB 998 IE]

German version: Angew. Chem. *78*, 718 (1966)

[3] *H. Spitzy* and *H. Ortner*, Microchem. J. *10*, 194 (1966).

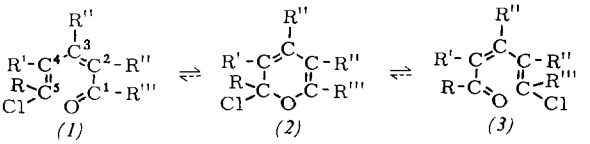
## Pentadiene-1,5-Halogen-Oxygen Exchange

*A. Roedig*, Würzburg (Germany)

Compounds of general structure *(1)* – with the *cis*-configuration at C-2/C-3 – rearrange rapidly and quantitatively in boiling $CCl_4$ into the acid halides *(3)* when R = Cl or Br and R''' = H, $CH_3$, or $C_6H_5$. The term "1,5-pentadiene halogen-oxygen exchange" is proposed to designate this thermal rearrangement. Its mechanism has been largely clarified by radioactive labelling and kinetic measurements [1].

This reaction was discovered with *cis*-perchloropentadienal *(1a)* [2] but is not restricted to perchlorinated pentadienal systems, as has been shown by study of compounds *(1d)* to *(1d)*. The *cis*-compound *(1e)* avoids the pentadiene-1,5-halogen-oxygen exchange by rearrangement to its *trans*-isomer; however, pentadienals containing chloro or bromo substituents on C-3 and C-2 are more stable in the *cis*-form [3].

Furthermore, experiments with [1-$^{14}$C]perchloropentadienoyl chloride *(1f)* have shown that pentadienal 1,5-halogen-oxygen exchange is not restricted to aldehydes and


*(1)* ⇌ *(2)* ⇌ *(3)*

*(a)*: R = R' = R'' = Cl; R''' = H
*(b)*: R = Br; R' = R'' = Cl; R''' = H
*(c)*: R = R' = Cl; R'' = Br; R''' = H
*(d)*: R = Cl; R' = $CH_3$; R'' = Br; R''' = H
*(e)*: R = R' = Cl; R'' = R''' = H
*(f)*: R = R' = R'' = R''' = Cl
*(g)*: R = $C_6H_5$; R' = R'' = Cl; R''' = H

ketones. If *(1f)* is heated for 48 h at 130 °C the radioactivity is distributed equally between C-1 and C-5. However, the data collected up to the present suggest that two halogen substituents on C-5 are essential for complete and irreversible pentadiene 1,5-halogen-oxygen exchange: the *cis*-form of *(1g)* appears merely to enter into an equilibrium with the pyran *(2g)*; the presence of the ketone *(3g)* in the mixture cannot be ascertained.

If complex-forming reagents ($FeCl_3$ or $SnCl_4$) are added to *(1)* during the rearrangement, pyrylium salts can be isolated in good yield[4], a fact that presents strong evidence for formation of the pyrans *(2)* as intermediates.

[Lecture at Saarbrücken (Germany), Jan. 21st, 1966]

[VB 988 IE]

German version: Angew. Chem. *78*, 722 (1966)


[1] *A. Roedig*, Angew. Chem. *76*, 276 (1964), Angew. Chem. internat. Edit. *3*, 317 (1964).

[2] *A. Roedig* and *G. Märkl*, Liebigs Ann. Chem. *659*, 1 (1962); *A. Roedig, R.Kohlhaupt*, and *G.Märkl*, Chem.Ber.*99*, 698 (1966).

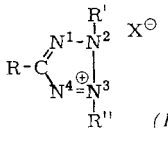
[3] *H. G. Viehe*, Chem. Ber. *93*, 1697 (1960); Angew. Chem. *75*, 793 (1963), Angew. Chem. internat. Edit. *2*, 622 (1963); *H. G. Viehe* and *E. Franchimont*, Chem. Ber. *96*, 3153 (1963); *H. G. Viehe, J. Dale*, and *E. Franchimont, ibid. 97*, 244 (1964).

[4] *A. Roedig, M. Schlosser*, and *H.-A. Renk*, Angew. Chem. *78*, 448 (1966); Angew. Chem. internat. Edit. *5*, 418 (1966).

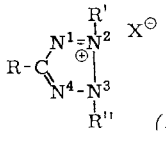

## The Nature of Tetrazolium Salts and Formazans


*C. Schiele*, Ulm (Germany)


The concensus of opinion regarding the nature of tetrazolium salts was summarized by *Nineham*[1] who formulated them as resonance hybrids between the structures *(1a)* and *(1b)*. However, from the observation of $\nu_{C=N(1)}$ and $\nu_{C-N(4)}$ vibrations at 1527–1544 $cm^{-1}$ and near 1150 $cm^{-1}$ we were able to establish that the system is not a resonance hybrid but occurs exclusively in the form *(1a)*.



*(1a)*

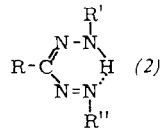


*(1b)*

Furthermore, it could be shown that there is a marked influence of aryl substituents on the carbon atom of the tetrazolium ring upon the ease of reduction of these compounds (measurement of the decomposition potential on Ag/Pt); this effect could even be used occasionally, *e.g.* when R = R′ = *p*-tolyl or *p*-chlorophenyl and R″ = phenyl, or when R = R″ = *p*-tolyl or *p*-chlorophenyl and R′ = phenyl, to differentiate between *N*(2)- and *N*(3)-substituted tetrazolium salts. These findings led to the postulation of a heterocycle with varying bond lengths between the N-2 and N-3 atoms of the ring, depending on the nature of the aryl substituent on the carbon atom in the ring. The occurrence of two modifications with each of eight solid tetrazolium perchlorates indicated the existence of tetrazolium salts which are stereoisomeric with regard to the arrangement of the aryl residue. The infrared spectra of these forms differ in the regions of their skeletal, $\gamma_{C-H}$, and ring deformation vibrations. They also give different Debye-Scherrer diagrams and different extinction coefficients in the ultraviolet and visible regions.

The occurrence of stereoisomers does not, however, explain why crystalline tetrazolium salts turn yellow when exposed to light. This discoloration is attributed by *Nineham*[1] to some structural characteristic of the compounds, but no explanation is given. The new absorption bands that appear between 400 and 450 mμ when layers of tetrazolium salts are irradiated can be interpreted when a photoisomerism caused solely by a change in position of the anion is assumed. This interpretation finds support in the results of infrared spectroscopic investigations.

Formazans *(2)* also exhibit a marked change in frequency of the C–N valence vibration in dependence on the *C*-aryl substituent. If formazans are examined in which only the *C*-aryl substituent is varied, an increase in the extinction of the chromophoric band from log ε = 4.1 to log ε = 4.2 and a



*(2)*

shift in the frequency of the C–N valence vibration from 1226 to 1236 $cm^{-1}$ are observed on passing from a substituent with a (+)-M effect to one with a (−)-I effect. These findings are indicative of an increase in the electron density in the N=C–N portion of the molecule and of an expansion along the N–H···N bonds associated with a weakening of the hydrogen bond. Consequently, the *C*-aryl residue and the "heterocycle" appear to be almost coplanar whereas both the hydrogen bridge and the *N*-aryl residues are not in a coplanar arrangement. In principle, therefore, the same picture is obtained for formazans as for tetrazolium salts, namely that the *C*-aryl substituent exerts a significant influence on the bonding and on the ring parameters in remote parts of the molecule.

[Lecture at Isny (Germany), April 20th, 1966]

[VB 994 IE]

German version: Angew. Chem. *78*, 683 (1966)


[1] *A. W. Nineham*, Chem. Reviews *55*, 355 (1955).


## New Facts about Aroma Essences


*F. Drawert*, Siebeldingen (Germany)


It was established using gas chromatography and radio-gas chromatography that there are considerable differences between the substances that cause the aromas of fruit and those of fruit juices prepared from the fruit. The fruity esters of apples (butyl acetate, amyl acetates, hexyl acetate, *etc.*) are split to varying degrees by hydrolases after damage of the fruit cells. Simultaneously enzymatic oxidations occur in the damaged (homogenized) fruit which lead to the formation of new aroma essences, which include 2-hexenal *(1)* and hexanal *(2)* in predominant proportions; these compounds therefore play a major part in determining the aroma and taste of apple juice. The precursor of *(1)* is linolenic acid, that of *(2)* is linoleic acid[1].

Numerous aroma essences are produced by yeast. The amounts of such substances vary when the sugar content of the fermentation solution is kept constant but its amino-acid content is varied. Model fermentations with *Saccharomyces cerevisiae* in an otherwise uniform culture medium revealed that various amino acids contribute differently to the formation of aroma substances in the yeast. Methionine and proline cause a higher formation of malic and tartaric acids relative to other amino acids.

[Lecture at Freiburg (Germany), April 29th, 1966]

[VB 993 IE]

German version: Angew. Chem. *78*, 683 (1966)

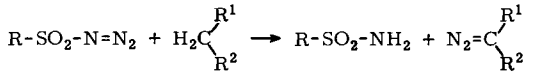

[1] *F. Drawert, W. Heimann, R. Emberger*, and *R. Tressl*, Liebigs Ann. Chem., in the press.


## Transfer of Diazo Groups: Mechanism and Preparative Importance


*M. Regitz*, Saarbrücken (Germany)

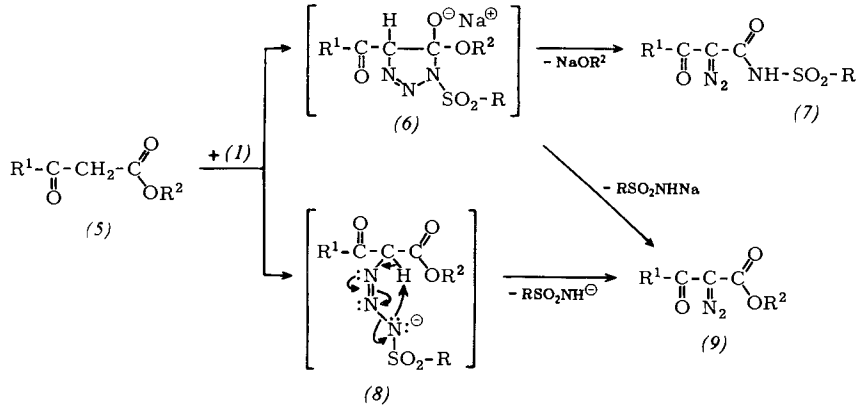

Transfer of diazo groups from sulfonyl azides *(1)* to active methylene compounds *(2)* occurs by exchange of the $N_2$ group of the azide for two H atoms of the methylene com-

pound *(2)*, with formation of sulfonamides *(3)* and diazo compounds *(4)*.



*(1)* *(2)* *(3)* *(4)*

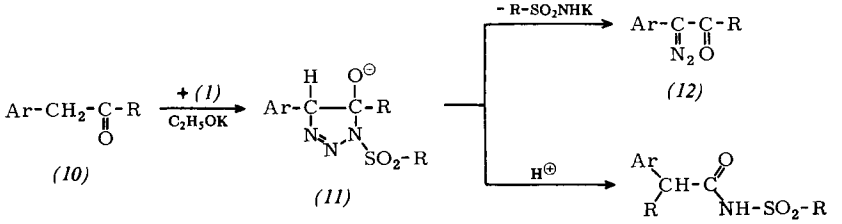
For β-dicarbonyl compounds of type *(5)* and for aryl-activated α-methylene ketones *(10)* some statements can be made about mechanism. Malonic esters *(5)*, $R^1$ = OR, and β-keto esters *(5)*, react with the azide *(1)* in ethanol/sodium ethoxide by loss of an alkoxy group to form diazo-*N*-sulfonyl-carboxamides *(7)*, probably by way of the triazoline *(6)*.



*(5)* *(6)* *(7)* *(8)* *(9)*

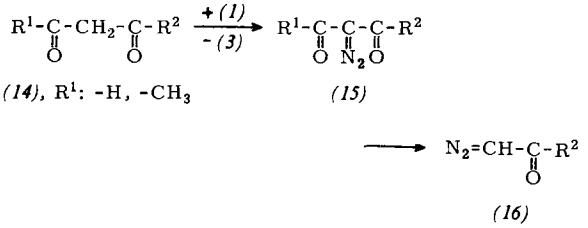
The reaction route *(5)* → *(8)* or *(6)* → *(9)* → *(7)* is excluded because diazo-carboxylic esters *(9)* do not react with sulfonamides *(3)* in ethanol/sodium ethoxide. Esters *(9)* are formed almost quantitatively from compounds *(5)* by transfer of diazo groups in acetonitrile/triethylamine, in which intermediates *(8)* are conceivable.

When aryl-activated methylene compounds *(10)* are used an unstable intermediate can be isolated, whose decomposition indicates its triazoline structure *(11)*: thus in alkaline medium they afford diazo ketones *(12)*, whereas acid hydrolysis yields *N*-sulfonylacetamides *(13)* with evolution of nitrogen and anionotropic migration of the group R.



*(10)* *(11)* *(12)* *(13)*

α-Methylene ketones such as acetophenone and acetic esters have insufficent $H^+$ activity for transfer of diazo groups, so the acylated derivatives *(14)* are treated with the azide *(1)* and after the transfer the activating group is removed solvolytically. If $R^1$ = H in *(14)*, compounds *(16)* can be obtained



*(14)*, $R^1$: -H, $-CH_3$ *(15)* *(16)*

directly, *i.e.* without isolation of the intermediate *(15)*. Diazoacetic esters and diazoacetophenones can be thus prepared[1].

[Lecture at Würzburg (Germany), May 20th, 1966]

[VB 996 IE]

German version: Angew. Chem. *78*, 684 (1966)

[1] *F. Menz*, Diploma Thesis, Universität Saarbrücken 1966.

## Structure of Metal Compounds

*K. Brodersen*, Erlangen (Germany)

As part of a systematic study of the structures of platinum-metal halides the crystal structure of palladium(II) bromide has been determined. X-Ray investigations of the dark brown, needle-shaped single crystals (prepared by chemical transport reactions) showed the following dimensions for the unit cell: a = 6.59 Å, b = 3.96 Å, c = 25.22 Å, β = 92.6°. Further elucidation of the structure showed that the palladium atoms are surrounded by four bromine atoms in a distorted square, and that each bromine atom has two palladium atoms as neighbors at distances of 2.34 Å and 2.57 Å, respectively. The coordination squares are joined in zig-zag chains. The compound is diamagnetic.

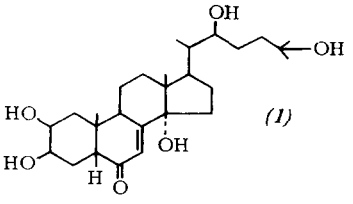
Infrared-spectroscopic studies of the complexes of ethylenediamine with silver(I) cyanide and thiocyanate, which are prepared by treating anhydrous solutions of the corresponding silver salts in pyridine with a solution of ethylenediamine in anhydrous ethanol, showed the diamine to be attached at *trans*-positions.

The compound $FePCl_8$ can be prepared from $FeCl_3$ and $PCl_5$ at 140 °C. The yellow adduct decomposes above 260 °C. Mössbauer spectra (chemical shift + 0.18 mm/sec at 295 °K and +32 mm/sec at 78 °K; quadrupole splitting 0.23 mm/sec) show that the iron(III) ion is surrounded by four chloride ions in a distorted tetrahedron. Infrared-spectroscopic study also indicates the presence of a distorted $FeCl_4$ tetrahedron, as is to be expected from the $d^5$ electron configuration of iron(III).

[Lecture at Kiel (Germany), May 26th, 1966] [VB 995 IE]

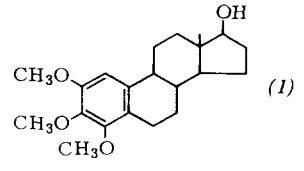
German version: Angew. Chem. *78*, 684 (1966)

**Synthesis of ecdysone** *(1)*, the moulting hormone of insects, was achieved by *U. Kerb, P. Hocks, R. Wiechert, A. Furlenmeier, A. Fürst, A. Langemann*, and *G. Waldvogel*, as well as by a different route by *J. B. Siddall, A. D. Cross*, and *J. H. Fried*, who communicated their results only three days later. The former synthesis starts from methyl 3,3-ethylenedioxy-bisnor-5-cholenate, which was converted into *(1)* in many steps, some of which were stereospecific. *Siddall, Cross*, and *Fried* obtained ecdysone from methyl 14α-hydroxy-2β,3β-isopropylidenedioxy-6-oxo-22,23-bisnor-5β-chol-7-enate in a synthesis that also contained many steps. / Tetrahedron Letters *1966*, 1387 and J. Amer. chem. Soc. *88*, 862 (1966) / –Kr. [Rd 481 IE]



*(1)*

**Polyalkoxyestranes, a new group of analgetic compounds,** have been synthesized by *L. R. Axelrod, P. N. Rao*, and *D. H. Baeder*. 2,3,4-Trimethoxy-1,3,5(10)-estratrien-17β-ol *(1)*, prepared from 3-(2-benzoyl-4-nitrophenoxy)-2-methoxy-1,3,5(10)-estratrien-17β-yl acetate, was particularly effective. It exists in two dimorphic forms. $LD_{50}$ is 175 ± 28 mg/kg mouse intravenously and > 500 mg/kg mouse orally. Intravenously it has 40 and 160 times the analgetic effect of morphine sulfate and meperidine, respectively. No estrogenic action was observed; no side effects were seen after chronic administration to animals. / J. Amer. chem. Soc. *88*, 856 (1956) / –De. [Rd 487 IE]



*(1)*

**The association of potassium bromide in the vapor phase** was studied by *K. Hagemark, M. Blander*, and *E. B. Luchsinger* by vapor density measurements in a liquid-gold isoteniscope. When the small proportion (< 5 %) of trimer present is neglected, least-square analysis of the results in the range 1175–1450 °K and $2.3–7.8\times10^{-4}$ moles/liter gives for the dimerization constant $K_2$ (in liters/mole) and for the vapor pressure p (in mm Hg)

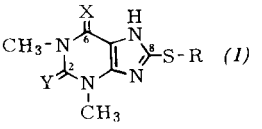
$$\log K_2 = -3.407 + 8378/T$$
$$\log p = 22.159 - 10824/T - 3.966 \log T$$

Dimensional analysis of the partition functions of gaseous salt molecules leads *inter alia* to the relation

$$\ln K_2(Td'/d) + 3 \ln (d'/d) = \ln K'_2 (T)$$

between the dimerization constants $K_2$, $K_2$ and internuclear distances d, d' of the monomers of an arbitrary salt and a reference salt, respectively. With NaI as reference salt, the calculated thermochemical quantities for the dimerization of KBr ($K_2$, $\Delta S^0$, $\Delta U^0$) are in excellent agreement with the experimental values. / J. physic. Chemistry *70*, 276 (1966) / –Da. [Rd 477 IE]

**8-(Alkylthio)thiotheophyllines are a new group of hypnotica,** according to *A. H. Dietz jr.* and *R. M. Burgison*. 8-(Alkylthio)theophyllines *(1)*, in which the oxygen at position 2 or 6 or both is replaced by sulfur were obtained by condensing the corresponding 8-mercaptothiotheophyllines with alkyl halides or sulfates. The hypnotic action of these compounds is comparable with those of thiopental and pentobarbital, but the new compounds are less toxic and cause fewer side reactions. / 151st Meeting, Amer. Chem. Soc. *1966*, I 18 / –De. [Rd 488 IE]

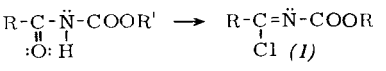


*(1)*

X, Y = O or S

**The stereochemistry of polymerization of methacrylic esters** has been studied by *T. Tsuruta, T. Makimoto*, and *H. Kanai*. They polymerized, *inter alia*, methyl, ethyl, isopropyl, and t-butyl methacrylate by means of radical (benzoyl peroxide) and anionic [$LiAlH_4$, $SrZn(C_2H_5)_4$, $C_6H_5MgBr$, n-$C_4H_9Li$, n-$C_4H_9MgBr$) initiators. The polymers were hydrolysed to polymethacrylic acids which were then esterified with methanol. The tacticities of the products were determined by NMR spectroscopy; calculation of the tacticity parameters shows that the arrangement of the penultimate unit depends on the natures of the ester group, catalyst, and solvent, as well as on the temperature and the polymerization mechanism. Examples: methyl methacrylate with benzoyl peroxide, retention of configuration ($P_{ddd}$, 1.0); with $Sr[Zn(C_2H_5)_4]$, inversion ($P_{dll}$, 0.52). The metal influences the stereochemistry in anionical polymerization. / J. macromolecular Chem. *1*, 31 (1966) / –Hl. [Rd 502 IE]

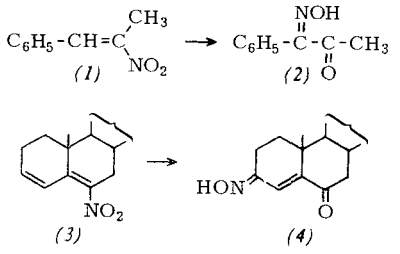
**N-(Alkoxycarbonyl)carbimidoyl chlorides** *(1)* have been synthesized for the first time by *R. Neidlein* and *R. Bottler*. Suspensions of *N*-acylcarbamidic esters, when heated with $PCl_5$ under reflux until HCl evolution ceased, gave the chlorides *(1)* as colorless to pale yellow oils that could be distilled in a vacuum and were stable for several weeks if moisture was excluded. The structure of the products was determined by infrared spectroscopy. Examples: R = $C_6H_5$, R' = $C_2H_5$, b.p. 100–103 °C/0.05 mm Hg, yield 73 %; R = *m*-$CH_3OC_6H_4$, R' = $C_2H_5$, b.p. 110–112 °C/0.03 mm, 53 %; R = $ClC_6H_4$, R' = $C_2H_5$, b.p. 105–108 °C/0.05 mm, 63 %; R = $CH_3C_6H_4$, R' = $C_2H_5$, b.p. 125–127 °C/0.05 mm, 48 %. / Tetrahedron Letters *1966*, 1069 / –Ma. [Rd 476 IE]



*(1)*

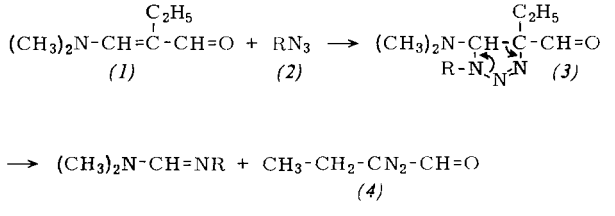
**Synthesis of chloro-, bromo-, and iodo-diacetylene** has been accomplished by *Else Kloster-Jensen* in a two-stage reaction. An ethereal solution of diacetylene is treated with the equivalent amount of butyl-lithium at –80 °C- under nitrogen. Then a solution of the halogen (1 mole) is added at –55 °C. The mixtures are freed from unchanged halogen by distillation at –40 °C and the products are purified by gas-liquid chromatography. Chloro- (m.p. –41 °C, yield *ca.* 30 %), bromo- (m.p. –18 °C, yield *ca.* 18 %), and iodo-diacetylene (m.p. –30 °C, yield *ca.* 59 %) polymerize at room temperature. The iodo-compound may explode. / Tetrahedron *22*, 965 (1966) / –Bu. [Rd 507 IE]

**A new photochemical rearrangement of nitroolefins** is described by *O. L. Chapman, P. G. Cleveland,* and *E. D. Hoganson.* Irradiation of 2-nitro-1-phenylpropene *(1)* in acetone under $N_2$ with light of $\lambda > 290$ mμ gives α-hydroximino-α-phenylacetone *(2)* in 81 % yield, both geometrical isomers being formed. The yields are lower if other solvents are used. A vinylogous rearrangement occurs on irradiation of 6-nitro-3,5-cholestadiene *(3)*, yielding 3-hydroximino-4-cholesten-



6-one *(4)*. Acetone presumably acts as sensitizer. The rearrangement may be intramolecular or may involve a dissociation-recombination mechanism in which the first step in each case is the rearrangement $R-NO_2 \rightarrow R-O-NO$. Chem. Commun. *1966*, 101 / –Ma. [Rd 468 IE]

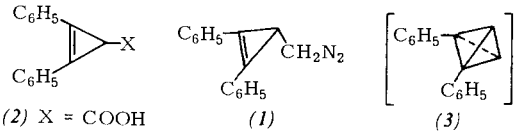
**α-Diazobutyraldehyde (4)**, the first aliphatic α-diazo-aldehyde, was obtained by *J. Kučera* and *Z. Arnold* by treating β-dimethylamino-α-ethylacrolein *(1)* with reactive organic azides *(2)* in an inert aprotic solvent. The reaction presumably involves the unstable intermediate *(3)*. The diazoaldehyde *(4)* is a yellow oil, distillable in vacuum at low



temperature, and can be kept for several days at 0 °C without significant decomposition ($\lambda_{max}$ = 249, 284, 381 mμ). It evolves $N_2$ with dilute acids or traces of Cu. The yields of aldehyde depend on the azide *(2)* used. The authors employed tosyl and picryl azides and cyanogen azide. / Tetrahedron Letters *966*, 1111 / –Ma. [Rd 471 IE]

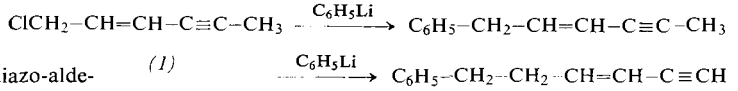
**A radical-pair mechanism of the Wittig rearrangement of anionized ethers** containing a tertiary carbon atom has been postulated by *P. T. Lansbury, V. A. Pattison, J. D. Sidler,* and *J. B. Bieber.* Reaction of methyl-lithium with benzyl t-butyl ether in ether/tetrahydrofuran for 2 days leads to a 51 % yield of 2,2-dimethyl-1-phenyl-1-propanol (α-t-butylbenzyl alcohol). Benzyl 1-norbornyl and 1-apocamphyl benzyl ether do not rearrange under these conditions. Stereochemical investigations have shown that migration of aliphatic ligands from oxygen to the neighboring carbanionic center on the α-benzyl carbon atom that is formed under the influence of the metalating agent involves fragmentation and re-combination. It must be concluded from the new results that the fragments from ligands containing tertiary carbon atoms are radicals. If fragmentation led first to a benzaldehyde/alkyl-lithium pair, then the bicyclic ligands should migrate faster than t-butyl, since 1-norbornyl-lithium is more stable than t-butyl-lithium in iodine/lithium exchange. On the other hand, it is known that the radical state of the bridgehead atom of bicycloheptane is less stable than that of a tertiary carbon atom in acyclic systems (ring strain). / J. Amer. chem. Soc. *88*, 78 (1966) / –Eb. [Rd 501 IE]

**Synthesis and properties of diphenylcyclopropenyldiazomethane** *(1)* were investigated by *E. H. White, G. E. Maier, R. Graeve, U. Zirngibl,* and *E. W. Friend.* The compound *(1)* was obtained in seven steps from 2,3-diphenylcyclopropenecarboxylic acid *(2)*. It is abnormally sensitive to protic solvents such as water and methanol and very sensitive to $O_2$. The half-life in $O_2$-free dilute solution at 25 °C is *ca.* 30 min.



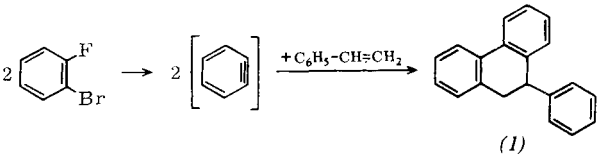
Thermal or photochemical decomposition does not, as was hoped, yield diphenyltetrahedrane *(3)*, but instead diphenylacetylene, benzoic acid, the azine of the aldehyde *(4)*, $N_2$, and polymers. / J. Amer. chem. Soc. *88*, 611 (1966) / –Ma. [Rd 470 IE]

**Rearrangement of *cis*-1-chloro-2-hexen-4-yne, containing a vinylacetylene system,** under the influence of phenyl-lithium has been reported by *J. Cymerman Craig* and *R. J. Young.* With phenyl-lithium at 0 °C, compound *(1)* affords about equal



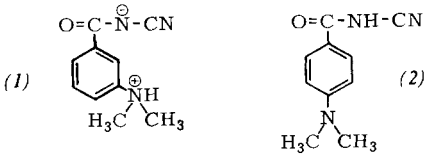
amounts of *cis*- and *trans*-6-phenyl-3-hexen-1-yne *(2)*, b.p. 47–48 °C/0.0004 torr, $n_D^{20}$ = 1.5670, in 3 hr. The structure of the product *(2)* is proved by infrared and ultraviolet spectroscopy. The driving force for the rearrangement, which is initiated by removal of a proton, is held to be provided by the formation of the terminal acetylide anion. / J. chem. Soc. (London) org. *C 1966*, 578 / –Kü. [Rd 499 IE]

**The reaction of benzyne with styrene** has been studied by *W. L. Dilling.* Addition of *o*-bromofluorobenzene to a mixture of Mg turnings and an excess of styrene in tetrahydrofuran at 60 °C, hydrolysis with water, and chromatography on



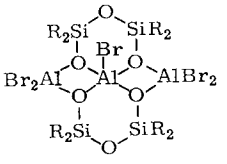
$Al_2O_3$ give 9,10-dihydro-9-phenylphenanthrene *(1)*, m.p. 79–80 °C, in 87 % yield. This compound may arise by a Diels-Alder reaction, loss of a proton, and nucleophilic addition of the second benzyne molecule. / Tetrahedron Letters *1966*, 939 / –Ma. [Rd 469 IE]

**Amino-N-cyanocarboxamides,** a new class of compounds, have been described by *J. C. Howard* and *F. E. Youngblood.* They obtained *e.g. N*-cyano-*m*- *(1)* and *N*-cyano-*p*-(*N,N*-dimethylamino)benzamide *(2)*, m.p. 156–157 °C and 147 to 148 °C, respectively, from reactions of the acid chlorides with sodium cyanamide in dimethylformamide. According to the infrared spectra, the solid compound *(2)* is in the uncharged



form, but the compound *(1)* is an inner salt. Both the corresponding carboxylic acids are uncharged in the solid state. / J. org. Chemistry *31*, 959 (1966) / –Kr. [Rd 504 IE]

**Compounds of aluminum with coordination number five** have been investigated by *M. Bonamico*. Earlier *Ercolani et al.* obtained, from trimethylsiloxyaluminum dichloride and octamethylcyclotetrasiloxane, a crystalline, stable aluminum-siloxane compound of empirical formula $C_8H_{24}Al_3Cl_5O_6Si_4$ *(1)*, which sublimed at 155 °C in a vaccum, as well as a polymer $[(CH_3)_2SiOAlClO]_n$. The bromine analogue *(2)* of *(1)* is monoclinic (space group $P2_1/n$) and colorless. One of



*(2)*, R: $-CH_3$

the 3 Al atoms has the coordination number 5; it is surrounded by four oxygen and one bromine atom; the other two Al atoms are tetracoordinated (2 O, 2 Br). X-Ray analysis gave a = 11.22, b = 13.48, c = 18.76 Å, β = 93 °52′. Z is probably 4. / Chem. Commun. *1966*, 135 / –Kr. [Rd 503 IE]

**Separation of enantiomers by gas chromatography** has been achieved by *E. Gil-Av*, *B. Feibush*, and *R. Charles-Sigler*. The solid carrier and the material to be separated must be chemically similar and interaction must be possible at many points. For this purpose the capillaries (internal diameter 0.25 mm; length 100 m) of capillary columns (75000 theoretical plates for *N*-trifluoroacetylvaline isobutyl ester) were charged with *N*-trifluoroacetyl-L-isoleucine lauryl ester or esters of other *N*-trifluoroacetyl-α-amino acid. The following esters were separated into two or four components (according to whether they contained one or two optically active C atoms per molecule) by using 0.3 to 0.6 μl of ethereal solution in a nitrogen stream at 100 to 200 °C: the isopropyl (retention times in min: 63.7:64.7), butyl (173:175.2), and cyclopentyl (366.8:373.2) ester of *N*-trifluoroacetylalanine; the isobutyl ester of *N*-trifluoroacetyl-alanine (102.9:104.5:108.6:110.7), -valine (171.5:175:180.5:184.7), and -leucine (341.2:34.8:360.8:369.5). Separation is the more successful the larger is the alkyl component; the methyl esters and such "foreign" compounds as 1-methylhexyl acetate are thus not separable. / Tetrahedron Letters *1966*, 1009 / –Jg. [Rd 490 IE]

# BOOK REVIEWS

**Landolt-Börnstein. Zahlenwerte und Funktionen aus Naturwissenschaften und Technik.** Gruppe II. Band 1: Magnetische Eigenschaften freier Radikale (Numerical Values and Functions from Science and Technology. Group II. Vol. 1: Magnetic Properties of Free Radicals). Edited by *K.-H. Hellwege*. Springer-Verlag, Berlin-Heidelberg-New York 1965. 1st Edit., x + 154 pp., DM 68.– (about $17.–).

The definition, production, and magnetic properties of free radicals are treated in a short introduction. Then follow literature references to the theory of ESR spectra (spin Hamilton operator, *g*-factor, coupling parameters, line widths, relaxation, calculation of spin density), and next the tables themselves with ESR data (*g*-factors, *a*-values) for neutral and ionic radicals, organic diradicals, and donor-acceptor complexes. An extensive list of references includes papers which have not been included in the tables (measurement of susceptibility; radicals formed by irradiation, electric discharge, on polymerization, or pyrolysis and in biological systems). The ESR spectroscopist and the "radical chemist" are here offered for the first time – and at a relatively favorable price – the possibility of having the experimental results in his field to his hand on his working desk. This book – presented in two languages – thus needs no further recommendation.

Because of the rapid expansion in the held a supplement or new edition will nevertheless soon be necessary. Then, it is suggested, some results that have not been included (*e.g.* on sulfur radicals) should be added, and references to Chemisches Zentralblatt or Chemical Abstracts should be given for difficultly accessible papers. At the same time factual errors should be corrected: *e.g.* section 2.2.4 alone contains 20 inaccuracies in the tables and literature, and references Ba5, He9, and Mu4 are missing.

*A. Rieker* [NB 474/327 IE]

**Metallkundliche Analyse** (Metallurgical Analysis). By *W. Koch*. Verlag Stahleisen GmbH., Düsseldorf – Verlag Chemie GmbH., Weinheim/Bergstraße 1965. 1st Edit., 497 pp., 394 figs., 80 tables, linen DM 135.– (about $34.–).

The purpose of metallurgical analysis is to clarify the structure of heterogeneous alloys by chemical-analytical investigations. A new book from *W. Koch* is particularly welcome as his name is so closely linked with progress in this field. However, as the author stresses, this progress should not lead to the illusion that metallurgical analysis has passed its first stages.

This book is concerned with the isolation, enrichment, separation, and determination of the structural components. One of its main sections is a detailed chapter on the electrochemical basis for electrolytic analysis of ferrous alloys, which takes into account the predominant importance of this method. For all the experimental procedures recorded in other chapters – whether X-ray analysis, isolation by an extraction-replica process, analysis by emission spectroscopy, or chemical separation of a multiphase material – in all cases the relevant principles of the procedure are briefly but clearly described, the suitability for the work in question is critically discussed, and comprehensive details help the experimental execution. The chapter on the modern method of X-ray microanalysis by means of an electron-beam microprobe is unfortunately rather short, yet the few examples are so chosen that readers can estimate the value of a microprobe for their special purposes. The chapter on characteristic properties of isolated structural ingredients, and the tables of properties, which amount to nearly 200 pages, describe the most important exclusions and inclusions in ferrous and some non-ferrous alloys. Most of these are interpreted with the aid of phase diagrams. The tables of properties contain, not merely various physical properties, but also extensive crystallographic data and Debye-Scherrer diagrams in their original sizes, so that in many cases the reader's own diagrams can be indexed by simple superposition.

Finally it deserves mention that the author has succeeded in conveying his comprehensive knowledge in an easily readable text.

*H. de Laffolie* [NB 475/328 IE]

**Steroid Spektrenatlas** (Atlas of Steroid Spectra) (in German and English). By *W. Neudert* and *H. Röpke*. Springer-Verlag, Berlin-Heidelberg-New York 1965. 1st Edit., viii + 471 pp., 36 illustr., 1111 spectral curves, linen DM 144.– (about $ 33.–).

This atlas characterizes 900 steroids by means of their infrared and ultraviolet spectra, melting points, and specific rotations. NMR spectra of 95 substances are also reproduced. These and other physical methods of characterizing steroids are described, and instructions are given for the preparation of peephole cards for steroids. The whole of the textual material and all the explanations are given in German and in English.

The material consists mainly of steroid hormones, pharmaceutical steroidal products, and intermediates in their synthesis. One looks in vain for an example of the steroid alkalo-

ids, cardenolides, or bufadienolides, and no natural bile acid is included. Even the choice of chromophoric systems is not as complete as is to be expected in a book with claims of this sort [there is, for instance, no 15-ketone or 9(11)-ene-12-one]. However, for the types that are described (170 in the infrared and 101 in the ultraviolet section) there are extensive data concerning band assignments and, above all, the small but significant shifts due to additional substituents; it is just such data which are of particular value in structure determination. For the ultraviolet spectra half-widths are given in each case in addition to $\varepsilon$; these are particularly important for narrow bands; unfortunately there is no indication that both $\varepsilon$ and the half-width are dependent on slit width, though their product is almost independent thereof.

The NMR spectra were measured on a 40 Mc instrument and thus do not show the quality that one has become accustomed to in recent years. Thus the tables contain only the chemical shifts, and spin-spin splitting is hardly ever described. On the other hand, the very valuable section on dipole moments of steroids is rich in tables and practical instructions. In cases where several polar groups are present the experimental dipole moment is always compared with the calculated value and an estimate of the conformation is attempted; for conjugated 3-ketones this is, however, discussed only for the twist form and for one of the two possible half-chair forms of ring A. Collection of data of this sort is a novelty in the steroid field and will induce many to carry out dipole-moment measurements.

Each chapter has a theoretical introduction on techniques; but these introductions often leave much to be desired. For instance, configuration is often confused with conformation, and in the correlation table for infrared bands, which is very clear in other respects, the chromophores are denoted only by numbers. In the ultraviolet section it is noted that polar solvents usually cause a bathochromic shift of the bands, but without indicating that just the opposite is true for $\pi$-$\pi^*$ bands. Remarkably, *Woodward*'s rules for dienes and unsaturated ketones are mentioned only in one short sentence, and are there erroneously assigned to the longest-wavelength ultraviolet bands whereas for enones they are valid only for the short-wavelength K bands. In the NMR section, which was originally written in English, there are uncorrect translations ("integral" values instead of "ganzzahlig", "Feldkonstanz of $10^{-8}$ gauss" instead of "Homogenität of $1:10^8$", *etc.*), and it is claimed, for instance, that a keto group does not influence the position of the signal of a neighbouring $CH_2$ group except with 11-ketones. The region given for the 12-methylene signal of the latter is in general not the correct one – it is correct only for compounds having an oxygen-rich side chain. The existence of long-distance couplings for $\sigma$-bonds is denied, and there is no reference to *Shoolery*'s rule or the *Karplus* equation, to *Zürcher*'s tables of the positions of methyl signals, or the types of spin-spin splitting.

The relation between specific rotation and configuration is regarded as too complex; yet, on the basis of *Klyne*'s and *Barton*'s work (not *Djerassi*'s, as stated), many configuraiotns can be determined by the method of molecular rotation differences (which, like the concept of molecular rotation, is not mentioned). It is unusual that hardly any literature is cited – neither review, nor handbook, nor original paper. Therefore it is very difficult for the user of the atlas to compare its data with those from other laboratories.

If these and other drawbacks could have been avoided, this atlas would have served also as a very good introduction into methods of instrumental analysis. The criticisms of the textual material should not, however, be held to diminish the great value that steroid chemists will find in the tables, which have been constructed with great care from extensive factual material, and in the rules deduced therefrom. Production of the book and reproduction of the illustrations are excellent, which indeed should be expected in view of the price, which unfortunately will be a severe hindrance to wide distribution.

*G. Snatzke* [NB 453/306 IE]

**Chemische Veränderungen von Stoffen durch energiereiche Strahlung.** (Chemical Changes of Materials by Energy-Rich Radiation). By *E. Rexer* and *L. Wuckel*. VEB Deutscher Verlag für Grundstoffindustrie. Leipzig 1965. 1st Edit., 275 pp., 74 figs., 78 tables, bound. MDN 32.– (*ca.* $ 8.00).

This book about radiation chemistry has the usual weakness of most of its predecessors in that, while it reviews a mass of material about the behavior of substances under the influence of ionizing radiation, it usually leaves open the question "Why?" This question is not answered by the many reaction sequences, whose necessity is not evident to the reader because details of experimental methods and methods of investigation are missing. The treatment covers gases, water, aqueous solutions, organic compounds, and polymers.

The introduction into the fundamentals of radiation chemistry is truly unfortunate. Kinetics, mass spectrometry, electron spin resonance, excited molecules, and the like are mentioned only incidentally. This part, written in phraseology that is often imprecise, contains also notable omissions and errors, *e.g.*: 1 curie is seen as the activity of 1 g of Ra in equilibirum with its decomposition products (p. 33), the output of a cobalt source is wrongly calculated since the fact that each $^{60}Co$ atom emits two $\gamma$-quanta is neglected (p. 36), data about mass absorption coefficients would be useful (p. 40), figure 3.2 contains an unexplained parameter (p. 49), the colour of F centers a function of the lattice constants and not the same as the absorption of the free metal atoms (p. 67), and the names of *Franck* and *Rabinowitch* do not appear in the discussion of the cage effect (p. 125). The description of radiation damage to solid bodies seems to have been derived from the secondary literature and is superfluous since crystalline inorganic and organic materials are not treated in the main section; here the omissions abound: for instance, only the least probable of the disorder models, that of *Brinkman*, is described; the problematics of disorder are not discussed at all (p. 79).

The book cannot serve as an introduction to radiation chemistry, and citation of the literature is, of course, incomplete. The production is satisfactory.

*Horst Müller* [NB 480/334 IE]

**Analytical Chemistry of Ruthenium.** By *T. D. Avtokratova*. Series: "Analytical Chemistry of Elements". Academy of Sciences of the U.S.S.R., Moscow 1962. English translation: Israel Program for Scientific Translations, Jerusalem 1963. 224 pp., 36 figs., 54 tables, 13 analytical schemes, $ 14.00

This book is the first of the translations of a series of new Russian monographs. The occurrence, properties, and use of ruthenium and its compounds are reported in an introductory chapter (use as pen points is omitted). Chapter 2 treats qualitative detection (20 pages). Here the expert will be especially pleased with the tables of color reactions with organic reagents that include the limits of detection, and the table of qualitative microreactions where those for the other five platinum metals are also listed In chapter 3 methods of determining ruthenium are described, arranged as gravimetry, titrimetric analysis, potentiometry, and spectrophotometry. Electrochemical methods including polarography, ultraviolet, and *X*-ray spectral analysis, as well as radiochemical methods, complete a rich section.

Chapter 4 contains methods of separation, much space being devoted to methods involving distillation of the tetroxide. The determination of ruthenium in raw materials, concentrates, osmiridium, slurries, slags, *etc.*, is described in chapter 5; the text is completed by 13 schemes for separation. An appendix treats ruthenium fluoride and the preparation of some ruthenium compounds.

Citation of the literature, with 784 references, appears complete up to 1960. In some cases the evaluation could

have been more critical. In addition to the analytical methods, this book contains much non-analytical information about the chemistry of ruthenium. The subject index is too short and makes reference to an individual item difficult. Those interested in platinum and nuclear chemistry will welcome this monograph. *H.-L. Grube* [NB 476a/329 IE]

**Analytical Chemistry of Molybdenum.** By *A. I. Busev*. Series: "Analytical Chemistry of Elements". Academy of Sciences of the U.S.S.R., Moscow 1962. English translation: Israel Program for Scientific Translations, Jerusalem 1964. 1st Edit., vi + 247 pp., numerous figs., $ 15.25.

This book forms part of a series of about 50 volumes being published under the title "Analytical Chemistry of Elements" by the Institute of Geochemistry and Analytical Chemistry of the Academy of Sciences, Moscow. The volumes all follow the same design in respect of content and presentation.

The present monograph begins with a discussion of the properties of molybdenum and its compounds, and continues with a description of the chemical reactions that are of importance for analysis of the metal. Physical, physicochemical, and chemical methods of analysis, and their use for determination of molybdenum in ores, semi-finished materials, and end products (metal, oxides, salts, and compounds), are treated in detail.

The presentation is particularly valuable because the practical importance of individual methods is indicated, which prevents the book from being an uncritical collection. The analyst will be able to obtain much useful information.

*H. Braun* [NB 476b/330 IE]

**High Resolution Spectra of Inorganic and Related Compounds.** Inorganic Spectra with Indexes and Binders. Published by Sadtler Research Lab., Inc., Philadelphia/Pa. 1965. 1st Edit., $160.00.

A card index of vibration spectra of "inorganic" compounds fills a gap in present documentation and can be expected to arouse the critical interest of chemists working in this field.

The first part of the collection, for which yearly supplements are foreseen as for the older "organic" series, is now available either as single sheets (format 21.5×28 cm²), printed on one side and contained in two strong ring binders, or as 16 mm microfilm. An edition on punched cards, which would have many advantages, is, however, not announced.

The 600 infrared spectra illustrated include coordination compounds such as $K_3[Fe(CN)_6]$, $(NH_4)_2[PtCl_4]$, and $[Ni(NH_3)_6]Cl_2$, as well as classical inorganic compounds such as LiF, $NH_4NO_3$, $AlCl_3$, $SiO_2$, $P_4S_{10}$, $CdCO_3$, and $PbCrO_4$. Their choice and arrangement is apparently according to receipt and origin of the material. This has the consequence that many classes of compounds such as halogens, boron hydrides, and simple metal(0) complexes are not considered here at all, whereas on the other hand spectra are given for borates ($MBO_3$) of indium, scandium, yttrium, and lanthanum and for 20 complexes of 2,4-pentanedione. The purity of the substances is described summarily as $> 98\,\%$.

The compounds characterized by vibration spectra in these two volumes are recorded together in three indexes, placed at the beginning: an alphabetical index, a molecular formula index, and – unnecessarily in view of the lack of order in the arrangement – according to the spectrum number. Issue of an index arranged according to functional groups is planned.

The vibration spectra were measured using capillary films, discs, and/or Nujol/Hostaflon suspensions between 4000 and 200 $cm^{-1}$ (2.5 to 50 μ) with a grating spectrograph and are reproduced linear in wave number. Thus a high degree of accuracy is obtained for the short-wave region which, however, is in many cases free from lines for inorganic compounds that contain no water of crystallization. Wave numbers of maxima and assignments of significant bands are not indicated.

The sheets contain the vibration spectrum (format 8×25 cm²), the firm's imprint (format 2×13 cm²), and the spectrum number, then the name, composition, formula weight, and sometimes a schematic structural formula of the substance, the origin of the sample, and the method of measurement. Physical data such as melting point, boiling point, refractive index, and density are given incompletely or not at all; criteria of purity and literature references are totally lacking.

As to detail, a very heterogeneous picture is presented by different sizes and kind of type, even sometimes handwriting, in different positions on the individual sheets. Like other alums (*e.g.* Y 51 S and Y 73 S), sodium aluminum sulfate dodecahydrate (Y 173 S) has the simple formula weight, as given correctly in the molecular formula index. On the other hand, the molecular formula index does not include the water of crystallization of ammonium cobalt hexahydrate that is given on the spectral sheet Y 208 S. It is proved that in nickel bis(biacetyl dioxime) (Y 266 S) coordination is to the nitrogen atoms and not to oxygen. In the reviewer's copy spectrum Y 370 S is missing.

In conclusion it must be stated that the present collection does close the documentation gap mentioned above but that many improvements could be effected. Its utility would in particular be raised by classification of the spectra, by a wider choice of substances, and, in view of the blank reverse pages, by the additions mentioned above.

*H. Bock* [NB 481/335 IE]

**Biology Data Book.** Edited by *P. L. Altman* and *D. S. Dittmer*. Federation of American Societies for Experimental Biology, Washington, D.C., 1964. 2nd Edit., 633 pp., numerous figs., $ 10.–.

In this book are collected data of particular concern to biologists. He who is interested in the pulse frequency of the bat, the expectation of life of the crocodile, or the number of eggs in herring roe, or who is looking for an authoritative comparison of the most poisonous snakes, the highest trees, or the fastest spread of organisms, can occupy himself contentedly with this book for many hours and find in the process a host of the most interesting facts from toxicology, ecology, and the inexhaustible reservoir of the biological collector's treasure. Here are presented to the biochemist most valuable data about the foods essential for every species and genus, about hormones, antibiotics, and antimetabolites, about enzymes and their properties. All in all, however, this industrious book is biological. Even the chapter headings will show, that unless he has wide-ranging biological interests, the chemist will find more satisfaction for his lexical curiosity than directly useful information.

The 155 tables concern the following physiological areas: genetics, cytology, reproduction, development, and morphogenesis; food, nutrition, and metabolism; breathing, life cyle, and blood; biological control, habitat, and adaptation. They are all compiled from the original papers by experts in the field, and contain very exhaustive references. However, as these references disclose, there has been little culling from the most modern literature, for the book is described as an abbreviated and improved version of the "Handbook of Biological Data" of 1956. It is questionable whether the citation of sources, obviously wanted by many readers, need have been quite so extensive. The scholastic was given a scientific alibi by quotation of older authorities. In such quotations the compilers are, however, too easily satisfied by a complicated chemical word – they do not explain it. For instance, among the physical properties of compounds there are none of the more modern characteristics, for the hexoses and pentoses no strucural formulae, for acids and bases no pK values (there are a few of these, but in reference to buffers).

There are some – not many – small blunders in the tables, but these can be set down to the labour of collation. It is misleading to compare, without comment, the height of Englishmen in 1926 with that of the Japanese in 1960. The colored illustration of blood cells can be misunderstood because normal and pathological forms are jumbled together after varied histological staining. The metabolism diagram is not very clear because the typeset photooffset printing is not sufficiently flexible. In the chapter on reaction kinetics everything is missing which the biochemist – or the biologist – expects to find there, from a useful table of buffers to a set of formulae for evaluation and calculation of metabolic results. It is true that a table of antilogarithms is given, but without any introduction to show how to use it in calculating pH values...

The book is extraordinarily wide-ranging in its collection and treatment of facts, and will certainly be useful to the biologist. It will be less valuable to the biochemist. It is probably unjust to review it in a journal designed for chemists.

*L. Jaenicke* [NB 469/322 IE]

**The Chemistry of the Antibiotics Used in Medicine.** By *R. M. Evans*. Pergamon Press, Oxford 1965. 1st Edit., viii + 226 pp., numerous illustr., 25 s (about $ 3.50).

This pocketbook is not aimed at the specialist but is intended to offer students and their teachers a review of the chemistry of the antibiotics used in medicine. This object is attained and the book thus fills a gap in the literature. The antibiotics are arranged from a biogenetic viewpoint, which allows the heterogeneous materials to be handled logically. A few antibiotics with antitumor activity are mentioned as well the compounds used therapeutically.

Short historical remarks and information about the production of the antibiotic are followed in each case by thorough treatment of the chemistry. In this treatment the author succeeds in pinpointing the steps essential for determination of structure; he also describes a few syntheses and partial syntheses. However, the sections on biogenesis are mostly unsatisfactory in that the author is content with mere listing of the results, which are then often interpreted inaccurately; in this section too the literature is very incompletely covered. Relevant references are also missing from the treatment of the stereochemistry of the sugars from macrolide antibiotics. In a short chapter on the mode of action of antibiotics the reader is told of some of the important results and problems in this field.

There is a subject index and the book is well printed and produced; the number of erroneous formulae is small. The main emphasis in the book is on the chemistry of antibiotics; *Zähner*'s excellent pocketbook on the biology of antibiotics may be recommended as compensation.

*H. Grisebach* [NB 460/313 IE]

**Dictionary of Organic Compounds.** Vol. 1–5. Compiled and edited by *Sir I. Heilbron †*, *A. H. Cook*, *H. M. Bunbury*, and *D. H. Hey*. Eyre & Spottiswoode Ltd. and E. & F. N. Spon Ltd., London 1965. 4th enlarged Edit., 3281 pp., 5 Vol. and 1 Supplement £ 100.

The last edition of "Heilbron-Bunbury" appeared in 1953 in four volumes. The new edition now published consists of five volumes and the first supplement. Further supplements are due to appear yearly, keeping the work up to date.

In its present form the work contains more than 40000 entries, 9000 more than in the previous edition. In addition 6000 new cross-references have been included.

A new feature is the inclusion of trade names, particularly for antibiotics, pharmaceuticals, and plant pesticides, and it was a good idea to give also literature references for radioactive and deuterium-labeled compounds. For instance, the entry for toluene includes five deuterated derivatives, one tritiated compound, and three $^{14}C$-compounds.

The entry name of each compound is followed by other possible designations, which, however unfortunately do not always appear as cross-references. Then the structural formula is given, often with all details of the configuration. It is very satisfactory that all the formulae are extremely clear, though the use of dots in place of valence bonds is disturbing, particularly for double bonds and triple bonds. After the molecular formula and molecular weight follow data – very short but kept intelligible – of the physical properties of the substance and its derivatives. For recent material NMR spectral data are included, when other properties are not yet reported in the literature. Next follow characteristic derivatives of the compound described, and, finally, the entry is completed by references to original papers.

This work contains such an unusual wealth of information in such a very short space that one cannot help but admire the editors' achievement. Yet one of the greatest advantages of the new edition of this lexicon is its up-to-dateness: the six volumes now presented contain the results in the chemical literature up to the end of 1964.

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# New Methods and Results in the Study of Polyacids

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*The present status of research on condensed vanadic, molybdic, and tungstic acids is reviewed. Information about the structure and formation of polyanions can be obtained by X-ray analysis and from nuclear magnetic resonance, infrared, and Raman spectra, as well as from complex formation in aqueous solution. Salts of the polyacids can be prepared in organic solvents by hydrolysis of esters of the metal oxoacids.*

## 1. Introduction

The chemistry of polyacids still presents many unsolved problems, although numerous compounds of this class have been known and studied for more than 100 years. Whereas preparative and analytical investigations predominated at first, attention later turned mainly to a systematic study of the state of the polyanions in aqueous solution [1, 3]. The measurement of diffusion and dialysis coefficients was used as the principal method for the determination of the pH ranges in which certain polyanionic species predominate, and the ranges in which strong aggregation occurs. The quantitative interpretation of these measurements, *i.e.* the determination of the degree of condensation of the anions, has sometimes led to erroneous results, since the relationships between diffusion coefficient and molecular weight are very complex [2]. Nevertheless, these investigations were of great value to further research in this field. Modern physical methods were later used to check, and in some cases to correct, the results, so that a fairly unanimous view on the size of the dominant particles in the most important polyanion systems has now been reached. However, many points of uncertainty still exist in this respect in the polymolybdate system.

[1] Cf. *G. Jander* and *K. F. Jahr*, Kolloid-Beih. *41*, 1 (1934).

[2] *K. F. Jahr, H. Kudelka*, and *J. Simon*, Z. Naturforsch., in press.

[3] *P. Souchay*: Polyanions et polycations. Gauthier-Villars, Paris 1963.

## 2. Methods for the Determination of the Degree of Condensation of Polyanions

A very accurate and universally applicable method for the determination of the size [*] of polynuclear complexes was developed by *Sillén* [4], who showed that for the formation of a polynuclear complex in accordance with Eq. (a)

$$pA + qB \rightleftharpoons A_pB_q \qquad (a)$$

the values of p and q can be calculated from equilibrium data. It is possible to recognize several ionic species existing together, and to determine the equilibrium constants. To obtain the required experimental data, the concentration of one component, *e.g.* $c_A$, is kept constant, and the concentrations of the other components are varied. Series of experiments are carried out with different fixed initial concentrations $c_A$, and the concentration of free A and/or B is found by EMF measurements.

Important results have also been obtained by salt cryoscopy. This method, which was known as early as 1895 [5], has been greatly improved in recent years by the use of thermistors. A comparison of the results of careful salt-cryoscopic investigations with those obtained by other methods shows that very useful

[*] The size of a complex is expressed by the degree of condensation, *i.e.* the number of metal atoms in the polyanion.

[4] *L. G. Sillén*, Acta chem. scand. *8*, 299, 318 (1954); *10*, 186, 803 (1956); *16*, 159 (1962).

[5] *R. Löwenherz*, Z. physik. Chem. *18*, 71 (1895).

results can be obtained by salt cryoscopy. The recent criticism[6] of this method therefore seems unjustified.

Ultracentrifugation has also proved a very successful means of measuring the degree of condensation. This method can also be applied to electrolytically dissociated compounds, provided an excess of a foreign electrolyte[7] is added to ensure complete decoupling of the oppositely charged ions. Like the cryoscopic measurements, determinations using the ultracentrifuge give only average degrees of condensation[*], but this method has the advantage that it is possible[8] to recognize whether the solution studied contains one type of particle or a mixture of particles of different weights.

A selection from the results obtained for polyvanadate, polymolybdate, and polytungstate solutions by various methods is shown in Table 1.

Table 1. Degrees of condensation in a number of polyanionic systems.

| Acidification x of the solution [a] | EMF measurements, deg. of condensation | Salt cryoscopy, av. deg. of condensation | Ultracentrifuge, av. deg. of condensation |
|---|---|---|---|
| Vanadates<br>2.00<br>(metavanadate) | 3 and 4 [9, 10] | 3.4 [15]<br>3.96 [16]<br>4.14–4.33 [17]<br>3.77 [18]<br>4 [19] | 4 [24] |
| 2.4–2.6<br>(orange polyvanadate) | 10 [11] | 8.1 [15]<br>9.58–9.85 [20]<br>9.2–9.9 [17]<br>9.7–10 [19] | 10–11 [25] |
| Molybdates<br>1.14<br>(paramolybdate) | 7 [12, 13] | 6.1 [21] | ≈6 [26], 7[27] |
| 1.50<br>(metamolybdate) | | 7.3 [21] | ≈9 [26], 8 [27] |
| 1.80 | ≈19 | 20 [21] | |
| Tungstates<br>1.167<br>(paratungstate) | 6 [14] | fresh soln.7 [22] [b]<br>14-day-old 9.4 [22, 23] | 7–8 [29]<br>8 [28] |
| 1.50<br>(metatungstate) | – | fresh soln. 6<br>aged soln. dil.6<br>aged soln.conc. 12 | 12 [27] |
| Soln. of a cryst. paratungstate | – | 11.6 [22] | 12 [29] |
| Soln. of a cryst. metatungstate | – | 11.4 [22] | |
| Soln. of amorphous Ψ-metatungstate | – | – | 24 [30] |

[a] The acidification x of a solution is the ratio of the number of hydrogen ions to the number of monomeric oxometalate ions.
[b] Slowly established equilibrium between hexamers and dodecamers.

[6] *R. S. Tobias*, J. inorg. nuclear Chem. *19*, 348 (1961).

[7] *T. Svedberg* and *K. O. Pedersen*: Die Ultrazentrifuge. Steinkopff, Dresden and Leipzig 1940, S. 21.

[*] The ultracentrifuge method gives a weight-average molecular weight $M_w = (\sum_i n_i M_i^2)/(\sum_i n_i M_i)$, whereas salt cryoscopy gives a number-average $M_n = (\sum_i n_i M_i)/(\sum_i n_i)$. The calculation of the average degree of condensation from $M_w$ and from $M_n$ can lead to differences, which are particularly marked for mixtures of particles of different sizes, *e.g.* a mixture of monomeric and hexameric species.

[8] *H. P. Stock*, Z. Naturforsch., *20b*, 933 (1965).

## 3. Some Polyanionic Systems

The polyanionic systems listed in Table 1 are described below in greater detail.

### (a) The Vanadate System

Acidification of a vanadate solution leads first to the formation of $HVO_4^{2-}$ ions, which exist in equilibrium with the dimeric $V_2O_7^{4-}$ ions, the position of the equilibrium depending on the vanadium concentration. Further acidification leads *via* $HV_2O_7^{3-}$ [9] to metavanadate ions $(VO_3)_n^{n-}$ by a route that has not yet been fully elucidated. A concentration-dependent equilibrium[10] exists at this stage between $V_3O_9^{3-}$ and $V_4O_{12}^{4-}$. The trimeric ion is detected only in very dilute solutions. Addition of further $H^+$ leads to the decavanadate ions[11] $V_{10}O_{28}^{6-}$, $HV_{10}O_{28}^{5-}$, and $H_2V_{10}O_{28}^{4-}$, and finally to the free acid $H_6V_{10}O_{28}$. The transition from the metavanadate to the decavanadate also proceeds by an unknown route; a short-lived red intermediate is observed in concentrated solutions[31]. Free decavanadic acid $H_6V_{10}O_{28}$ exists in equilibrium with a compound $V_2O_5 \cdot x\,H_2O$ of higher molecular weight[32]. On further acidification, the monomeric cation $VO_2^+$ is formed by degradation reactions, the details of which are not yet known.

Depending on the acidification, the crystalline compounds obtained from polyvanadate solutions are divanadates $M_4V_2O_7$, metavanadates $(MVO_3)_\infty$, which

[9] *N. Ingri* and *F. Brito*, Acta chem. scand. *13*, 1971 (1959).

[10] *F. Brito*, *N. Ingri*, and *L. G. Sillén*, Acta chem. scand. *18*, 1557 (1964).

[11] *F. J. C. Rossotti* and *H. Rossotti*, Acta chem. scand. *10*, 957 (1956).

[12] *Y. Sasaki*, *I. Lindqvist*, and *L. G. Sillén*, J. inorg. nuclear Chem. *9*, 93 (1959).

[13] *Y. Sasaki* and *L. G. Sillén*, Acta chem. scand. *18*, 1014 (1964).

[14] *Y. Sasaki*, Acta chem. scand. *15*, 175 (1961).

[15] *G. Schwarzenbach* and *G. Parissakis*, Helv. chim. Acta *41*, 2425 (1958).

[16] *K. F. Jahr* and *L. Schoepp*, Z. Naturforsch. *14b*, 467 (1959).

[17] *O. Glemser* and *E. Preisler*, Z. anorg. allg. Chem. *303*, 303 (1960).

[18] *K. F. Jahr*, *H. Schroth*, and *J. Fuchs*, Z. Naturforsch. *18b*, 1133 (1963).

[19] *A. W. Naumann* and *C. J. Hallada*, Inorg. Chem. *3*, 70 (1964).

[20] *K. F. Jahr* and *L. Schoepp*, Z. Naturforsch. *14b*, 468 (1959).

[21] *G. Wegener*, Dissertation, Freie Universität Berlin 1964.

[22] *H. Ressel*, Dissertation, Technische Universität Berlin 1961.

[23] *I. Hapke*, Dissertation, Technische Universität Berlin 1955.

[24] *H. P. Stock* and *K. F. Jahr*, Z. Naturforsch. *18b*, 1134 (1963).

[25] *O. Glemser* and *E. Preisler*, Z. anorg. allg. Chem. *303*, 316 (1960).

[26] *J. Aveston*, *W. Anacker*, and *J. S. Johnson*, Inorg. Chem. *3*, 735 (1964).

[27] *O. Glemser* and *W. Holznagel*, Angew. Chem. *72*, 918 (1960); *O. Glemser*, *W. Holznagel*, and *J. S. Ali*, Z. Naturforsch. *20b*, 192 (1965).

[28] *O. Glemser* and *W. Höltje*, Z. Naturforsch. *20b*, 398 (1965).

[29] *J. Aveston*, Inorg. Chem. *3*, 981 (1964).

[30] *O. Glemser* and *W. Höltje*, Z. Naturforsch. *20b*, 492 (1965).

[31] *G. Jander*, *K. F. Jahr*, and *H. Witzmann*, Z. anorg. allg. Chem. *217*, 65 (1934).

[32] *K. F. Jahr*, *J. Fuchs*, and *F. Preuss*, Chem. Ber. *96*, 556 (1963).

have a chain structure, decavanadates $M_6V_{10}O_{28}$, $M_5HV_{10}O_{28}$, and $M_4H_2V_{10}O_{28}$, and "hexavanadates" $(M_2V_6O_{16})_\infty$, which have a layer structure [33,34] (M = univalent metal). Nearly all vanadates contain water of crystallization.

### (b) The Molybdate System

Diffusion experiments and salt-cryoscopic and spectrophotometric measurements show that molybdate solutions contain condensed ions after the addition of even small quantities of acid. The existence of $Mo_7O_{24}^{6-}$ may be regarded as certain; this anion is formed in accordance with

$$7\ MoO_4^{2-} + 8\ H^+ \rightleftharpoons Mo_7O_{24}^{6-} + 4\ H_2O \qquad (b)$$

and hence has its maximum stability when the acidification x is 1.14 ($8H^+/7MoO_4^{2-}$). The average degree of condensation increases rapidly at acidifications higher than 1.50. Figure 1 shows the average degree of condensation P of acidic molybdate solutions as found in our salt-cryoscopic measurements [21].

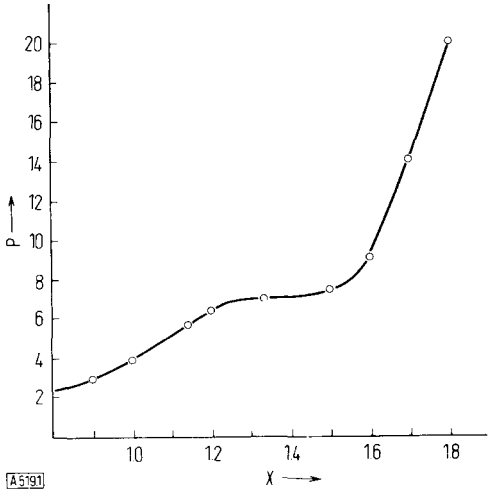



Fig. 1. Average degree of condensation p of polymolybdate ions as a function of the acidification x, from salt-cryoscopic measurements [21].

*Byé* [35], who found that the degree of condensation decreased again at $x > 1.14$, evidently failed to make adequate allowance for the influence of hydrogen ions on the freezing point depression. The main difficulty in the elucidation of the molybdate system is the fact that several polyanionic species exist in every pH range, in rapidly established equilibria.

Crystalline products obtained from acidic molybdate solutions include paramolybdates $3M_2O{\cdot}7MoO_3{\cdot}nH_2O$, "trimolybdates" $M_2O{\cdot}3MoO_3{\cdot}nH_2O$, and metamolybdates $M_2O{\cdot}4MoO_3{\cdot}nH_2O$ (M = univalent metal). Numerous products [36] with still higher molybdenum contents have been isolated from more strongly acidic solutions. However, it is not yet certain whether these are single compounds.

[33] *S. Block*, Nature (London) *186*, 540 (1960).

[34] *A. D. Kelmers*, J. inorg. nuclear Chem. *21*, 45 (1961).

[35] *J. Byé*, Ann. Chimie *20*, 463 (1945).

[36] Gmelins Handbuch der anorganischen Chemie, System Nr. 53, 8th. Edit., Verlag Chemie, Berlin 1935, p. 113.

### (c) The Tungstate System

Acidification of tungstate solutions leads first to the rapid formation of a hexameric [38] ion, the paratungstate ion A [39].

$$6\ WO_4^{2-} + 7\ H^+ \rightleftharpoons [HW_6O_{21}{\cdot}x\ aq]^{5-} + (3\text{-}x)\ H_2O \qquad (c)\ [*]$$

This ion slowly comes to equilibrium, *via* at least one intermediate [40] (the paratungstate ion B [40]), with a dodecameric ion [22,29,30] (the paratungstate ion Z [**] $[W_{12}O_{36}(OH)_{10}]^{10-}$ or $[W_{12}O_{40}(OH)_2]^{10-}$). In a still slower reaction, part of the equilibrium mixture is converted into monotungstate $WO_4^{2-}$ and "true" metatungstate $[W_{12}O_{38}(OH)_2]^{6-}$. Rapid addition of 9 $H^+$ to 6 $WO_4^{2-}$ ($x = 1.50$) leads *via* $[HW_6O_{21}{\cdot}x\ aq]^{5-}$ to another hexatungstate ion (the metatungstate ion A [41] $[HW_6O_{20}{\cdot}x\ aq]^{3-}$, which changes very slowly, again *via* at least one intermediate, the Ψ-(pseudo-) metatungstate ion [39,41,41a], into the dodecameric "true" metatungstate ion.

The crystalline products obtained from acidic tungstate solutions are paratungstates $5M_2O{\cdot}12WO_3{\cdot}nH_2O$ and metatungstates $3M_2O{\cdot}12WO_3{\cdot}nH_2O$. A sodium salt having the composition $Na_2O{\cdot}2WO_3{\cdot}5H_2O$ [42] is also known. The addition of $K^+$ or $Ba^{2+}$ to Ψ-metatungstate solutions leads to amorphous precipitates having the composition $K_2O$ or $BaO{\cdot}4WO_3{\cdot}nH_2O$ [39].

## 4. Determination of the Structure

The aim of further investigations must be to determine the structures of the polyions present in solution, and to discover how they are interconverted. Since the structure of dissolved particles cannot be determined directly, except in a few particularly favorable cases, this aim can only be achieved by a combination of methods.

The elucidation of structures in many fields of chemistry has been greatly assisted by models developed on the basis of theoretical considerations. However, attempts to develop a structural model for polyanions generally fail simply because the compositions of the ions are not

[37] Cf. *D. L. Kepert*, Progr. inorg. Chem. *4*, 199 (1962).

[38] *H. Schulz* and *G. Jander*, Z. anorg. allg. Chem. *162*, 141 (1927); *G. Jander*, *D. Mojert*, and *Th. Aden*, *ibid. 180*, 129 (1929); *K. F. Jahr* and *H. Witzmann ibid. 208*, 145 (1932).

[39] *P. Souchay*, Ann. Chimie *18*, 61, 169 (1943).

[*] aq = structural water, cf. Section 4.

[40] *G. Ewald*, Diploma Thesis, Humboldt-Universität Berlin 1951.

[**] The nomenclature used is that proposed by *D. L. Kepert* [37]. Paratungstate B was formerly called paratungstate $A_2$, and paratungstate Z was called paratungstate B.

[41] *G. Jander* and *U. Krüerke*, Z. anorg. allg. Chem. *265*, 244 (1951).

[41a] Ψ-Metatungstate solutions probably contain several species, mainly hexamers in dilute solutions, and mainly more highly aggregated particles, regarded by *C. Jander* and *D. Exner* as dodecamers, in concentrated solution [43]. According to more recent studies [43a], however, the latter are more likely 24-fold aggregates, since particles of ionic weight 6450 have been found in a solution of the amorphous potassium Ψ-metatungstate.

[42] *E. L. Simons*, Inorg. Chem. *3*, 1079 (1964).

accurately known, since the degree of condensation and the charge are not sufficient to give the exact composition of an ion. Since polyanions may contain structural water (aq), which forms neutral OH groups with the oxygen atoms present, the number of oxygen and hydrogen atoms in the ion cannot be found directly. For example, it is impossible to decide from investigations in aqueous solution whether paratungstate A has the composition $[W_6O_{20}(OH)]^{5-}$ or *e.g.* $[W_6O_{19}(OH)_3]^{5-}$ (also written as $[HW_6O_{21}\cdot H_2O]^{5-}$). Even in crystalline compounds, it is often difficult to tell whether or not structural water is present. Even isobaric or isothermal degradation and the study of infrared spectra do not always lead to an accurate answer. Probably the greatest promise is shown by nuclear magnetic resonance measurements [44], but until more experience has been gained, the information obtainable will remain qualitative.

The development of structural models for polyions is further complicated by the fact that the coordination number of the metal ions towards oxygen is unknown. The ionic radii of $V^{5+}$ (0.59 Å), $Mo^{6+}$ (0.65 Å), and $W^{6+}$ (0.65 Å) permit either tetrahedral or octahedral coordination.

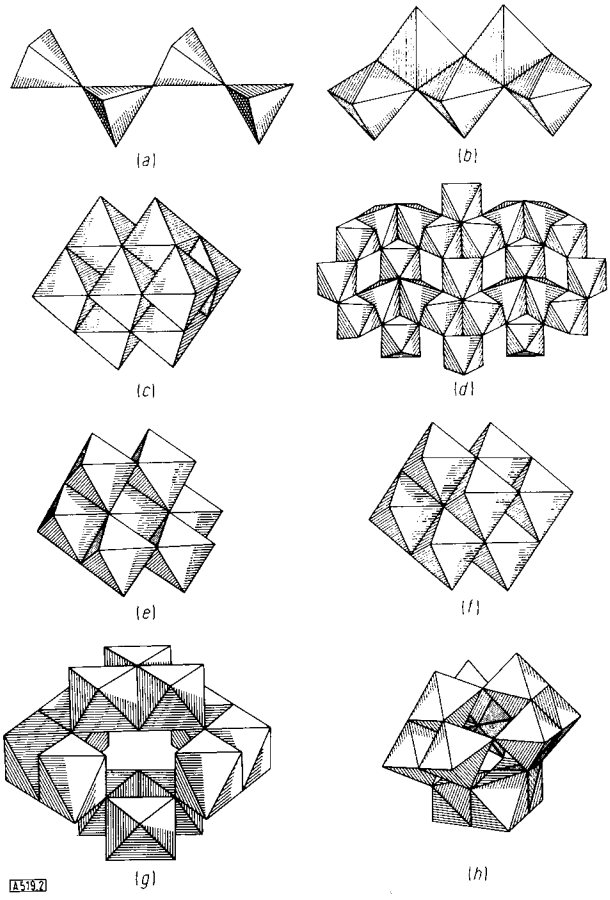
## 5. Importance and Results of X-Ray Structure Investigations

The basis of structure determinations is therefore X-ray studies on crystalline compounds. However, it must be established in every case that the structure of the polyanions in solution is the same as, or at least very similar to, that of the crystalline compounds. This equivalence cannot be assumed. For example, crystalline metavanadates contain long chains of linked $VO_4$ tetrahedra [45] or $VO_5$ units [46] (trigonal bipyramids), whereas the aqueous solution contains tetravanadate or trivanadate ions (cf. Figs. 2a and 2b).

The structures in the crystal and in solution can be compared with the aid of Raman and infrared spectrography and NMR measurements. Thus *Aveston* [26, 29] found close agreement between the Raman spectra of crystalline and dissolved heptamolybdates and paratungstates Z.

The infrared spectra of crystalline and dissolved polytungstates were studied by *Spitzyn et al.* [47, 48]. However, no definite conclusions could be drawn, since agreements were found as well as differences. It was concluded from NMR measurements on decavanadate solutions [49] that three differently bound vanadium atoms were present in the ratio 2:6:2. However, this result cannot be reconciled with the decavanadate structure found by *Evans jr.*, *Swallow*, and *Barnes* [50] for $Ca_3V_{10}O_{28}\cdot 16H_2O$ and $K_2Zn_2V_{10}O_{28}\cdot 16H_2O$. Other investigations (cf. Section 8a) indicate that the structure of decavanadate ions in solution differs from that in crystals. It is also possible that not all the crystalline decavanadates contain the same polyanion [51].

Unfortunately, very few X-ray structure investigations have been carried out on salts of polyacids; moreover, some of the existing investigations are incomplete, since only the heavy metal positions, but not the positions of the oxygen atoms could be determined. The great scattering power of heavy metal atoms (particularly tungsten) for X-rays makes it extremely difficult to locate the oxygen atoms. Other properties of the salts of isopolyacids, *e.g.* large unit cells, poor crystallizing power, and tendency towards twinning, also make them particularly difficult subjects for X-ray structure analysis. Fig. 2 shows the structures of isopolyacids that have been studied by the X-ray method.




A519.2

Fig. 2. Anions of the salts: (a) $KVO_3$ [45], (b) $KVO_3\cdot H_2O$ [46], (c) $K_2Zn_2V_{10}O_{28}\cdot 16H_2O$ and $Ca_3V_{10}O_{28}\cdot 16H_2O$ [50], (d) $K_2V_6O_{16}$ [33], (e) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ [52], (f) $(NH_4)_4Mo_8O_{26}\cdot 4H_2O$ [52], (g) $Na_{10}W_{12}O_{36}(OH)_{10}\cdot 23H_2O$ [53]. — (h) "True" metatungstate ion $[H_2W_{12}O_{40}]^{6-}$ (isomorphous with $H_3PW_{12}O_{40}\cdot 5H_2O$) [54].

*Lipscomb* [55] has questioned the correctness of the paratungstate Z structure (Fig. 2g). *Lindqvist* determined only the tungsten positions, and the positions of the oxygen atoms

[43] *G. Jander* and *F. Exner*, Z. physik. Chem. *A 190*, 195 (1942).

[43a] *O. Glemser*, *W. Holznagel*, *W. Höltje*, and *E. Schwarzmann*, Z. Naturforsch. *20b*, 725 (1965).

[44] Cf. *O. Glemser*, Angew. Chem. *73*, 785 (1961).

[45] *H. T. Evans jr.* and *S. Block*, Amer. Mineralogist *39*, 327 (1954); *H. T. Evans jr.*, Z. Kristallogr., Kristallometr., Kristallphysik., Kristallchem. *114*, 257 (1960).

[46] *C. L. Christ*, *J. R. Clark*, and *H. T. Evans jr.*, Acta crystallogr. *7*, 801 (1954).

[47] *V. I. Spitzyn* and *V. J. Kabanow*, Z. anorg. allg. Chem. *322*, 248 (1963).

[48] *A. A. Babushkin*, *G. V. Yuknevich*, *Yu. F. Berezkina*, and *V. I. Spitzyn*, Russ. J. inorg. Chem. *4*, 373 (1959).

[49] *O. W. Howarth* and *R. E. Richards*, J. Chem. Soc. (London) *1965*, 864.

[50] *H. T. Evans jr.*, *A. G. Swallow*, and *W. H. Barnes*, J. Amer. chem. Soc. *86*, 4209 (1964).

[51] *A. M. Bystroem* and *H. T. Evans jr.*, Acta chem. scand. *13*, 377 (1959).

[52] *I. Lindqvist*, Ark. Kemi *2*, 325, 349 (1950).

[53] *I. Lindqvist*, Acta crystallogr. *5*, 667 (1952).

[54] *J. F. Keggin*, Nature (London) *131*, 908 (1933); *132*, 351 (1933); Proc. Roy. Soc. (London) *A 144*, 75 (1934); *J. W. Illingworth* and *J. F. Keggin*, J. chem. Soc. (London) *1935*, 575; *R. Signer* and *H. Gross*, Helv. chim. Acta *17*, 1076 (1934).

[55] *W. N. Lipscomb*, Inorg. Chem. *4*, 132 (1965).

were estimated on steric grounds. *Lipscomb* showed that the observed X-ray intensities agree equally well with another structural model (Fig. 3) containing fewer oxygen atoms ($W_{12}O_{42}$ instead of $W_{12}O_{46}$).Thus the formula of the crystalline paratungstates Z would be $M_{10}W_{12}O_{36}(OH)_{10}\cdot nH_2O$ according to *Lindqvist*, and $M_{10}W_{12}O_{40}(OH)_2\cdot n\ H_2O$ according to *Lipscomb*. The results obtained in the isobaric degradation of potassium paratungstate $5K_2O\cdot 12WO_3\cdot 11H_2O$ and from the infrared spectra of its degradation products[87] agree more closely with *Lipscomb*'s formula (only one mole of structural water).

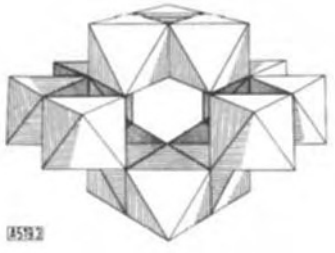


Fig. 3. Structure of the anion of sodium paratungstate $Na_{10}W_{12}O_{40}(OH)_2$, according to *Lipscomb* [55].

The data available at present are insufficient to show how these polyions are formed in solution and how they are interconverted. It is therefore extremely important to detect as many as possible of the intermediates, which must exist, but which are not yet known, since they occur only transiently or only in very low equilibrium concentrations.

## 6. Detection of Intermediate Polyanions

Some possibility of detecting short-lived intermediates is offered by a method described by *Meier* and *Schwarzenbach*[56]. The acidification of vanadate and tungstate solutions was followed potentiometrically in a flow apparatus permitting very rapid mixing of reaction solutions (in about 5 msec). Since condensations proceed much more slowly than protonations and deprotonations, these measurements were intended to detect the protonation stages of anions and polyanions with a minimum of interference from accompanying condensations. Not only known polyanions were detected, but also a short-lived ($10^{-2}$ sec) polytungstate ion, which is probably tetrameric, and which the authors formulate as $H_5W_4O_{16}^{3-}$[57]. It is interesting in this connection to note that *Hüllen*[58] detected a tetratungstate ion as one of the building units in hydrated lithium tungstate $Li_2WO_4\cdot 4/7\ H_2O$ by X-ray structure analysis (see Fig. 4).

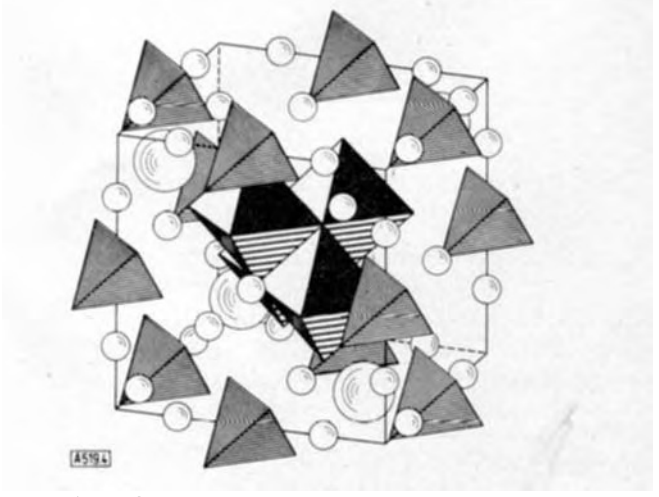


Fig. 4. Structure of $Li_2WO_4\cdot 4/7\ H_2O$ [58]. Large spheres: $H_2O$; small spheres: $Li^+$; tetrahedra: $WO_4^{2-}$; group of four octahedra: $W_4O_{16}^{8-}$.

[56] *J. Meier* and *G. Schwarzenbach*, Helv. chim. Acta *40*, 907 (1957).

## 7. Salt Formation in Organic Solvents by Hydrolysis of Esters of Metal Oxoacids

A method for the preparation of salts of polyacids previously not obtainable from aqueous solution was discovered by *Jahr*, *Fuchs*, and co-workers[59]. Complete hydrolysis of an ester of a metal oxoacid dissolved (generally as the monomer) in organic solvents leads normally to a highly condensed metal oxide hydrate. The condensation proceeds *via* the same intermediates as in the acidification of the metalate solution. The intermediate polyacids can be intercepted as salts if the organic solution contains a base, a salt, or a buffer mixture. This method of precipitating salts of polyacids from organic solvents, which involves only very small quantities of water, is very useful not only from the preparative point of view, but also for the investigation of structures, since it is possible in this way to obtain anhydrous compounds. It is then very much easier to determine whether the polyanions contain structural water, and if so, how much. The method also offers new preparative possibilities, since solubility relationships in organic solvents are different from those in water. Polyanions that have been definitely detected in aqueous solution, but of which no crystalline salts have so far been obtained because other polyanions present in the equilibrium form sparingly soluble salts, can be obtained as crystalline salts in this way.

Thus the only previously known crystalline paratungstates were of the Z type, with dodecameric anions. Hydrolysis of tetramethyl tungstate(VI), $WO(OCH_3)_4$, in the presence of piperidine has now led to a pentapiperidinium hexatungstate[59a–61], $(C_5H_{11}NH)_5HW_6O_{21}$, or $(C_5H_{11}NH)_5H_3W_6O_{22}$, the reactions of which show that it contains the paratungstate A ion. The corresponding ammonium and pyridinium salts can also be prepared in this way. We have also obtained salts of paratungstate ions B, which occur as intermediates in the conversion of paratungstate A into paratungstate Z, by hydrolysis of tetramethyl tungstate (VI) in the presence of a solution of potassium or ammonium acetate in methanol[62]. The X-ray diagrams of ammonium paratungstates A, B, and Z are shown in Fig. 5.

[57] *G. Schwarzenbach* and *J. Meier*, J. inorg. nuclear Chem. *8*, 302 (1958); *G. Schwarzenbach*, *G. Geier*, and *J. Littler*, Helv. chim. Acta *45*, 2601 (1962).

[58] *A. Hüllen*, Naturwissenschaften *51*, 508 (1964). We thank Dr. *Hüllen*, Berlin, for this illustration.

[59] *K. F. Jahr* and *J. Fuchs*, Chem. Ber. *96*, 2457 (1963).

[59a] X-ray studies on this salt are being carried out in our institute by *A. Hüllen* and *G. Henning*.

[60] *K. F. Jahr*, *J. Fuchs*, and *P. Witte*, Angew. Chem. *76*, 581 (1964).

[61] *K. F. Jahr*, *J. Fuchs*, *P. Witte*, and *E. P. Flindt*, Chem. Ber. *98*, 3588 (1965).

[62] *J. Fuchs*, *K. F. Jahr*, and *E. P. Flindt*, unpublished work.

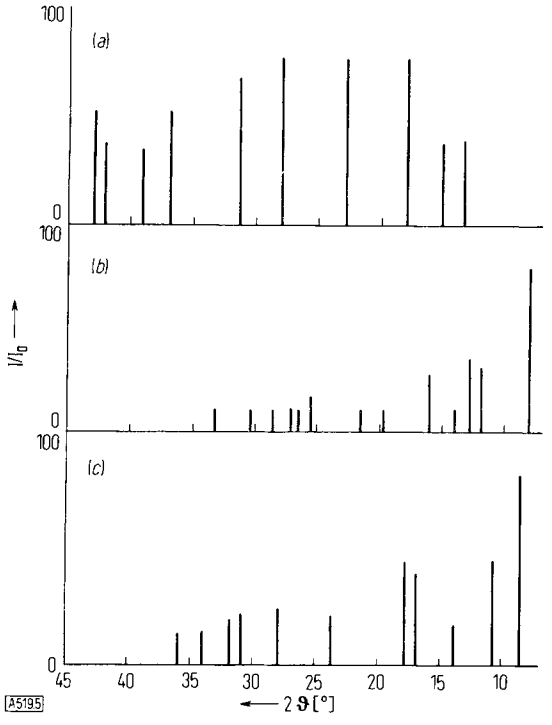



Fig. 5. Relative X-ray intensities ($Cu_{K\alpha}$ radiation) of (a) ammonium paratungstate A, (b) ammonium paratungstate B, (c) ammonium paratungstate Z (Analytical composition: 5 $(NH_4)_2O \cdot 12\ WO_3 \cdot x$ solvent. A and B contain methanol; Z contains water).

Although the compositions are practically identical [$5(NH_4)_2O \cdot 12 WO_3 \cdot x$ solvent; the A and B salts contain methanol, and Z contains water], the compounds differ considerably in their chemical properties. Thus a freshly prepared aqueous solution of ammonium paratungstate Z is neutral, whereas solutions of paratungstates A and B are distinctly acidic. Unlike the other two salts, the paratungstate A is very soluble and reacts vigorously with $H_2O_2$ [63], the resulting solution being strongly acidic.

Salt-cryoscopic measurements indicate that the paratungstate ion B is hexameric, *i.e.* has the composition $[HW_6O_{21} \cdot x\ aq]^{5-}$. It is not yet known whether the difference between paratungstates A and B is due to a change in the content of structural water or to a rearrangement. Interestingly, a further hydrogen in the paratungstate ion B can be replaced by metal ions to give $[W_6O_{21} \cdot x\ aq]^{6-}$. The hydrolysis of tungstate esters in the presence of potassium acetate in ethanol yielded a salt having the ratio 6 $K_2O$:12 $WO_3$; the X-ray diagram of this salt shows that its structure is practically the same as that of the paratungstate B obtained from methanolic solution, in which the ratio is 5 $K_2O$:12 $WO_3$. The infrared spectra of 6 $K_2O \cdot 12\ WO_3 \cdot x\ H_2O$ are so similar to those of the $Na_2O \cdot 2\ WO_3 \cdot 5\ H_2O$ obtained from aqueous solution that we also regard the latter as a salt of the same hexatungstic acid, and denote it by the formula $[Na_6W_6O_{21} \cdot x\ aq] \cdot (15\text{-}x)H_2O$.

Another advantage of the use of organic solvents for the preparation of salts of polyacids is that compounds that are immediately hydrolysed in water can be prepared. For example, *Jahr*, *Fuchs*, and *Oberhauser* [64] prepared a tetra-n-butylammonium tungstate $[N(C_4H_9)_4]_2O \cdot 6\ WO_3$, which is more strongly acidic than any of the polytungstates isolated so far from aqueous solutions, and which is therefore an intermediate stage between metatungstate and the tungsten oxide hydrates. The salt is insoluble in water, but readily soluble in acetone, from which it can be recrystallized. If a little water is added to the acetone solution, the polyanion decomposes and a tungsten oxide hydrate separates out. The degree of condensation of the anion is not yet known. The salt is obtained from acetone as very well-formed, highly refractive crystals [59a].

Interesting results have also been obtained in the study of the hydrolysis of a molybdate ester. Hydrolysis of the diethyl molybdate - ammonia adduct $3\ MoO_2(OC_2H_5)_2 \cdot 2\ NH_3$ [65] in an ethanolic solution of ammonia and ammonium chloride led to an ammonium trimolybdate of the composition $2(NH_4)_2O \cdot 6\ MoO_3 \cdot H_2O$ [66]. The structure of the "trimolybdates" is not yet known. The poor crystallizability of these compounds and their tendency towards twinning have so far made an X-ray structure elucidation impossible. *Lindqvist* [52] believes that the unit cell of the "trimolybdates" contains heptamolybdate $[Mo_7O_{24}]^{6-}$ and octamolybdate ions $[Mo_8O_{26}]^{4-}$ in the ratio 1:1. This structure is certainly not correct for the salt prepared by the hydrolysis of esters, since it must be assumed from the preparation conditions that the water present in the compound, the quantity of which can be accurately determined from the water consumed during hydrolysis, is structural water, *i.e.* that it is present in the form of OH groups. Though the degree of condensation of the polyanion is not given unambiguously by the analytical results (it could also be a multiple of 6), it is very probable from the results of these and other experiments (see Section 8) that the salt is a hexamolybdate $(NH_4)_4[H_2Mo_6O_{21}]$ or $(NH_4)_4[Mo_6O_{19}(OH)_2]$.

A particularly thorough study has been made of the hydrolysis of t-butyl orthovanadate, $(C_4H_9)_3VO_4$, in the presence of bases [67–69]. All types of polyvanadates that can be obtained from aqueous solution can also be prepared in organic solvents. The strength of the base present during the hydrolysis determines whether the product obtained is a divanadate, a metavanadate, a decavanadate, or a hexavanadate, the deciding factor in aqueous solution being the pH. In addition to the above salts, a hydrogen divanadate $K_3HV_2O_7$ [68] has been obtained by the hydrolysis of t-butyl orthovanadate in the presence of potassium t-butoxide; this confirms the existence of the $HV_2O_7^{3-}$ ion, discovered by *Ingri* and *Brito* [9] in equilibrium studies by *Sillén*'s method.

## 8. Complex Formation with Polyanions

### (a) Complex Formation with Polyvanadate Ions

Salt formation is not the only means by which a polyanionic species can be detected in an equilibrium mixture. Many polyanions form complexes with cations

[63] *K. F. Jahr* and *E. Lother*, Ber. dtsch. chem. Ges. *71*, 1127 (1938).

[64] *K. F. Jahr*, *J. Fuchs*, and *R. Oberhauser*, unpublished work.

[65] *A. Nebelung* and *K. F. Jahr*, Z. Naturforsch. *19b*, 654 (1964).

[66] *A. Nebelung*, Dissertation, Freie Universität Berlin 1965.

[67] *J. Fuchs* and *K. F. Jahr*, Chem. Ber. *96*, 2460 (1963).

[68] *J. Fuchs*, *K. F. Jahr*, and *A. Nebelung*, Chem. Ber. *98*, 3582 (1965).

[69] *J. Fuchs*, *K. F. Jahr*, *A. Eberhard*, and *F. Preuss*, Chem. Ber. *98*, 3610 (1965).

in solution. In many cases the polyanion very probably retains its structure and acts as a polydentate ligand, so that information about the size of the polyanion can be obtained from the composition of the complex. Even the fact that complexes are formed at all sometimes gives an indication of their structure. During the titration of a sodium decavanadate solution with a solution of a neutral salt of a bivalent or trivalent cation, for example, we observed [32] that the conductivity of the solution does not increase linearly. Very strong complex formation takes place, particularly with trivalent cations. From the titration curve, formation of a 1:1 complex was deduced. The extent of complex formation depends on the radius as well as the charge of the cation, and increases with increasing ionic radius. A particularly interesting effect is that resulting from the presence of a neutral salt during the titration of free decavanadic acid $H_6V_{10}O_{28}$ with alkalis. Figure 6 shows the course of a conductometric titration of free decavanadic acid with NaOH in the absence and in the presence of strontium nitrate.

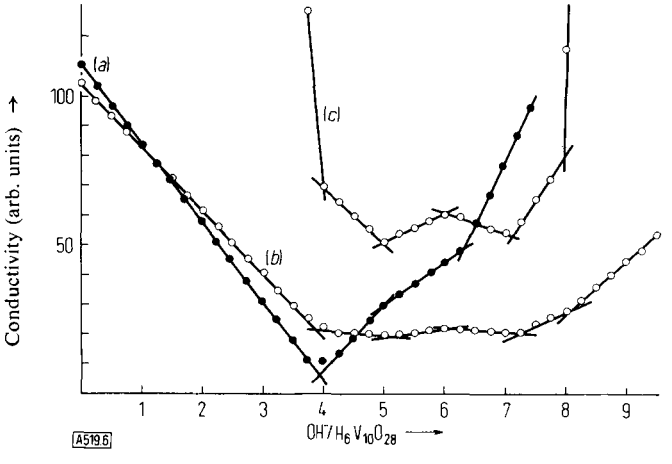



Fig. 6. Conductometric titration of 10 ml of $H_6V_{10}O_{28}$ (0.01 M with respect to $V_2O_5$) with 0.05 N NaOH [curve (a)] [32], and a corresponding titration after addition of 1 ml of 0.1 N $Sr(NO_3)_2$ solution [curve (b)]. Curve (c) shows a section of (b) with a 15-fold increase in sensitivity.

In the presence of $Sr^{2+}$, decavanadic acid consumes but 8 instead of 6 equivalents of $OH^-$. Similar changes in the titration curve are caused by other metal ions. When trivalent cations ($Al^{3+}$, $La^{3+}$, $Ce^{3+}$) or $Be^{2+}$ are present, 9 $OH^-$ are consumed.

Our interpretation of this phenomenon is as follows. The decavanadate ion probably is approximately spherical with a cavity in the center. A hydrated cation can enter this cavity, where it is fixed by complex formation. Owing to the field effect of the oxygen atoms surrounding the cation, protons are removed from the enclosed $[M(H_2O)_x]^{2+}$ and can be neutralized by $OH^-$. This leaves a monomeric hydroxide or an oxometalate ion, *e.g.* $[Be(OH)_3]^-$, in the interior of the complex. On the basis of this interpretation, the titration of $H_6V_{10}O_{28}$ in the presence of *e.g.* $Sr^{2+}$ may be formulated as shown in the following equations:

$$H_6V_{10}O_{28} + 4\ OH^- = H_2V_{10}O_{28}^{4-} + 4\ H_2O$$

$$H_2V_{10}O_{28}^{4-} + Sr(H_2O)_n^{2+} = [Sr(H_2O)_nH_2V_{10}O_{28}]^{2-} \quad (d)$$

$$[Sr(H_2O)_nH_2V_{10}O_{28}]^{2-} + OH^- = [Sr(H_2O)_nHV_{10}O_{28}]^{3-} + H_2O$$

$$[Sr(H_2O)_nHV_{10}O_{28}]^{3-} + OH^- = [Sr(H_2O)_nV_{10}O_{28}]^{4-} + H_2O$$

$$[Sr(H_2O)_nV_{10}O_{28}]^{4-} + OH^- = [Sr(OH)(H_2O)_{n-1}V_{10}O_{28}]^{5-} + H_2O$$

$$[Sr(OH)(H_2O)_{n-1}V_{10}O_{28}]^{5-} + OH^- = [Sr(OH)_2(H_2O)_{n-2}V_{10}O_{28}]^{6-} + H_2O$$

Only a few symmetrical structures are conceivable for a decavanadate ion having the formula $[V_{10}O_{28}]^{6-}$ if the central cavity is assumed to be large. The only structural units possible in this case are $VO_4$ tetrahedra, since $VO_6$ octahedra or $VO_5$ units give only very compact structures with no central cavity. The structure proposed [32] for the decavanadate ion in solution is shown in Fig. 7.

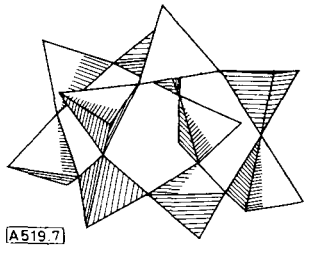



Fig. 7. Proposed structure of $V_{10}O_{28}^{6-}$ in solution [32].

### (b) Complex Formation with Polymolybdate Ions

If a few drops of methyl red are added to a molybdate solution of acidification 1.5, the color of the solution changes from red to yellow after a short time [70,71]. Surprisingly, the solution remains yellow when strong mineral acid is added. Conductometric titrations show the formation of a complex containing methyl red and molybdenum in the ratio 1:12. The yellow color of the methyl red in the strongly acidic solution can be understood only if it is assumed that the indicator molecule is bound in the center of a dodecamolybdate ion, and that the situation is similar to that in conventional inclusion compounds of indicators with cyclodextrins [72, 73], in which the indicator also does not exhibit its normal color.

The formation of complexes thus indicates that molybdate solutions of acidification above 1.5 contain dodecameric anions which, like the decavanadate ion, are approximately spherical, hollow, and can form inclusion complexes. Naturally, nothing can be said about the concentration of polyanions in the solution. It is quite possible that only a small part of the molybdenum is in the form of dodecameric particles, and that it is only the formation of the relatively stable complex that displaces the equilibrium in favor of this polyanion. The rate of formation of the "inclusion complex" is greatest in solutions of acidification x = 1.65 to 1.7. The yellow solution becomes red again on addition of concentrated phosphoric acid, which evidently displaces the indicator anion to form a more stable complex. The methyl red complex is also rapidly destroyed by alkalis, owing to breakdown of the polyanion. It is possible, by very careful addition of $OH^-$, to achieve the apparently paradoxical

[70] *C. Thieme*, Dissertation, Freie Universität Berlin; see here for the UV spectra.

[71] *K. F. Jahr*, Angew. Chem. *76*, 236 (1964); Angew. Chem. internat. Edit. *3*, 320 (1964).

[72] *F. Cramer*: Einschlußverbindungen. Springer, Berlin-Göttingen-Heidelberg 1954, p. 87.

[73] *W. Broser*, Z. Naturforsch. *8b*, 722 (1953).

result that the color of the solution changes from yellow to red, since the dodecamolybdate ion is destroyed at a pH at which methyl red is normally red. The yellow indicator anion is then formed when an excess of $OH^-$ is added.

We have carried out an intensive study of the complexing power of molybdate solutions of acidification less than 1.50 towards cations and towards acids that can form heteropoly compounds [74,75]. Many cations can react with polymolybdate ions in solution to form complexes, nearly all of which are very unstable. $Al^{3+}$ forms a very stable complex having an Al:Mo ratio of 1:6. The complexes formed by orthotelluric acid and periodic acid are still more stable.

In this case, too, a relation is apparent between the stability of the complex and the ionic radius of the complex former. The radii of $Al^{3+}$ (0.55 Å), $Te^{6+}$ (0.56 Å), and $I^{7+}$ (0.50 Å) are very similar. These complexes, which are formed in relatively weakly acidic solution, require extensive measurements for the determination of their compositions, since the complexing equilibrium depends not only on the concentration of ligand ratio, but also to determine the charge on the hydrogen ion concentration. However, the dependence of the equilibrium on pH also has the advantage that it is not only possible to determine accurately the nucleus: ligand ratio, but also to determine the charge on the complex and to establish the occurrence of protonation stages. We have elucidated these reactions to a large extent [75] by simultaneous thermometric, conductometric, and potentiometric titrations.

The methods used will be illustrated for the complex formation between periodic acid and molybdate ions. When an $HMoO_4^-$ solution (x = 1.00) is titrated with periodic acid, the thermometric and conductometric titration curves contain discontinuities and the potentiometric curve contains inflections at the molar ratios $H_5IO_6/HMoO_4^-$ = 1:7 and 1:3. However, it would be erroneous to conclude that complexes with the ratios I:Mo = 1:7 and 1:3 have been formed. In fact, the discontinuities are due to a 1:6 complex $[IMo_6O_{24}]^{5-}$ which is initially formed by only a part of the molybdenum [reaction (e)].

$$7\ HMoO_4^- + H_5IO_6 \rightleftharpoons [IMo_6O_{24}]^{5-} + MoO_4^{2-} + 6\ H_2O \quad (e)$$

change in slope at I:Mo = 1:7

One-seventh of the molybdate cannot enter into complex formation at first, owing to the deficiency in $H^+$.

An interesting phenomenon is observed in this titration. Owing to the consumption of $H^+$ and the consequent conversion of $HMoO_4^-$ into $MoO_4^{2-}$ the pH initially increases rapidly for a time during the titration, although the titrant is the relatively strong periodic acid.

Since periodic acid itself can supply $H^+$ [*], the remaining molybdate is finally converted into the complex ion [reaction (f)]. If the titration is carried out at different initial acidification, the discontinuities and inflections occur at different values of the ratio $H_5IO_6/MoO_4^{2-}$ [*]. The composition of the complex can be found by mathematical treatment of the results obtained when molybdate solutions of various acidifications are titrated with periodic acid.

$$6\ HMoO_4^- + 2\ H_5IO_6 \rightleftharpoons [IMo_6O_{24}]^{5-} + H_4IO_6^- + 6\ H_2O \quad (f)$$

change in slope at I: Mo = 1:3

The complexing processes can in general be formulated as follows:

$$n\ MoO_4^{2-} + p\ H^+ + m\ H_5IO_6 \rightleftharpoons [I_mMo_nO_s]^{(2s-6n-7m)-} + (5m + p)/2\ H_2O \quad (g)$$

where $s = 4n-(7m-p)/2$

If the acidification x of the molybdate solution is varied and the atomic ratio I/Mo = Z determined for the initially incomplete complex formation (when all the $H^+$ present have been consumed) and for the final complex formation (when all $MoO_4^{2-}$ is converted into complex), it is found that Z = mx/p and Z = −x + (m + p)/n, respectively; it is then possible to establish sets of integral values for m; p; n.

The values found for complex formation with periodic acid are 6; 7; 1 and multiples of this set, such as 12; 14; 2. These sets give Equations (h) and (i).

$$6\ MoO_4^{2-} + 7\ H^+ + H_5IO_6 \rightleftharpoons [IMo_6O_{24}]^{5-} + 6\ H_2O \quad (h)$$

$$12\ MoO_4^{2-} + 14\ H^+ + 2\ H_5IO_6 \rightleftharpoons [I_2Mo_{12}O_{48}]^{10-} + 12\ H_2O \quad (i)$$

The question of whether the mononuclear complex $[IMo_6O_{24}]^{5-}$ or a polynuclear complex is formed cannot be answered on the basis of the titrations; with the ultracentrifuge, however, *Stock* [76] obtained a value of 1110 for the ionic weight of the complex ion ($M_{theor.}$ for $[IMo_6O_{24}]^{5-}$ is 1086.5), showing that the reaction proceeds according to Eq. (h). Other experimental points can be easily interpreted by the formation of the protonation stages $[HIMo_6O_{24}]^{4-}$, $[H_2IMo_6O_{24}]^{3-}$, $[H_3IMo_6O_{24}]^{2-}$, and $[H_4IMo_6O_{24}]^-$.

Complex formation between polymolybdate ions and orthotelluric acid is more versatile than the reaction with periodic acid. Salts having the composition $M_6TeMo_6O_{24}\cdot nH_2O$ have been known for some time [77], complex formation in solution, on the other hand, was first studied in 1963 by *Gross* [74]. Conductivity measurements showed that in addition to the 1:6 complex, other complexes with different Te:Mo ratios occur. By spectrophotometric studies [78] (molar ratio method) and by salt-cryoscopic titrations [79] we found the Te:Mo ratios in these compounds to be 1:7 and 1:12. The charges on the complexes were determined by simultaneous thermometric, conductometric, and potentiometric titrations. The ions found in addition to $[TeMo_6O_{24}]^{6-}$ were $[HTeMo_7O_{28}]^{7-}$ (or $[TeMo_7O_{27}(OH)]^{7-}$) and $[H_6TeMo_{12}O_{48}]^{12-}$ (or $[TeMo_{12}O_{42}(OH)_6]^{12-}$). The ionic weight of the 1:6 complex was determined with the aid of the ultracentrifuge [80] ($M_{exp.}$, 1163; $M_{theor.}$ for $[TeMo_6O_{24}]^{6-}$, 1087.3). Information about the relative stabilities of the complexes was obtained by salt-cryoscopic titrations.

[74] *K. F. Jahr, J. Fuchs, M. Gross,* and *L. Klingebiel,* unpublished work.

[75] *G. Wiese,* Dissertation, Freie Universität Berlin, 1965.

[*] Periodic acid acts as a monobasic acid throughout the pH range investigated (2.5 to 7.5).

[*] This example shows clearly the erroneous conclusions that can be reached in the study of complex formation unless measurements are performed with a sufficiently wide range of starting conditions.

[76] *K. F. Jahr, J. Fuchs,* and *G. Wiese,* Z. Naturforsch. *21b,* 11 (1966).

[77] Cf. [36], p. 322.

[78] *E. Gegner,* Diploma Thesis, Freie Universität Berlin 1963; *K. F. Jahr* and *E. Gegner,* unpublished work.

[79] *H. Schroth,* Dissertation, Freie Universität Berlin 1964.

[80] *H. G. Bubam,* Diploma Thesis, Freie Universität Berlin 1964.

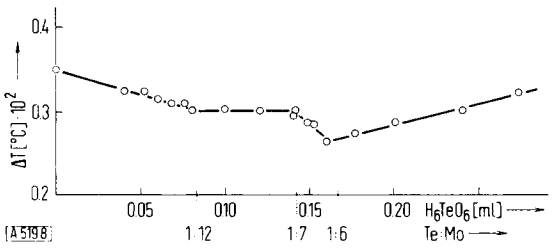



Fig. 8. Relative freezing point depression ΔT in the salt-cryoscopic titration of 2.5 ml of 0.3 M $Na_2MoO_4$ solution having an acidification x = 1.14 with 0.06 M $H_6TeO_6$, measured in the Glauber's salt-ice eutectic.

It can be seen from Figure 8 that the 1:6 complex is the most stable. The freezing-point depressions obtained almost[*] coincided with those expected for $[TeMo_6O_{24}]^{6-}$ although the measurements, which were carried out in the Glauber's salt-ice eutectic, had to be made at a very low concentration ($\approx$ 0.01 g-atom of Mo/l) because of the low solubility of sodium hexamolybdatotellurate. The eutectic freezes at −1.125 °C. The 1:7 and 1:12 complexes are more strongly dissociated than the 1:6 complex. It is very interesting to observe how the stability of the 1:6 complex depends on the acidity of the molybdate solution (Fig. 9).

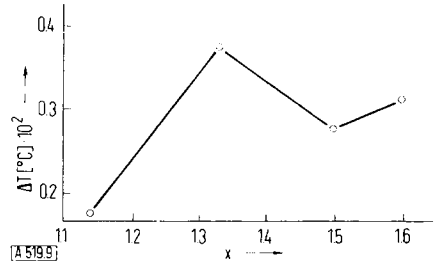



Fig. 9. Relative freezing point depression ΔT produced by $[TeMo_6O_{24}]^{6-}$ in the Glauber's salt-ice eutectic, as a function of the acidification x of the molybdate solution.

The stability of this complex, which corresponds formally to the acidification x = 1.00, increases once more above x = 1.33 (Eq. (j)]. This can be explained by the

$$6\ H^+ + 6\ MoO_4^{2-} + Te(OH)_6 \rightleftharpoons [TeMo_6O_{24}]^{6-} + 6\ H_2O \quad (j)$$

assumption that the concentration of the ligands that react with the orthotelluric acid is lower at x = 1.33 than in more acidic (x = 1.50) and less acidic (x = 1.14) solutions (see below).

This assumption is supported by observations made during the study of complex formation between polymolybdate ions and $Al^{3+}$. The curves obtained by thermometric, conductometric, and potentiometric titrations of acidic molybdate solutions with $Al_2(SO_4)_3$ solution show not only changes in slope indicating completion of complex formation, but also discontinuities and inflections that must be due to other causes. The results can be explained if it is assumed that the $Al^{3+}$ can react only with a certain polyanion, which itself corresponds formally to x = 1.50. Such a polyanion would have to carry one-half of a negative charge per Mo atom, *e.g.* $[HMo_2O_7 \cdot x\ aq]^-$, $[Mo_4O_{13} \cdot x\ aq]^{2-}$, $[HMo_6O_{20} \cdot x\ aq]^{3-}$, $[Mo_8O_{26} \cdot x\ aq]^{4-}$ [Eq. (k)].

$$9\ H^+ + 6\ MoO_4^{2-} + y\ H_2O \rightleftharpoons [HMo_6O_{20} \cdot x\ H_2O]^{3-} + (y - x + 4)\ H_2O \quad (k)$$

The evaluation of the results gives the formula $[H_6AlMo_6O_{24}]^{3-}$ for the aluminum complex.

The results obtained in the investigation of complex formation and hydrolysis of molybdate esters can be readily explained and related to many other facts if it is assumed that the acidification of a molybdate solution leads to consecutive reactions:

The initially formed $HMoO_4^-$ ions rapidly form a cyclic polyanion containing 6 Mo atoms. The $HMoO_4^-$ ions may be held together by hydrogen bonds; the formula of the particle would then be $[H_6Mo_6O_{24}]^{6-}$. In contrast to the tungstate system, in which a polyanion containing 6 W atoms is stable, the hexamolybdate ion is stabilized by combination with an ion of suitable radius. Thus in a pure molybdate solution, the heptamolybdate ion $[Mo_7O_{24}]^{6-}$ is formed. In the presence of $H_5IO_6$ or $Te(OH)_6$, on the other hand, the heterocomplexes $[IMo_6O_{24}]^{5-}$ and $[TeMo_6O_{24}]^{6-}$ or $[H_6TeMo_{12}O_{48}]^{12-}$ are formed. We regard $[H_6TeMo_{12}O_{48}]^{12-}$ as a complex in which the $Te^{6+}$ is situated between two $Mo_6O_{24}$ rings, as in a sandwich compound. The reason for the greater stability of $[TeMo_6O_{24}]^{6-}$ in relation to $[MoMo_6O_{24}]^{6-}$ (heptamolybdate) is probably that the smaller $Te^{6+}$ ion fits into the hexamolybdate ring even better than $Mo^{6+}$.

This view agrees closely with the results obtained by *Evans*[81] in the X - ray structure analysis of $(NH_4)_6TeMo_6O_{24} \cdot 7\ H_2O$, according to which the $Te^{6+}$ ion is situated in the center of a ring of six $MoO_6$ octahedra, whereas in $[Mo_7O_{24}]^{6-}$ the seventh Mo atom lies outside the plane of the ring, so that this particle has a "bowl shape" (Fig. 2e). This shape evidently enables the formation of the complex $[HTeMo_7O_{28}]^{7-}$. In view of the unsymmetrical structure of the heptamolybdate ion, which according to *Aveston*[26] probably has a similar structure in solution to that in the crystal, the tendency towards complex formation is understandable. Many compounds of composition

$$M^I_4M^{II}Mo_7O_{24} \text{ and } M^I_3M^{III}Mo_7O_{24},$$

which could be regarded as purely salt-like, probably are complexes. For example, from the color of $(NH_4)_3Ce^{III}Mo_7O_{24} \cdot 24\ H_2O$, which is orange-yellow even in solution, although $Ce^{3+}$ is colorless, *Barbieri*[82] assumed it to be a complex.

As was also found by *Sasaki*[12,13] with the aid of the Sillén method, the heptamolybdate ion is stable over a wide range of acidifications, and exists in solutions with x > 1.14 as the protonated species $[HMo_7O_{24}]^{5-}$ or $[H_2Mo_7O_{24}]^{4-}$. Complex formation between the heptamolybdate ion and orthotelluric acid (1:7 complex) has been detected even in solutions with x = 1.33 both by the simultaneous thermometric, conductometric, and potentiometric titrations and by salt-

[*] The expected freezing-point depression was $0.259 \times 10^{-2}$. The results of the salt-cryoscopic titration give only the relative change in the number of particles. To find the absolute degree of condensation, series of measurements must be carried out over a wide range of concentrations.

[81] *H. T. Evans jr.*, J. Amer. chem. Soc. *70*, 1291 (1948).

[82] *G. A. Barbieri*, Atti Accad. Lincei (Roma) *17*, 1, 540 (1908).

cryoscopic titrations). However, solutions with x = 1.33 also contain other types of particles, as has been shown by ultracentrifugation experiments [80]. On the other hand, the existence of $(NH_4)_4H_2Mo_6O_{21}$, which is prepared by hydrolysis of molybdate esters, indicates the occurrence of $[H_2Mo_6O_{21}]^{4-}$.

The question of the existence of a definite polymolybdate ion corresponding to an acidification x = 1.33 was disputed for a long time, since no changes in slope were observed in the curves obtained in potentiometric and conductometric titrations of molybdate solutions with acid (except by *R. H. Saxena* and *G. P. Saxena* [83]). A change in slope can, however, be observed in accurate thermometric titrations; we attribute this change to the formation of the $[H_2Mo_6O_{21}]^{4-}$ anion, from which the "trimolybdates" may be derived. We assume that the heptamolybdate ion becomes less stable as a result of protonation, and is partly converted into this hexamolybdate ion (which now has a different structure), possibly according to

$$H_2Mo_7O_{24}^{4-} + H_2O \rightleftharpoons H_2Mo_6O_{21}^{4-} + H_2MoO_4 \quad (I)$$

The complexing reactions in solutions with $x < 1.50$, and particularly the reaction with $Al^{3+}$, can be readily understood if it is assumed that the anion $[H_3Mo_6O_{21}]^{3-}$ is formed in these solutions by protonation of $[H_2Mo_6O_{21}]^{4-}$. This protonation also must be associated with a change in structure, since it would otherwise be impossible to explain the fact that $Al^{3+}$ reacts with $[H_3Mo_6O_{21}]^{3-}$ ($[HMo_6O_{20}\cdot H_2O]^{3-}$), but not with $[H_2Mo_6O_{21}]^{4-}$; the simultaneous thermometric, conductometric, and potentiometric titrations have shown that complex formation with $Al^{3+}$ is preceded by formation of a polymolybdate that corresponds to x = 1.50 (cf. p. 697). Orthotelluric acid also fails to react with $[H_2Mo_6O_{21}]^{4-}$, but probably reacts with $[H_6Mo_6O_{24}]^{6-}$ and $[H_3Mo_6O_{21}]^{3-}$. This provides a simple explanation for the stability minimum of $[TeMo_6O_{24}]^{6-}$ at x = 1.33.

In addition to hexameric polymolybdate ions, the solution with x = 1.50 must contain also dodecameric anions, since it is otherwise impossible to explain the complex formation with methyl red. It is not yet known whether this solution contains appreciable quantities of octamolybdate ions. Many authors believe that the octamolybdate ion $[Mo_8O_{26}]^{4-}$ is the major component of solutions with x = 1.50. The main arguments for this view are the facts that this anion [52] is present in crystalline ammonium metamolybdate, and that the average degree of condensation of the solution is approximately 8. However, no really conclusive evidence has so far been produced. On the basis of our views on the interconversions of polymolybdate ions, an octamolybdate would be quite feasible, since a protonated heptamolybdate ion should condense with an $HMo_4^-$ ion just as with a molecule of orthotelluric acid. No octamolybdate ion has been detected by complex formation. However, this ion probably cannot be expected to form complexes if its structure is similar to that envisaged by us for the $[HTeMo_7O_{28}]^{7-}$ ion, *i.e.* a compact, approximately spherical particle. Thus we can neither confirm nor deny the existence of the octamolybdate ion.

No further details on the relationships in more strongly acidic molybdate solutions ($x > 1.50$) are available at present.

[83] *R. H. Saxena* and *G. P. Saxena*, Z. physik. Chem. N.F. *29*, 181 (1961).

### (c) Complex Formation with Polytungstate Ions

Interesting results [84] have also been obtained in the investigation of complex formation by polytungstates in solution. The paratungstate ions A and B (which can be produced by acidification of $WO_4^{2-}$ solutions to x = 1.167) react with bivalent and trivalent cations to form complexes having the atomic ratio $M^{2+}$ or $M^{3+}$: W = 1:6. The most stable complexes are those formed with cations of radius ≈ 0.75 Å, whereas polymolybdate ions prefer cations having a radius of about 0.5 Å. In solutions containing paratungstate Z, the same complexes are formed only after about 24 hours.

Complex formation with cations ($M^{2+}$:W = 1:12) has also been observed in solutions of free metatungstates, and even in solutions of free metatungstic acid. The intensity of the complex formation depends on the charge and on the ionic radius, and decreases roughly in the order: $La^{3+} > Yb^{3+} > Al^{3+} \approx Ba^{2+} > Cd^{2+} \approx Sr^{2+} > Ca^{2+} \approx Cu^{2+} \approx Zn^{2+} \approx Mn^{2+} \approx Co^{2+} \approx Ni^{2+} > Mg^{2+} > Be^{2+} \approx Cs^+$.

No complex formation has been observed with $Rb^+$ or the lighter alkali metals. Phosphoric acid does not react with metatungstates or metatungstic acid. Metatungstate solutions prepared by acidification of $WO_4^{2-}$ solutions to x = 1.50 react with cations only after boiling for several hours or after prolonged standing (about 200 days), *i.e.* only after "true metatungstate ions" have been formed. On the other hand, freshly acidified solutions react, though only weakly, with phosphoric acid. This result provides further confirmation of *Jander*'s observation [41] that acidification to x = 1.50 does not lead immediately to the pseudotungstate ion, but results first in the formation of metatungstate ion A; recently this observation has been repeatedly questioned. The metatungstate ion and the pseudometatungstate ion evidently differ from the paratungstate ions A and B, not only in the degree of protonation, but also in their structures; otherwise, it would be impossible to explain the failure of the first two to form complexes with cations.

Paratungstate solutions (both A and Z) that have been aged for a long time exhibit the complexing reactions of the "true" metatungstate ion. This confirms again that a slow "dismutation" takes place in paratungstate solutions, with formation of the acidic metatungstate ion and the basic monotungstate ion [85,86]. These two are probably the only thermodynamically stable tungstate ions.

## 9. Closing Remarks

Attempts to obtain information about the nature of the isopolyanions present in a solution from the composition of complexes of the polyanions with cations which have been detected in the solution meet with difficulties similar to those encountered in attempts to apply

[84] *P. Scharner*, Dissertation, Freie Universität Berlin 1965.

[85] *G. von Knorre*, Ber. dtsch. chem. Ges. *18*, 2362 (1885).

[86] *R. Kubens*, Dissertation, Humboldt-Universität Berlin 1952

conclusions based on the crystalline state to the dissolved state. A complex of this nature may be formed in one of two ways:

1. The central cation reacts with monomers or small isopolyanions;

2. The central cation reacts with the preformed isopolyanion.

Only in the second case can reliable conclusions regarding the isopolyanion be based on the structure of the complex.

Both reactions evidently are possible in the formation of hetero-complexes. Thus the fact that "true" metatungstate ions do not react with phosphoric acid shows very clearly that, for example, the dodecatungstatophosphate ion, which is similar to the true metatungstate ion [54], can be formed in accordance with 1; it is formed on acidification of a solution containing monotungstate and phosphate ions. The complexes we have described, on the other hand, evidently are formed in accordance with 2, so that there is a direct relation between these complexes and the isopolyanions originally present in the solution. Some of the many reasons for this conclusion are:

The formation of *different* complexes with cations from paratungstate solutions of the same concentration and pH but of different ages would not be understandable if the heterocomplexes were formed from fragments and not from the different polytungstate ions present in each case.

True metatungstate ions and decavanadate ions are broken down only slowly in alkaline solutions. Since complex formation with these polyanions is instantaneous, it is hardly possible that it could proceed *via* fragments.

The reaction of methyl red with molybdate in the ratio 1:12 could not be explained without assuming the prior existence of dodecamolybdate ions with cavities capable of accommodating the dye.

We have attempted in this paper to outline, with the aid of some examples, the present state of research on polyacids, and to describe a number of new methods that have contributed to progress in this field. New insights into the chemistry of the polyacids will undoubtedly be gained in the future by the use of numerous and versatile chemical and physical methods, and by a logical combination of all the individual results.

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German version: Angew. Chem. *78*, 725 (1966)
Translated by Express Translation Service, London

[87] *K. Lohoff*, Dissertation, Freie Universität Berlin 1966.

# Aryl-$\Delta^2$-pyrazolines as Optical Brighteners

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*Di- and triaryl-$\Delta^2$-pyrazolines and their derivatives can be used as optical brighteners for synthetic fibers and plastics. The heterocycles are readily obtainable by several methods, e.g. condensation of ß-halogeno- or ß-dialkylaminopropiophenones with phenylhydrazine. A number of relationships can be detected between substitution and optical properties.*

## 1. Introduction

The use of organic fluorescent dyes for the optical brightening of textiles, paper, and plastics and as additives in detergents has shown a rapid increase in recent years. Without additives these materials are not pure white; they absorb in the short wavelength region of the visible spectrum, and consequently appear more or less yellowish. The use of optical brighteners, which emit blue-violet fluorescence, leads not merely to the compensation of this so-called "blue deficiency", but to an increase in the remission of the material above 100 % (relative to magnesium oxide as standard), since the blue-violet fluorescence gives the impression of increased whiteness (cf. Fig. 1).

As with organic dyestuffs, the compounds used in industry for this purpose can be grouped into a small number of types [1]. By far the most important optical

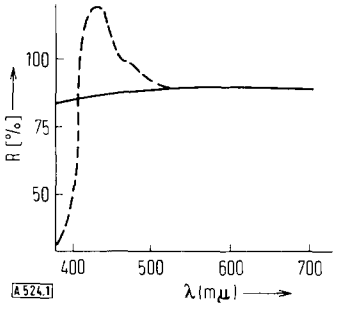
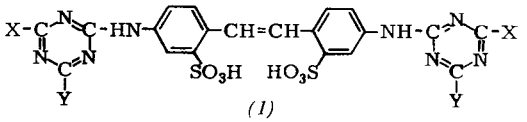



Fig. 1. Re-emission R of unbleached cotton cloth without optical brightener (——) and with optical brightener (– – –) (MgO = 100%).

brighteners are derived from 4,4′-diaminostilbene-2,2′-disulfonic acid [2]. The triazine derivatives *(1)* of this compound [3] are particularly suitable.

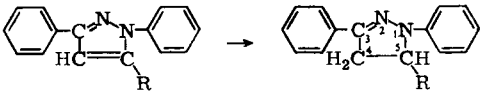


*(1)*

X and Y, *e.g.*: $NH_2$, $NH-CH_3$, $NH-CH_2-CH_2-OH$, $N(CH_2-CH_2-OH)_2$, morpholino, $NH-C_6H_5$, $NH-C_6H_4-SO_3H$, $OCH_3$, Cl.

Substances of other classes [2] which have recently been used for the optical brightening of synthetic fibers and plastics include coumarin derivatives, bisoxazolyl- and bisimidazolylethylenes, and the di- and triaryl-$\Delta^2$-pyrazolines described here.

This class of substances was discovered in 1888 by *Knorr* and *Laubmann* [4], who prepared 1,3,5-triphenyl-$\Delta^2$-pyrazoline *(2a)* and 1,3-diphenyl-$\Delta^2$-pyrazoline *(2b)* [5] by the reduction of the pyrazoles with sodium in ethanol.



*(2a)*, R = $C_6H_5$
*(2b)*, R = H

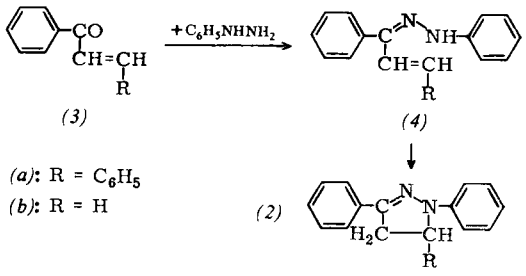
The remarkable fluorescence of the arylpyrazolines in organic solvents was observed already in this first, rather inefficient synthesis. However, it was more than 60 years before any technical use was made of this property.

Many other syntheses have been developed for arylpyrazolines [5a]. With the usual numbering of the pyrazoline ring the syntheses can be arranged according to how the ring members are joined by condensation or addition.

## 2. Syntheses of $\Delta^2$-Pyrazolines

### a) Principle 1,2 + 3,4,5

The reaction of phenylhydrazine with benzylideneacetophenones *(3a)* [4,6] leads initially to the phenylhydrazone *(4a)* of the α,β-unsaturated ketone, which can in some cases be isolated [7]. Ring closure is particularly easy with benzylideneacetophenone derivatives containing electron-donating groups [8]. The reaction, which is very general, is preferably carried out in glacial acetic acid or in a solution containing acetic acid



*(3)* *(4)*

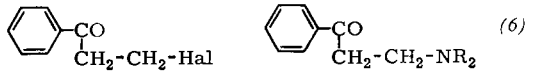
*(a)*: R = $C_6H_5$
*(b)*: R = H

*(2)*

Similarly, the diphenylpyrazoline *(2b)* can be prepared from phenyl vinyl ketone *(3b)* and phenylhydrazine [9]. Any substituted arylhydrazines may also be used instead of phenylhydrazine [10].

Even the cyclization of phenyl vinyl ketone 2,4-dinitrophenylhydrazone, which is opposed by the electron-attracting nitro groups, proceeds in boiling glacial acetic acid in the presence of hydrobromic acid [11].

However, it is not necessary to use the often unstable α,β-unsaturated ketones for the preparation of arylpyrazolines. The synthesis can also be carried out with compounds that behave as aryl vinyl ketones under the conditions of the ring closure. The most important compounds of this type are the β-halogenopropiophenones *(5)* [12] and the Mannich bases *(6)* obtained from acetophenone, formaldehyde, and secondary amines [13]. The reaction of these compounds with arylhydrazines also leads smoothly *via* the hydrazones to the arylpyrazolines.



*(5)* *(6)*

The β-halogenopropiophenones, which may also contain other substituents in the α or β positions, are prepared by Friedel-Crafts acylation of aromatic compounds with β-halogenopropionyl chloride. It should be noted that the simple members of this series, *e.g.* β-chloropropiophenone itself, are powerful skin irritants.

The Mannich bases *(6)* can be prepared from many secondary amines, such as dimethylamine [14], piperidine [15], or morpholine [16]. Ammonia may also be used as the base, and in

[1] *S. Petersen*, Angew. Chem. *61*, 17 (1949).

[2] *H. Gold* in: Ullmanns Encyklopädie der technischen Chemie. 3rd Ed., Vol. 11, p. 688, Urban u. Schwarzenberg, München-Berlin, 1960.

[3] *H. Gold*, Chem. Labor Betrieb *14*, 405 (1963).

[4] *L. Knorr* and *H. Laubmann*, Ber. dtsch. chem. Ges. *21*, 1209 (1888).

[5] *L. Knorr* and *P. Duden*, Ber. dtsch. chem. Ges. *26*, 115 (1893); cf. *K. v. Auwers*, *ibid. 65*, 833 (1932).

[5a] *B. H. Chase* and *J. M. Evans*, J. chem. Soc. (London) *1964*, 4825.

[6] *K. v. Auwers* and *H. Voss*, Ber. dtsch. chem. Ges. *42*, 4422 (1909).

[7] *L. C. Raiford* and *H. L. Davis*, J. Amer. chem. Soc. *50*, 160 (1928).

[8] *T. L. Jacobs* in *R. C. Elderfield*: Heterocyclic Compounds. Vol. 5, p. 45, Wiley, New York, 1957.

[9] *A. Schäfer* and *B. Tollens*, Ber. dtsch. chem. Ges. *39*, 2188 (1906).

[10] Brit. Pat. 670857 (June 3rd, 1949); Brit. Pat. 698253 (Oct. 14th, 1953), both Ilford Ltd., Inv.: *J. D. Kendall* and *G. F. Duffin*.

[11] *W. M. Chambers* and *M. L. Willard*, J. Amer. chem. Soc. *82*, 3374 (1960); cf. *R. F. Curtis*, *C. H. Hassel*, and *J. Weatherstone*, J. chem. Soc. (London) *1962*, 3831.

[12] *H. Rupe* and *F. Schneider*, Ber. dtsch. chem. Ges. *28*, 957 (1895); *H. Kashiwagi*, Bull. chem. Soc. Japan *26*, 355 (1953); Chem. Abstr. *49*, 6879c (1955); *E. Profft*, *F. Runge*, and *A. Jumar*, J. prakt. Chem. (4), *1*, 57 (1955); *A. Jumar*, *ibid.* (4), *3*, 238 (1956).

[13] *F. F. Blicke*, Org. Reactions *1*, 303 (1942).

[14] *A. Jacob* and *J. Mandinaveitia*, J. chem. Soc. (London) *1937*, 1929.

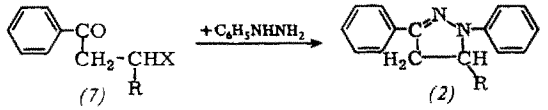
[15] *H. B. Nisbet*, J. chem. Soc. (London) *1945*, 126.

[16] *R. A. Harradence* and *F. Lions*, J. Proc. Roy. Soc. New South Wales *72*, 233 (1939); Chem. Zbl. *1939*, I, 4959.

this case the product is *(6)* with R = 2-phenoxyethyl [17]. The acetophenones are particularly cheap starting materials. These last two methods are especially useful for the manufacture of pyrazolines.

Moreover, Mannich bases can be prepared, not only from acetophenone, but also from butyrophenone and β-phenylpropiophenone [18]. In these cases the formaldehyde and secondary amines condense on the α-methylene group of the ketone, and the reaction of the product with phenylhydrazine then gives pyrazolines with further substituents in position 4.

For the sake of completeness, mention should also be made of other propiophenones *(7)* that contain replaceable groups in the β position, and which can react with phenylhydrazine to give pyrazoline derivatives *(2)*.

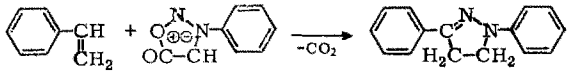



*(7)* *(2)*

| X | R | Ref. | X | R | Ref. |
|---|---|---|---|---|---|
| OH | H | [19] | Se–$C_6H_5$ | $C_6H_5$ | [23] |
| $OC_2H_5$ | H | [20] | $CH_2$–CO–$C_6H_5$ | $CH(CH_3)_2$ | [24] |
| SH | $C_6H_5$ | [21] | 2-Quinolyl- | $C_6H_5$ | [25] |
| S–$C_6H_4$-*p*-$CH_3$ | $C_6H_5$ | [22] | nitromethyl | | |

### b) Principle 1,2,5 + 3,4

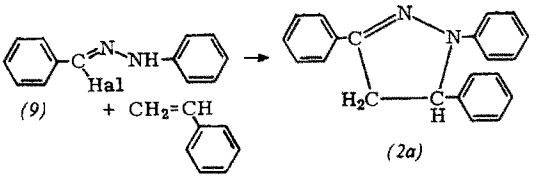
Pyrazoline syntheses based on the principle of 1,3-dipolar addition proceed particularly smoothly. Thus phenylsydnone *(8)* loses carbon dioxide when heated in xylene in the presence of styrene,1,3-diphenylpyrazoline *(2b)* being formed in high yield [26].




*(8)* *(2b)*

### c) Principle 1,2,3 + 4,5

Another example of a 1,3-dipolar addition is the reaction of α-halogenobenzaldehyde phenylhydrazone *(9)* with styrene in the presence of an acid acceptor [27]. The product is 1,3,5-triphenylpyrazoline *(2a)*.

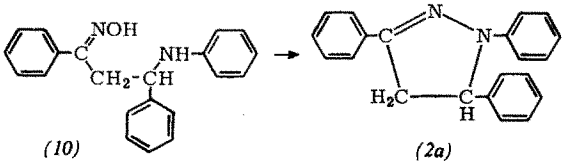


*(9)* *(2a)*

Any substituted arylsydnones or halogenobenzaldehyde phenylhydrazones may also be used as starting materials for the last two syntheses. Substituted styrenes are often difficult to obtain, and styrenes with sulfonic acid, sulfonamide, or nitro groups in the β-position do not react. Olefins such as acrylonitrile, acrylic esters, or butadiene may also be used instead of styrene.

### d) Pyrazoline Ring Closure Between Positions 1 and 2

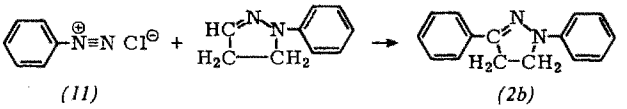
A peculiar synthesis of 1,3,5-triphenylpyrazoline *(2a)* is the elimination of water from β-anilino-β-phenylpropiophenone oxime *(10)* [28]. In this case the N–N ring bond is formed last.



*(10)* *(2a)*

### e) Introduction of Aromatic Substituents into the Preformed Pyrazoline Ring

$\Delta^2$-Pyrazolines with no substituent in position 3 react in this position with aromatic diazonium salts *(11)* [29]. The coupling is carried out in the presence of pyridine or sodium acetate.



*(11)* *(2b)*

Finally, 1-unsubstituted 3-arylpyrazolines can be arylated in position 1 with 2,4-dinitrochlorobenzene [11]. 2,4,6-Trichlorotriazine can also be used in this reaction, and in this case the product is 1-(4,6-dichloro-s-triazin-2-yl)-3-phenyl-$\Delta^2$-pyrazoline.

## 3. Constitution and Fluorescence of Arylpyrazolines

Surprisingly, arylpyrazolines with at least two aryl units in positions 1 and 3 exhibit strong fluorescence, although the molecule *(2)* in its classical formulation does not have continuous conjugation. Benzalacetophenone phenylhydrazone *(4a)* does not fluoresce; however, tri-

[17] *H. Schäfer* and *B. Tollens*, Ber. dtsch. chem. Ges. *39*, 2186 (1906).

[18] U.S.-Pat. 2740793 (April 3rd, 1956), Ilford Ltd., Inv.: *J. D. Kendall* and *G. F. Duffin*.

[19] *K. Bodendorf* and *B. Binder*, Arch. Pharmaz. *287*, 453 (1954); *H. Moe* and *B. B. Carson*, J. org. Chemistry *24*, 1768 (1959).

[20] *L. Panizzi* and *M. Sbrillo-Siena*, Gazz. chim. ital. *73*, 335 (1943).

[21] *B. Tometta* and *S. Agnello*, Ann. Chimica *48*, 581 (1958).

[22] *B. H. Nicolet*, J. Amer. chem. Soc. *53*, 3066 (1931).

[23] *H. Gilman* and *L. F. Carson*, J. Amer. chem. Soc. *73*, 1074 (1951).

[24] *R. H. Wiley et al.*, J. org. Chemistry *23*, 732 (1958).

[25] *L. Zalukajevs* and *E. Vanags*, Žhur. obsc. Chim. *30*, 145 (1960).

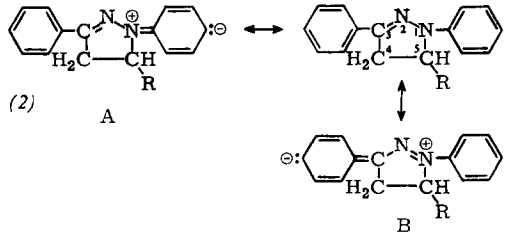
[26] *R. Huisgen*, *A. Gotthardt*, and *R. Grashey*, Angew. Chem. *74*, 30 (1962); Angew. Chem. internat. Edit. *1*, 49 (1962); cf. *V. F. Vasil'eva*, *V. G. Yashunskii*, and *M. M. Shuchkina*, Žur. obšč. Chim. *30*, 698 (1960).

[27] *R. Huisgen*, *M. Seidel*, *G. Wallbillich*, and *H. Knupfer*, Tetrahedron *17*, 3 (1962).

[28] *A. Hassner* and *H. J. Michelson*, J. org. Chemistry *27*, 298 (1962).

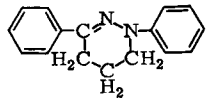
[29] *C. F. Duffin* and *J. D. Kendall*, J. chem. Soc. (London) *1954*, 408; U.S.-Pat. 2610969 (Sept. 16th, 1952), Ilford Ltd., Inv.: *J. D. Kendall* and *C. F. Duffin*.

phenylpyrazoline *(2a)*, derived from *(4a)* through rearrangement, shows a strong blue-violet fluorescence in organic solvents. Thus, pyrazoline ring closure limits the rotational freedom of the phenylhydrazone system; the molecule is fixed in a planar arrangement through action of the ring members 4 and 5. The aromatic nuclei in positions 1 and 3, required for fluorescence, interact by way of mesomeric canonic forms [30].



*(2)* A B

The planarity of the molecule, which is essential for fluorescence [31], is disturbed when the phenyl groups of the arylpyrazolines carry large substituents in the *o*-position. A marked decrease in fluorescence is observed in these cases. We also found that compounds containing one extra ring member, *e.g.* 1,3-diphenyl-1,4,5,6-tetrahydro-1,2-diazine [*] *(12)*, do not fluoresce; *(12)* is non-planar.

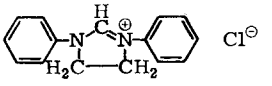


*(12)*

*Neunhoeffer* and *Rosahl* [30] found that it is not possible to formulate a mesomeric ground state in which an aromatic substituent in position 5 of the pyrazoline enters into the conjugated system. In fact, substitution in position 5 has no great influence on the absorption and fluorescence maxima, whereas aryl nuclei in positions 1 and 3 are essential to the fluorescence: thus neither 1-phenylpyrazoline nor 1,5-phenylpyrazoline exhibits fluorescence. The weak fluorescence of 3-methyl- and 3-trifluoromethyl-1,5-diphenylpyrazoline is attributed by *Neunhoeffer et al.* [32] to hyperconjugation.

It should be mentioned that the aromatic substituents on the pyrazoline ring may be replaced by heterocycles or by styryl groups without loss of the ability to fluoresce. However, the extension of the conjugated system by one double bond, as in the styryl group, leads to yellow products with a yellow-green fluorescence, which cannot be used for optical brightening [33]. Compounds of this type are recommended as fluorescent dyes [34].

A compound closely related to 1,3-diphenylpyrazoline is 1,3-diphenyl-$\Delta^1$-imidazolinium chloride *(13)*, which is formally derived from the former by transposition of C and N. No resonance forms with continuous conjugation are possible, and consequently fluorescence does not occur.



*(13)*

Compound *(13)* is formed by elimination of water from *N,N'*-diphenylethylenediamine and formic acid in the presence of hydrochloric acid [35].

## 4. Arylpyrazolines as Optical Brighteners

The use of fluorescent arylpyrazolines for optical brightening of textiles was first proposed by Ilford Ltd. [36], Essex. As in the case of the phthalocyanine dyes, which were modified by substitution to adapt them to the desired technical use, efforts were made to suitably modify the available fluorescent arylpyrazolines.

The simplest change consists in the introduction of substituents into the aromatic rings. However, modifications of this nature are subject to limitations, since many substituents cause a marked bathochromic shift of the absorption and fluorescence maxima; this is the case *e.g.* with an amino or acetylamino group in the phenyl ring on N-1. Substituents that impart color to the compounds cannot be considered. A *p*-nitro group of the phenyl group on N-1 gives a compound that emits orange-yellow fluorescence, while corresponding subsitution of the phenyl ring on C-3 completely extinguishes the fluorescence [37, 33].

The first arylpyrazolines used in practice nad a sulfonic acid group on the phenyl ring on N-1 [38]. These are prepared by the 1,2 + 3,4,5 principle (Section 2a), a phenylhydrazinesulfonic acid being used instead of phenylhydrazine. Owing to the presence of the sulfonic acid group, the molecule is water soluble; it is adsorbed on wool like an acid dye, and thus imparts optical brightening.

Products with other useful properties are obtained when the phenyl nucleus on N-1 also contains a sulfonamide group $SO_2-NH_2$ [39] or a sulfonyl group [40], *e.g.* $SO_2-CH_3$. Compounds of these types are again best prepared from the corresponding substituted phenylhydrazines. These products are not soluble in water. However, they are absorbed from aqueous dispersions onto polyacrylonitrile (Dralon or Orlon), and even when added in small percentages to the spinning solutions of the polymers, *e.g.* in dimethylformamide, they impart to these fibers an outstanding, white appearance. Other synthetic fibers such as polyamide or cellulose acetate can also be brightened. Moreover, these optical brighteners can also be used in detergents for poly-

[*] Prepared from $\gamma$-chlorobutyrophenone and phenylhydrazine in methanol/pyridine; m.p. 139–140 °C.


[30] *O. Neunhoeffer* and *D. Rosahl*, Z. Elektrochem., Ber. Bunsenges. physik. Chem. *57*, 81 (1953).

[31] *T. Förster*: Fluoreszenz organischer Verbindungen. Vandenhoeck und Ruprecht, Göttingen 1951.

[32] *O. Neunhoeffer, G. Alsdorf*, and *H. Ulrich*, Chem. Ber. *92*, 252 (1959).

[33] *F. Strauss*, Ber. dtsch. chem. Ges. *51*, 1458 (1918).

[34] Ger. Pat. 953518 (Dec. 8th, 1953), Ciba, Inv.: *A. E. Siegrist.*

[35] *M. May et al.*, J. Amer. chem. Soc. *73*, 3067 (1951).

[36] Brit. Pat. 669590 (June 3rd, 1949), Ilford Ltd., Inv.: *J. D. Kendall* and *G. F. Duffin.*

[37] *O. Neunhoeffer* and *H. Ulrich*, Chem. Ber. *88*, 1123 (1955).

[38] Ger.Pat. 919411 (June 3rd, 1950), Ilford Ltd., Inv.: *J. D. Kendall* and *G. F. Duffin.*

[39] Ger.Pat. 1080963 (March 3rd, 1956), Farbenfabriken Bayer, Inv.: *A. Wagner, A. Schlachter*, and *H. Marzolph.*

[40] Ger.Pat.1102407 (Oct.1st,1959),Farbenfabriken Bayer, Inv.: *A. Wagner, O. Bayer, C. Süling*, and *H. Groene*; Belg. Pat. 629875 (March 21st, 1963), Farbenfabriken Bayer; Belg. Pat. 609589 (Oct. 25th, 1961), *Hickson* and *Welch*; Belg. Pat. 631367 (April 22nd, 1963), Farbwerke Hoechst.

amides. One disadvantage of these products is that they are not resistant to chlorite.

The color of the fluorescent light depends to some extent on the positions of the substituents. The most useful products are those with electron attracting substituents in the *p*-position of the phenyl ring on N-1. Isomeric compounds with a cyano, sulfonic acid, sulfonamide, or sulfonyl group [12] in the *p*-position of the phenyl ring on C-3 are too yellow for practical purposes. In the first case, the effect of the electron attracting substituents is to increase the contribution of the canonical form A of the pyrazoline ring (see Section 3); the preferred form in the second case, on the other hand, is form B.

A chloro-substituent in the phenyl ring on C-3 has been found to have a particularly favorable influence on the intensity of the fluorescence (cf. Section 3). On the other hand an aryl ring in position 5 simply increases the weight, and does not improve the intensity of the fluorescence.

Useful brighteners are also obtained when a carboxyl group is introduced into the diarylpyrazoline molecule. Since this is an electron-attracting substituent, the above rules regarding its position apply. Thus the 4-(3-aryl-pyrazolinyl)benzoic acids [1-(carboxyphenyl)-3-aryl-pyrazolines] [41] are particularly valuable. Hard soap, which is yellowish in the crude form, appears pure white when these products are added. They are also added during the melt-spinning of polyamide fibers such as Perlon or Nylon. Since they are monofunctional carboxylic acids, they are attached to the polymer chains by predominantly covalent (amide) bonding; therefore, they also act as chain-terminating agents, and may be used in the production of the polyamide. Thus the attachment of the optical brightener to the fiber is particularly firm and resistant to washing.

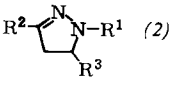
Esterification of pyrazolines containing carboxyl groups [40,42] leads to products which are insoluble in water. These products can again be used as brighteners to be added during spinning, and they may also be used as additives for detergents and as brighteners for plastics.

A special group are the cationic water-soluble pyrazolines [43], which can be applied in the same way as basic dyes. Possible starting materials for the preparation of these substances include substituted sulfonamides, *e.g.* having the formula pyrazoline $SO_2-NH-(CH_2)_n-NR_2$, or esters containing basic groups, such as parazoline-$CO-O-CH_2-CH_2-NR_2$. The tertiary amino groups in these compounds are subsequently quaternized.

Finally, pyrazolines (and other fluorescent systems) containing polymerizable unsaturated groups [44] have been described; these can be incorporated into plastics by copolymerization. The importance of the arylpyrazolines as brighteners is mainly in connection with the optical brightening of plastics and synthetic fibers.

We conclude with a brief description of a number of relationships between the absorption and fluorescence maxima of simple pyrazolines [45]. The absorption maxima and the fluorescence maxima of nine pyrazolines in methanolic solution were determined, and the fluorescence maxima of these were also determined after absorption on cellulose acetate (cf. Table 1).

Table 1. Absorption and fluorescence maxima of nine pyrazoline derivatives *(2)* in methanolic solution, and their fluorescence maxima after adsorption on cellulose acetate.



*(2)*

| $R^1$ | $R^2$ | $R^3$ | M.p. (°C) | Absorption maximum (methanol) | | Fluorescence maximum (methanol) | | Fluorescence maximum (cellulose acetate) | | Δν Abs.–fluor. [b] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | λ (mμ) | E/mmole | λ (mμ) | band height [a] | λ (mμ) | band height [a] | |
| $C_6H_5$ | $C_6H_5$ | H | 153 | 354 | 9.4 | 470 | 16.7 | 440 | 67 | 6950 |
| $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | 135 | 356 | 8.5 | 470 | 40.5 | 435 | 34 | 6810 |
| $C_6H_5$ | *p*-Cl–$C_6H_4$ | H | 130 | 362 | 10.7 | 475 | 34.8 | 449 | 76.5 | 6570 |
| $C_6H_5$ | *p*-Br–$C_6H_4$ | H | 130 | 364 | 10.6 | 475 | 39.8 | 449 | 72 | 6410 |
| *p*-Cl–$C_6H_4$ | $C_6H_5$ | H | 135–137 | 356 | 10.4 | 468 | 31.4 | 439 | 66.5 | 6740 |
| *p*-Cl–$C_6H_4$ | *p*-Cl–$C_6H_4$ | H | 174–175 | 363 | 11.6 | 471 | 51.5 | 447 | 74.5 | 6310 |
| 3,4-$Cl_2$–$C_6H_3$ | $C_6H_5$ | H | 124 | 354 | 11.2 | 453 | 72 | 434 | 82.5 | 6150 |
| 3,4-$Cl_2$–$C_6H_3$ | *p*-Cl–$C_6H_4$ | H | 140 | 363 | 12.7 | 458 | 100 | 439 | 100 | 5710 |
| $C_6H_5$ | $C_6H_5$ | $CH_3$ | 105 | 357 | 9.7 | 475 | 18.7 | 442 | 76 | 6950 |

[a] Band heights relative to the eighth compound (= 100).
[b] Difference between absorption and fluorescence maxima of the solution spectrum (in wave numbers).

The differences in constitution between these pyrazolines are relatively small. It is, therefore, surprising to find that a number of rules can be deduced from the results: Halogenation in the phenyl ring on C-3 leads to a shift of the absorption maximum toward longer wavelengths, and the absorption and fluorescence maxima are situated closer together. As the number of chlorine atoms in the molecule is increased, the intensity of the absorption maximum as expressed by the molar extinction also increases; this increase is even more pronounced in the case of the fluorescence maximum. A fact not shown by the relative band heights in Table 1 is that the fluorescence maxima on cellulose acetate are about 30 times as intense as in methanolic solution. The unexpectedly weak

[41] Ger.Pat. 1104483 (Oct. 10th, 1955), Farbenfabriken Bayer, Inv.: *A. Wagner* and *S. Petersen*.

[42] Belg. Pat. 572498 (Oct. 29th, 1958), Unilever.

[43] Belg. Pat. 606740 (July 31st, 1961), Farbenfabriken Bayer; Belg. Pat. 610946 (Nov. 29th, 1961), Geigy.

[44] German Published Pat. Appl. 1102407 (Oct. 1st, 1959), Farbenfabriken Bayer, Inv.: *A. Wagner, O. Bayer, C. Süling* and *H. Groene*.

[45] *M. Pesteiner, A. Berger*, and *A. Wagner*, SVF (Schweiz. Vereinig. Färbereifachleuten) Fachorgan Textilveredlung *19*, 420 (1964).

fluorescence of the second compound [*(2a)*] on cellulose acetate may be due to decreased absorption or to hindrance on the fiber of the absorption position which most strongly favors fluorescence. The last column in the Table gives the difference (in wave numbers) between the absorption and fluorescence maxima in the solution spectra. The intensity of the fluorescence band increases as this difference in position decreases, and this yields some information about the radiationless energy loss. The differences between the absorption and fluorescence spectra on the fiber were not determined, but it is clear from a comparison of the positions of the fluorescence maxima in solution and on the fiber that the attachment of the pyrazoline molecule to the fiber leads to a decrease in the radiationless energy loss, as is shown by the much higher value of the fiber fluorescence as compared with the solution fluorescence [*].

The facts described here are not sufficient to permit the accurate determination of specific applications of aryl-$\Delta^2$-pyrazolines as optical brighteners. Other factors such as the tint of the brightened article, adsorption, and durability must also be closely examined. – Arylpyrazolines have also found interest as scintillators [24, 26].

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Translated by Express Translation Service, London

[*] The measurements were carried out with a Zeiss PMQII spectrophotometer. We are grateful to Dr. *A. Berger* for her help with the experiments.

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# New Methods of Preparative Organic Chemistry VI [*]

## Synthesis of Isocyanates and Carbodiimides

BY DR. H. ULRICH AND DR. A. A. R. SAYIGH

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*The reaction of 1,3-disubstituted ureas and 1-arylsulfonyl-3-alkylureas with phosgene permits the preparation of a number of isocyanates and sulfonyl isocyanates that had not previously been described, or that were difficult to prepare. 1,3-Disubstituted thioureas and 1-aryl-(or alkyl)sulfonyl-3-alkylthioureas give carbodiimides. Thionyl chloride and phosphorus pentachloride react with the urea derivatives in the same way as phosgene. Oxalyl chloride reacts with ureas to form parabanic acid derivatives, whereas with thiourea it gives 2-imino-1,3-thiazolidine-4,5-diones, which can isomerize to parabanic acid derivatives.*

### I. Introduction

It has been known for some time that isothiocyanates [1] and carbodiimides [2] can be prepared from 1,3-disubstituted thioureas and phosgene. The only phosgenation of 1,3-disubstituted ureas that had previously been studied was that of 1,3-diphenylurea above 150 °C, which leads to phenyl isocyanate [3]. The present paper describes the reaction of other 1,3-disubstituted ureas with phosgene to form isocyanates. The authors have developed a simple reaction principle [Equations (a) and (b)], which permits the preparation of a number of mono- and diisocyanates that were not previously obtainable by direct phosgenation of the corresponding primary amines.

In the preparation of an isocyanate RNCO, a primary amine or sulfonamide is converted into the urea derivative by treatment with a readily obtainable alkyl or aryl isocyanate R'NCO; the reaction of the product with phosgene then yields RNCO and the starting isocyanate R'NCO:

$$RNH_2 + R'NCO \rightarrow RNH{-}CO{-}NHR' \quad (a)$$

$$RNH{-}CO{-}NHR' + COCl_2 \rightarrow RNCO + R'NCO + 2HCl \quad (b)$$

R, R' = aryl, alkyl, arylsulfonyl

Thus the overall reaction is equivalent to the phosgenation of an inert amine or of an amine that is not accessible to direct phosgenation.

Another reaction of 1,3 disubstituted ureas and thioureas with phosgene, *i.e.* chlorination, has been described by *Eilingsfeld*, *Seefelder*, and *Weidinger* [4]. This reaction leads to *C,C*-dichloromethylenediamines $RHN{-}CCl_2{-}NHR$ (sometimes formulated as chloroformamidinium chlorides $[RNH{-}CCl{=}NHR]^{\oplus}Cl^{\ominus}$),

[*] The papers in the preceding series have been published in three volumes by Verlag Chemie, Weinheim/Bergstr.; English editions: Academic Press, New York-London. – Volumes IV and V are in preparation.

[1] *S. J. Assony*: The Chemistry of Isothiocyanates in Organic Sulfur. Pergamon Press, New York 1961, Vol. I, p. 330.

[2] *H. G. Khorana*, Chem. Reviews *53*, 145 (1953).

[3] *W. Hentschel*, Ber. dtsch. chem. Ges. *17*, 1284 (1884).

[4] *H. Eilingsfeld, M. Seefelder*, and *H. Weidinger*, Angew. Chem. *72*, 836 (1960).

which give carbodiimides on dehydrochlorination. Thionyl chloride or oxalyl chloride should also be suitable for the chlorination [4].

We have found that the result of the reaction of 1,3-disubstituted ureas with phosgene, thionyl chloride, or phosphorus pentachloride, *i.e.* whether it leads to isocyanates (*via* allophanoyl chloride) and/or to chloroformamidinium chlorides [see Equations (f), (j), and (k)] is largely dependent on the substituents.

## II. Synthesis of Isocyanates

### 1. Elimination of Isocyanates from Substituted Ureas

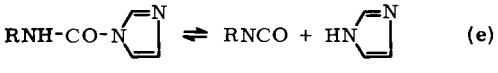
Isocyanates should be easily obtainable from urea derivatives by elimination, *i.e.* without the use of phosgene. In reactions of this type, however, only a part of the molecule can be utilized. The elimination of $NH_3$, which permits the production, *e.g.*, of α-naphthyl isothiocyanate in high yields from α-naphthylthiourea [5], does not occur with all urea derivatives. *Sowa* [6] recently prepared isobutyl isocyanate from isobutylurea by this method.

$$(CH_3)_2CH-CH_2-NH-CONH_2 + BF_3 \rightarrow (CH_3)_2CH-CH_2-NCO + H_3NBF_3 \quad (c)$$

Another example is the preparation of methyl isocyanate from 3-methyl-1,1-diphenylurea [7].

$$(C_6H_5)_2N-CO-NHCH_3 \rightarrow (C_6H_5)_2NH + CH_3NCO \quad (d)$$

Though diphenylamine is a weaker base than 3-methyl-1,1-diphenylurea, this elimination proceeds only at high temperatures (240–290 °C). On the other hand, imidazole-1-carboxamides, which may be regarded as urea derivatives [8], react even at room temperature in suitable solvents.



(e)

The disadvantages of the eliminations (c)–(e) are the possibile recombination of the products and the fact that only part of the urea derivative is used in the formation of the isocyanate [*e.g.* in (d), the formation of one mole of methyl isocyanate (M.W. 57) is accompanied by the formation of one mole of diphenylamine (M.W. 169)].

### 2. The Reaction of 1,3-Disubstituted Ureas with Phosgene [8a]

The phosgenation of 1,3-disubstituted ureas [Equation (b)] could give two moles of isocyanate and two moles of hydrogen chloride (*e.g.* phosgenation of 1,3-diphenylurea [3]), and would, therefore, be much more productive than the elimination method.

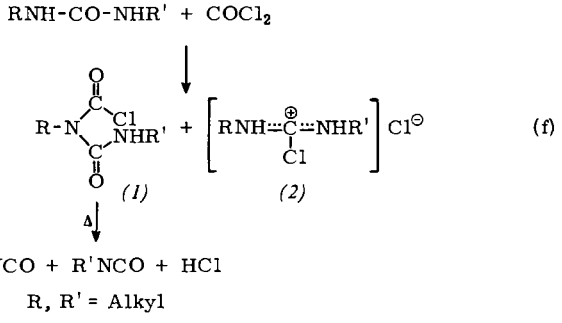
1,3-Diphenylurea reacts with phosgene only above 150 °C. The compound first dissociates, so that the reaction corresponds to the phosgenation of aniline [9,10]:

$$C_6H_5NH-CO-NHC_6H_5 \rightarrow C_6H_5NCO + C_6H_5NH_2$$
$$C_6H_5NH_2 + COCl_2 \rightarrow C_6H_5NCO + 2\,HCl$$

Since 1,3-diarylureas generally form isocyanates on melting, it is reasonable to assume that the reaction with phosgene is generally applicable.

The more strongly basic 1,3-dialkylureas react with phosgene even at room temperature, but this reaction is reported to yield chloroformamidinium chlorides *(2)* [4], which are unsuitable for the preparation of isocyanates.

We have found that the reaction of 1,3-dialkylureas with phosgene at room temperature leads to 2,4-dialkylallophanoyl chlorides *(1)* and/or 1,3-dialkylchloroformamidinium chlorides *(2)* [11].



(f)

R, R' = Alkyl

Among the 1,3-dialkylureas studied so far, it has been found that the reaction leads predominantly to attack on the nitrogen and formation of the allophanoyl chloride *(1)* if the alkyl substituent is attached to the nitrogen by a primary carbon atom. If, on the other hand, the carbon atom adjacent to the nitrogen is secondary, attack on the oxygen leads almost exclusively to the chloroformamidinium chloride *(2)*. The yields of *(1)* and *(2)* obtained from various 1,3-dialkylureas under identical conditions (reaction of RNH–CO–NHR' and phosgene at 2 °C in 1,2-dichloroethane) are listed in Table 1. 1-Butyl-3-phenylurea was also used for comparison.

Table 1. Formation of *(1)* and *(2)* according to Equation (f).

| Comp. | R | R' | *(1)* Yield [%] | *(2)* Yield [%] |
|---|---|---|---|---|
| *(a)* | $CH_3$ | $CH_3$ | 71 | 28 |
| *(b)* | n-$C_4H_9$ | n-$C_4H_9$ | 70.5 (V, 1) [a] | 24 |
| *(c)* | n-$C_{18}H_{37}$ | n-$C_{18}H_{37}$ | 69 | 28 |
| *(d)* | i-$C_3H_7$ | i-$C_3H_7$ | 6.7 | 75.6 [b] |
| *(e)* | c-$C_6H_{11}$ | c-$C_6H_{11}$ | 12.5 | 77.8 |
| *(f)* | n-$C_4H_9$ | $C_6H_5$ | *ca.* 100 | — |

[a] Details of a preparation are given in Section V, 1.
[b] Also 8.2% of *(4)*, R = R' = i-$C_3H_7$.

The physical properties of a number of 2,4-disubstituted allophanoyl chlorides *(1)* are decribed in Table 2.

[5] *J. Cymerman-Craig, M. Moyle,* and *R. A. White,* J. chem. Soc. (London) *1956*, 659.

[6] *F. J. Sowa,* US-Pat. 3013045 (Dec. 12th, 1961); Chem. Abstr. *56*, 8632 (1962).

[7] *W. Siefken,* Liebigs Ann. Chem. *562*, 75 (1949).

[8] *H. A. Staab,* Angew. Chem. *74*, 407 (1962); Angew. Chem. internat. Edit. *1*, 351 (1962).

[8a] In collaboration with Dr. *J. N. Tilley.*

[9] *H. Eckenroth* and *M. Wolf,* Ber. dtsch. chem. Ges. *26*, 1463 (1893).

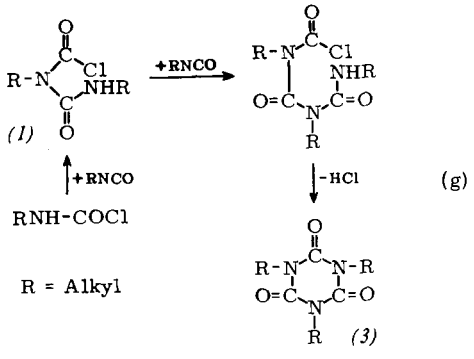
[10] *W. B. Bennet, J. H. Saunders,* and *E. E. Hardy,* J. Amer. chem. Soc. *75*, 2101 (1953).

[11] *H. Ulrich, A. A. R. Sayigh,* and *J. N. Tilley,* J. org. Chemistry *29*, 2401 (1964).

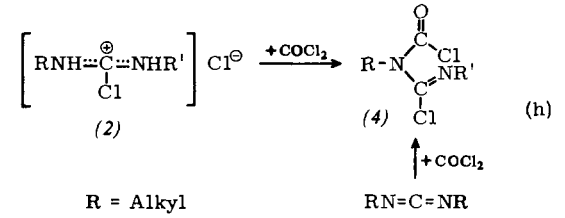
Table 2. Physical properties of 2,4-disubstituted allophanoyl chlorides RN(COCl)CO–NHR′ *(1)*.

| Comp. | M.p. [°C] | B.p. [°C/Torr] | $\tilde{\nu}$NH [cm$^{-1}$] | $\tilde{\nu}$C=O [cm$^{-1}$] |
|---|---|---|---|---|
| *(1a)* | 36 | 54/0.15 | 3355 | 1740 |
| *(1b)* | — | 98/0.5 | 3310 | 1718 |
| *(1c)* | 68–69 | | 3345 | 1745 |
| *(1d)* | 63 | | 3310 | 1725 |
| *(1e)* | 127–128 | | 3390 | 1718 |
| *(1f)* | 40–44 | | — | — |

As expected, the compounds *(1)* decompose into isocyanate and HCl when heated above 100 °C in an inert solvent [12]. The yields are almost quantitative (cf. procedure in Section V, 2). If the solution contains more than 10% of *(1)* or if the heating is carried out in the absence of solvent, the products include not only isocyanates, but also isocyanurates *(3)*. These are formed by the reaction of the 2,4-disubstituted allophenoyl chlorides with the isocyanates produced.




Since 2,4-dimethyl- and 2,4-di-n-butylallophanoyl chlorides are obtained in a yield of about 50% when equimolar quantities of the corresponding carbamoyl chloride and isocyanate are heated, the formation of isocyanurates *(3)* during the phosgenation of monoalkylamines is very probably due to reactions (f) and (g). An excess of phosgene should be avoided in reaction (f), since the chloroformamidinium chloride formed as a by-product reacts further to form an *N,N′*-dialkylchloroformamidine-*N*-carbonyl chloride*(4)* [13]. The structure of this product was established by independent synthesis from carbodiimides and phosgene [13, 14].




| | B.p. [°C/Torr] | $\tilde{\nu}$C=O [cm$^{-1}$] | $\tilde{\nu}$C–N [cm$^{-1}$] |
|---|---|---|---|
| *(4a)*, R = R′ = n-$C_4H_9$ (V, 3) | 86/0.5 | 1745 | 1760 |
| *(4b)*, R = R′ = c-$C_6H_{11}$ | 140–142/0.8 | 1745 | 1760 |

[12] *A. A. R. Sayigh, J. N. Tilley,* and *H. Ulrich*, J. org. Chemistry *29*, 3344 (1964).

[13] *H. Ulrich* and *A. A. R. Sayigh*, J. org. Chemistry *28*, 1427 (1963).

[14] *P. Fischer*, German Pat. 1131661; (June 20th, 1962), Farbenfabriken Bayer A.-G.; Chem. Abstr. *58*, 1401 (1963).

Diphenyl carbonate may also be used instead of phosgene. For example, *Morschel* and *Skopalik* [15] recently prepared alkyl isocyanates from 1,3-dialkylureas and diphenyl carbonate. Dialkylureas in which a primary carbon atom is attached to the nitrogen again gave much higher yields of isocyanate than those in which the nitrogen atoms carry secondary carbon atoms.

$$RNH{-}CO{-}NHR + (C_6H_5O)_2CO \rightarrow 2\,RNCO + 2\,C_6H_5OH$$

R = Alkyl

However, the use of carbonates instead of phosgene has the disadvantage that the products readily undergo further reaction with one another.

### 3. The Reaction of 1-Arylsulfonyl-3-alkylureas with Phosgene

The reaction of 1-arylsulfonyl-3-alkylurea with phosgene leads to attack exclusively on the alkyl-substituted nitrogen owing to the acidity of the proton in α-position to the sulfonyl group; the resulting allophanoyl chlorides decompose immediately to give the corresponding isocyanates and hydrogen chloride. Thus, in the reaction of 1-*p*-toluenesulfonyl-3-n-butylurea with phosgene, we obtained good yields of *p*-toluenesulfonyl isocyanate and n-butyl isocyanate (see Section V, 4).

Table 3. Preparation of sulfonyl isocyanates $RSO_2NCO$ and isocyanates R′NCO by reaction of 1-arylsulfonyl-3-alkylureas $RSO_2NH{-}CO{-}NHR'$ with phosgene.

| R | B.p. [°C/Torr] | Yield [%] | R′ | B.p. [°C/Torr] | Yield [%] | Temp. [°C] |
|---|---|---|---|---|---|---|
| *p*-$CH_3{-}C_6H_4$ | 91–92/0.5 | 88.8 | n-$C_4H_9$ | 115 | 85 | 130 [a] |
| *p*-$CH_3{-}C_6H_4$ | 91–92/0.5 | 84.5 | $C_2H_5OCH_2CH_2$ | 140–142 | 76 | 80–150[b] |
| *p*-$Cl{-}C_6H_4$ | 92–93/0.4 | 57.9 | n-$C_3H_7$ | 83–84 | 70 | 130 [a] |

Solvents: [a] chlorobenzene; [o] dichlorobenzene.

$$p\text{-}CH_3{-}C_6H_4{-}SO_2NH{-}CO{-}NHC_4H_9 + COCl_2 \rightarrow p\text{-}CH_3{-}C_6H_4{-}SO_2NCO + C_4H_9NCO + 2\,HCl$$

The reaction takes place above 50 °C; only a small excess of phosgene is necessary for complete reaction. This reaction may be used as the second step in the preparation of isocyanates from amines which cannot be directly phosgenated, and which, therefore, must be converted into urea derivatives. An example is the phosgenation of 1-*p*-toluenesulfonyl-3-ethoxyethylurea, which leads to a good yield of the desired ethoxyethyl isocyanate.

Since alkyl isocyanates have much lower boiling points than sulfonyl isocyanates, they can be easily separated from the latter by fractional distillation. Some examples are given in Table 3.

Difficulties are encountered in the direct phosgenation of sulfonamides to obtain sulfonyl isocyanates. For example, sulfonamides react with phosgene only above 200 °C, and at this temperature the S–N bond is broken, with the result that the yields are unsatisfactory. The yields of more than 80% reported by *Krzikalla* [16] have not been confirmed by other workers [17].

[15] *H. Morschel* and *C. Skopalik*, German Pat. 1154090 (Sept. 12th, 1963), Farbenfabriken Bayer A.-G.; Chem. Abstr. *60*, 2158 (1964).

[16] *H. Krzikalla*, German Pat. 817602 (Oct. 18th, 1951), Badische Anilin & Soda Fabrik; Chem. Abstr. *47* 2206 (1953).

[17] *C. King*, J. org. Chemistry *25*, 352 (1960); *F. Effenberger* and *R. Gleiter*, Chem. Ber. *97*, 1576 (1964).

The arylsulfonyl isocyanates, which were formerly difficult to obtain, can now be readily prepared by phosgenation of 1-arylsulfonyl-3-alkylureas. It is even simpler not to use the isocyanates, but to add catalytic quantities of an isocyanate to the sulfonamides.

$$RSO_2NH_2 + COCl_2 + R'NCO \rightarrow RSO_2NCO + 2\,HCl \qquad (i)$$

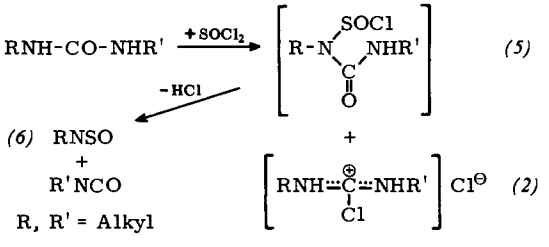
The sulfonyl isocyanates prepared by this method, most of them for the first time, are listed in Table 4.

Table 4. Preparation of sulfonyl isocyanates $RSO_2NCO$ according to Equation (i). Catalyst: n-butyl isocyanate [18]; solvent: boiling chlorobenzene, and boiling *o*-dichlorobenzene in the case of the nitrobenzenesulfonyl isocyanates.

| R | M.p. [°C] | B.p. [°C/Torr] | Yield [%] |
|---|---|---|---|
| $C_6H_5$ | | 79–83/0.7 | 85.8 (V, 5) |
| 4-$CH_3$–$C_6H_4$ | | 91–92/0.5 | 92.5 |
| 2,5-$(CH_3)_2C_6H_3$ | | 95–97/0.5 | 60.5 |
| 4-F–$C_6H_4$ | | 94–95/0.5 | 73 |
| 4-Cl–$C_6H_4$ | | 92–93/0.4 | 89 |
| 2,5-$Cl_2C_6H_3$ | | 118–120/0.5 | 32 |
| 3,4-$Cl_2C_6H_3$ | | 128–130/0.6 | 91.3 |
| 4-Br–$C_6H_4$ | 38–40 | 117–120/1.2 | 89.5 |
| 4-$CH_3O$–$C_6H_4$ | | 130–133/0.4 | 87.8 |
| 4-$O_2N$–$C_6H_4$ | 70–73 | 137–143/0.4 | 81.1 (V, 6) |
| 3-$O_2N$–$C_6H_4$ | 84–86 | 152–153/1.0 | 78 |

### 4. Reaction of 1,3-Disubstituted Ureas with Thionyl Chloride

The reaction of 1,3-disubstituted ureas with thionyl chloride was found to follow the same pattern as the reaction with phosgene. Ureas containing primary alkyl groups are preferentially attacked on the nitrogen, whereas those containing secondary alkyl groups undergo reaction on the oxygen atom. Since the intermediates *(5)* are dehydrochlorinated even at room temperature, the reaction leads to mixtures that contain isocyanates and sulfinylamines *(6)* as well as chloroformamidinium chlorides *(2)*.

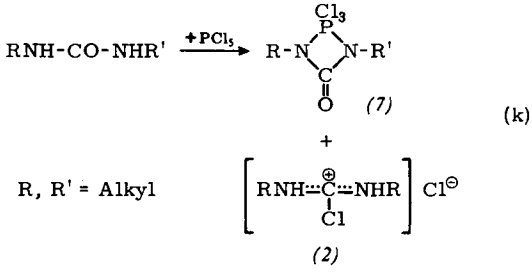



(j)

1,3-Di-n-butylurea gave n-butyl isocyanate with 88% yield. The yields of sulfinylamine are somewhat lower, since part of this product reacts with the hydrogen chloride liberated (cf. Section V, 7).

### 5. Reaction of 1,3-Disubstituted Ureas with Phosphorus Pentachloride

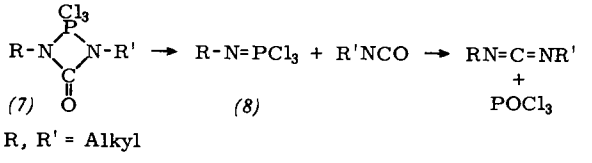
In the reaction of 1,3-disubstituted ureas containing primary alkyl substituents, the attack again takes place preferentially on the nitrogen. Thus, 1,3-diaza-2-$P^V$-phosphetidinones *(7)* were first prepared by this method (cf. Section V, 8)[19,21]. On the other hand, 1,3-disubstituted ureas containing secondary alkyl groups give only minor amounts of this compound, the main products again being chloroformamidinium chlorides *(2)*.




(k)

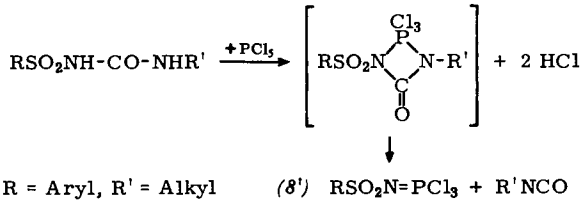
The compounds *(7)*, which contain a strained four-membered ring, have their characteristic C=O absorption at 1785 $cm^{-1}$.

When heated, the 1,3,2-diazaphosphetidinones *(7)* decompose into trichlorophosphazenes*(8)*and isocyanates, which react to form carbodiimides and phosphorus oxychloride[20].




### 6. Reaction of 1-Arylsulfonyl-3-alkylureas with Phosphorus Pentachloride

In the reaction of 1-arylsulfonyl-3-alkylureas, the intermediate containing the four-membered ring could not be isolated, but the decomposition products were obtained in good yields[21]. The sulfonyltrichlorophosphazenes *(8')* do not react with isocyanates (cf. Section V, 9).




### 7. Reaction of 1,3-Disubstituted Ureas with Oxalyl Chloride

For the sake of completeness, the reaction of oxalyl chloride with 1,3-dialkylureas should also be mentioned here. In contrast to the reaction with phosgene, it leads exclusively to 1,3-disubstituted parabanic acids *(9)*; no

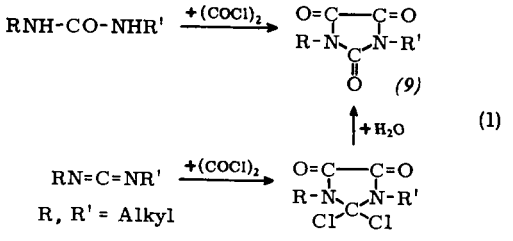
[18] Replacement of the n-butyl isocyanate by phenyl- or cyclohexyl isocyanate leads to approximately the same yield.

[19] *H. Ulrich* and *A. A. R. Sayigh*, Angew. Chem. *76*, 647(1964); Angew. Chem. internat. Edit. *3*, 585 (1964).

[20] *H. Ulrich* and *A. A. R. Sayigh*, Angew. Chem. *74*, 900(1962); Angew. Chem. internat. Edit. *1*, 595 (1962); J. chem. Soc. (London) *1963*, 5558.

[21] *H. Ulrich* and *A. A. R. Sayigh*, J. org. Chemistry *30*, 2779 (1965).

chlorination to form chloroformamidinium chlorides was observed. The structure of the parabanic acid derivatives obtained was established by infrared spectroscopy and by independent synthesis from carbodiimides and oxalyl chloride [22].



As early as 1913, *Biltz* and *Topp* [23] obtained parabanic acid derivatives *(9)* from 1,3-dimethylurea and 1,3-diethylurea. We found that ureas containing secondary and tertiary alkyl substituents also give only parabanic acid derivatives. Acyl isocyanates have recently been obtained by the reaction of amides with oxalyl chloride [24].

The physical properties of the 1,3-disubstituted parabanic acids synthesized are summarized in Table 5.

Table 5. 1,3-Disubstituted parabanic acid derivatives *(9)*, R = R', obtained according to Equation (1).

| R | M.p. [°C] | Yield [%] |
|---|---|---|
| i-$C_3H_7$ | 88–90 | 99 |
| n-$C_4H_9$ | 28–29 | 81.4 |
| t-$C_4H_9$ | 95 | 95.6 (V, 10) |
| c-$C_6H_{11}$ | 174–175 | 96 |

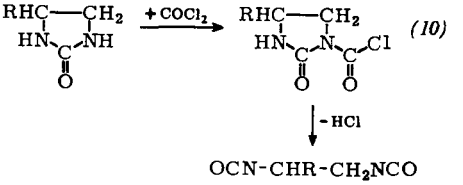
The reaction of 1-arylsulfonyl-3-alkylureas with oxalyl chloride also leads exclusively to 1,3-disubstituted parabanic acids [*(9)*, R = R''$SO_2$]. The reaction takes place on gentle heating, and the yields are almost quantitative [25,26].

## III. Synthesis of Diisocyanates

### 1. Reaction of Cyclic Ureas with Phosgene [8a]

The indirect methods for the synthesis of diisocyanates are of interest only when the diamines cannot be phosgenated directly. We have, therefore, confined ourselves to the synthesis of short-chain alkylene diisocyanates, since short-chain alkylenediamines are converted into polymeric ureas on direct phosgenation [7].

As in the case of the 1,3-dialkylureas, the reaction of five-membered cyclic ureas (2-imidazolidinones) with phosgene takes place almost exclusively on the nitrogen, with formation of cyclic allophanoyl chlorides (2-imidazolidinone-1-carbonyl chloride) *(10)* [11] (cf. Section V, 11). These compounds undergo dehydrochlorination at room temperature in the presence of an HCl acceptor (*e.g.* triethylamine) to give diisocyanates. In contrast to the case of the open-chain allophanoyl chlorides, this reaction can be accelerated with catalytic quantities of Lewis acids, *e.g.* $FeCl_3$, and tertiary amines such as collidine [12] (cf. Section V, 12).



Since the cyclic ureas are readily obtainable from 1,2-alkylenediamines and $CO_2$, this provides a simple method for the industrial production of alkylene diisocyanates.

### 2. Reaction of 1-Arylsulfonyl-3-alkylureas with Phosgene

Difficulties are also encountered in the phosgenation of long-chain alkylenediamines, such as 1,6-diaminohexane. Owing to the low solubility of alkylenediamine dihydrochlorides, a long reaction time and a considerable excess of phosgene are required. Moreover, the long reaction times favor the formation of by-products. For example, ω-chloroalkyl isocyanates are formed in this way, and these can only be removed by careful fractionation [7]. It is essential that the monofunctional by-products are eliminated before the isocyanates are used for the production of polyurethanes.

Alkylenediamines and sulfonyl isocyanates give 1,1'-alkylenebis-(3-arylsulfonylureas) *(11)* in almost quantitative yields [27]. These compounds, unlike the free amines, react readily with only a small excess of phosgene [28].

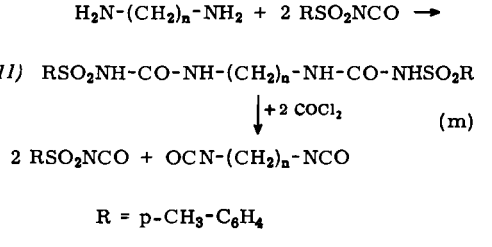


Table 6. Preparation of alkylene diisocyanates according to Equation (m) [*].

| n | OCN–$(CH_2)_n$–NCO Yield [%] | *p*-$CH_3$–$C_6H_4$–$SO_2$NCO Yield [%] | Temp. [°C] |
|---|---|---|---|
| 3 | 40.0 | 75.6 | 127–130[a] |
| 4 | 62.7 | 70.8 | 127–130[a] |
| 4 | 75.0 | 78.0 | 170–180[b] |
| 6 | 95.5 | 67.0 | 130–140[b] |

Solvents: [a] chlorobenzene; [b] *o*-dichlorobenzene.

[22] *H. D. Stachel*, Angew. Chem. *71*, 246 (1959).

[23] *H. Biltz* and *E. Topp*, Chem. Ber. *46*, 1387 (1913).

[24] *A. J. Speziale* and *L. R. Smith*, J. org. Chemistry *27*, 3742 (1962).

[25] *H. Ulrich* and *A. A. R. Sayigh*, J. org. Chemistry *30*, 2781 (1965).

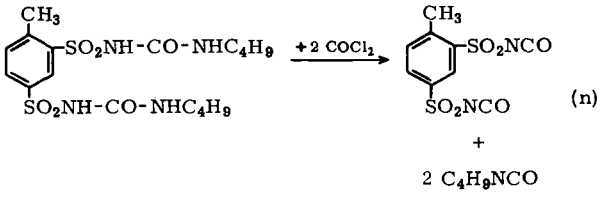
[26] *P. J. Stoffel*, J. org. Chemistry *29*, 2794 (1964).

[*] The yields were determined by gas chromatography. F & M instrument (Model 720); carrier gas: helium; column packing: silicone rubber; column length: 1.8 m.

[27] *E. Habicht*, US-Pat. 2962530; (Nov. 29th, 1960), Cilag-Chemie Ltd.; Chem. Abstr. *55*, 1750g (1961).

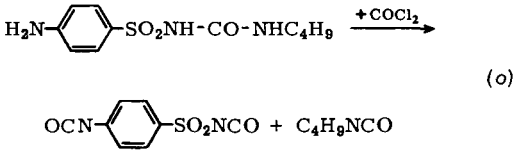
[28] *H. Ulrich*, *B. Tucker*, and *A. A. R. Sayigh*, J. org. Chemistry, in press.

The phosgenation of a bis-sulfonyl compound also permitted the synthesis of the first bis(sulfonyl isocyanate)[29] [Equation (n)].




(n)

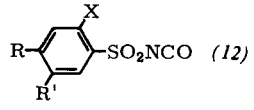
Another possibility for the preparation of interesting compounds is offered by the direct phosgenation of sulfanilylureas. This leads to difunctional compounds, in which the sulfonyl isocyanate group is much more reactive than the isocyanate group, despite the fact that the reactivity of the latter is increased by the sulfonyl isocyanate group. The reactivity of the isocyanate group on a benzene nucleus can be still further reduced by substituents (*e.g.* $OCH_3$) on the ring.




(o)

The physical properties of a number of isocyanatobenzenesulfonyl isocyanates are listed in Table 7.

Table 7. Isocyanatobenzenesulfonyl isocyanates *(12)* prepared according to Equation (o).



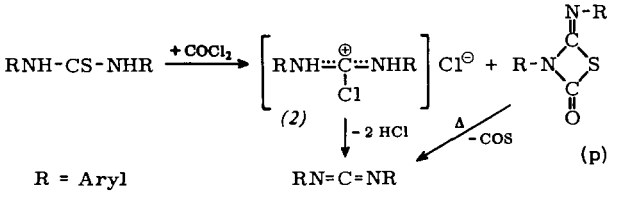

*(12)*

| R | R' | X | M.p. [°C] | B.p. [°C/Torr] | Yield [%] |
|---|---|---|---|---|---|
| NCO | H | H | 40—44 | 115—120/0.4 | 64.3 (V, 13) |
| H | NCO | H | | 135—136/1.1 | 45.7 |
| NCO | $OCH_3$ | $OCH_3$ | | 160—181/0.09—1.0 | 31 |

## IV. Synthesis of Carbodiimides

### 1. Reaction of 1,3-Disubstituted Thioureas with Phosgene

The "desulfurization" of 1,3-disubstituted thioureas is the classic method for the preparation of carbodiimides. Phosgene has proved to be a particularly useful desulfurizing agent, since it reacts at room temperature with




(p)

[29] After the completion of our work, *J. Smith jr., T. K. Brotherton*, and *J. W. Lynn*, J. org. Chemistry *30*, 1260 (1965), described the preparation of *p*-isocyanatobenzenesulfonyl isocyanate and of a number of bis(sulfonylisocyanates) by direct phosgenation of sulfonamides in nitrobenzene.

[30] *W. Will*, Ber. dtsch. chem. Ges. *14*, 1486 (1881).

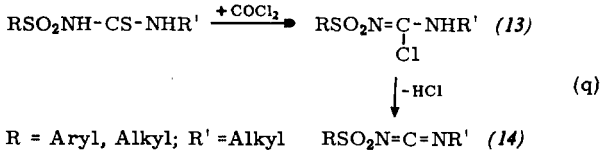
thioureas containing aliphatic and aromatic substituents (cf. Section V, 14). Whereas aliphatic thioureas form chloroformamidinium chlorides *(2)*, aromatic thioureas also give thiazetidinones as by-products[30]. No attack on nitrogen was observed.

Since the basicity of the nitrogen is considerably reduced in the aromatic chloroformamidinium chlorides, these compounds lose hydrogen chloride when heated[31]. Direct phosgenation above 100 °C yields isothiocyanates as by-products. An excess of phosgene must be avoided, since chloroformamidinium chlorides can be readily converted into *N*-carbonyl chlorides in accordance with Equation (h)[13].

Phosphorus pentachloride may be used instead of phosgene for the conversion of thioureas into chloroformamidinium chlorides. However, the reaction in this case yields thiophosphoryl chloride, which, if possible, should be removed before the liberation of the carbodiimides[32].

### 2. Reaction of 1-Aryl(or Alkyl)sulfonyl-3-alkylthioureas with Phosgene

The reaction of 1,3-disubstituted thioureas with acyl chlorides can also be applied to sulfonylthioureas. Thus sulfonylchloroformamidines have been obtained in good yields by the reaction of 1-aryl(or alkyl)sulfonyl-3-alkylthioureas with phosgene (cf. Section V, 15). These can be readily converted into sulfonylcarbodiimides by heating or by the use of an HCl acceptor[33,34] (cf. Table 8). As expected, phosphorus pentachloride reacts in a similar manner.




*(13)*

*(14)*

(q)

Table 8. Sulfonylcarbodiimides *(14)* prepared according to Equation (q).

| R | R' | B.p. [°C/Torr] | $n_D^{24.5}$ | Yield [%] |
|---|---|---|---|---|
| $CH_3$ | $C_2H_5$ | 98—100/0.5 | 1.4830 | 68.0 |
| $CH_3$ | n-$C_3H_7$ | 92/0.25 | 1.4812 | 73.3 |
| $CH_3$ | n-$C_4H_9$ | 103—105/0.3 | 1.4798 | 79.5 (V, 16) |
| $C_6H_5$ | $C_2H_5$ | 139—144/0.2 | 1.5500 | 47.6 |
| *p*-$CH_3$—$C_6H_4$ | $C_2H_5$ | 147—151/0.25 | 1.5475 | 40.2 |
| $C_6H_5$ | n-$C_4H_9$ | 151—155/0.1 | 1.5380 | 40.0 |
| *p*-$CH_3$—$C_6H_4$ | n-$C_4H_9$ | 159—162/0.2 | 1.5412 | 47.3 |

1-Arylsulfonyl-3-arylureas react with phosgene to form 4-sulfonylimino-1,3-thiazetidin-2-ones (cf. Section V, 17). In contrast to the thiazetidinones obtained by

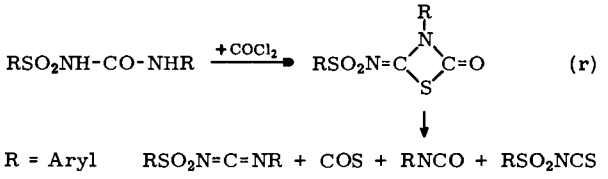
[31] *H. Ulrich* and *A. A. R. Sayigh*, US-Pat. Appl. 255169.

[32] Phosphorus sulfide trichloride reacts with carbodiimides in the absence of solvents.

[33] *H. Ulrich* and *A. A. R. Sayigh*, Angew. Chem. *76*, 781 (1964); Angew. Chem. internat. Edit. *3*, 639 (1964).

[34] *H. Ulrich, B. Tucker*, and *A. A. R. Sayigh*, Tetrahedron *22*, 1565 (1966).

*Will*[30] from 1,3-diarylthioureas, the sulfonyl derivatives decompose to form the four products expected [34].



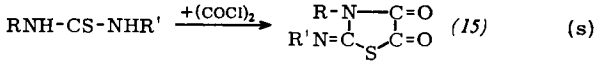
$$RSO_2NH\text{-}CO\text{-}NHR \xrightarrow{+COCl_2} RSO_2N{=}C\langle \text{N(R)}\,\text{S}\,C{=}O \quad (r)$$

$$R = \text{Aryl} \quad RSO_2N{=}C{=}NR + COS + RNCO + RSO_2NCS$$

*(14)*

### 3. Reaction of 1,3-Disubstituted Thioureas with Oxalyl Chloride

The reaction of 1,3-dialkylureas with oxalyl chloride leads only to parabanic acid derivatives [25] (cf. Section II, 7). *Blitz* and *Topp* [23] obtained small yields of 2-thioparabanic acid derivatives from 1,3-disubstituted thioureas and oxalyl chloride. This result is surprising, since in our opinion acyl halides always attack thioureas on the sulfur. We obtained good yields of 2-amino-1,3-thiazolidine-4,5-diones from thioureas and oxalyl chloride [25] (cf. Table 9; RNH–CS–NHR′ was treated with oxalyl chloride in 1,2-dichloroethane with cooling followed by heating at about 84–86 °C for 30 min).



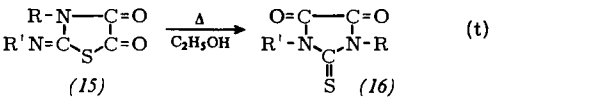
$$RNH\text{-}CS\text{-}NHR' \xrightarrow{+(COCl)_2} R\text{-}N(\text{C=O})\text{-}C(\text{=O})\text{-}S\text{-}C(R'){=}N \quad (15) \quad (s)$$

R = Alkyl, Aryl; R′ = H, Alkyl, Aryl

Table 9. 2-Imino-1,3-thiazolidine-4,5-diones *(15)* prepared according to Equation (s).

| R | R′ | M.p. [°C] | Yield [%] |
|---|---|---|---|
| $n\text{-}C_3H_7$ | H | 208–209 | 63 |
| $i\text{-}C_3H_7$ | H | 204–205 | 49 |
| $c\text{-}C_6H_{11}$ | H | 204–205 | 46.1 |
| $n\text{-}C_4H_9$ | $n\text{-}C_4H_9$ | 130 | 80.6 |
| $C_6H_5$ | $C_6H_5$ | 129–130 | 76.5 (V, 18) |

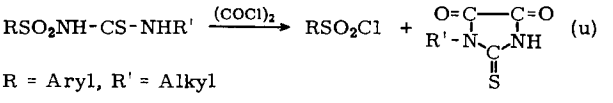
When warmed in alcohol, the 2-iminothiazolidine-4,5-diones *(15)* isomerize to give the thioparabanic acid derivatives *(16)* obtained by *Biltz* and *Topp* [23] and by *Stoffel* [26].



$$R\text{-}N(\text{C=O})\text{-}C(\text{=O})\text{-}S\text{-}C(R'){=}N \quad (15) \xrightarrow[C_2H_5OH]{\Delta} O{=}C\text{-}N(R)\text{-}C(\text{=S})\text{-}N(R')\text{-}C{=}O \quad (16) \quad (t)$$

### 4. Reaction of 1-Arylsulfonyl-3-alkylthioureas with Oxalyl Chloride

The reaction of 1-arylsulfonyl-3-alkylthioureas with oxalyl chloride leads to sulfonyl chlorides and alkylthioparabanic acids, as indicated in Equation (u).



$$RSO_2NH\text{-}CS\text{-}NHR' \xrightarrow{(COCl)_2} RSO_2Cl + O{=}C\text{-}N(R')\text{-}C(\text{=S})\text{-}NH\text{-}C{=}O \quad (u)$$

R = Aryl, R′ = Alkyl

This is probably again due to isomerization of the initially formed iminothiazolidinedione during the working-up of the reaction mixture (cf. Section IV, 3).

## V. Procedures

#### 1. *N,N′-Di-n-butylallophanoyl chloride (1b)* [11]

56 g (0.3 mole) of 1,3-di-n-butylurea in 216 ml of benzene is added dropwise to a solution of 73.3 g (0.74 mole) of phosgene in 300 ml of benzene at 8–10 °C. Nitrogen is passed through the reaction mixture to remove the hydrogen chloride formed. The solution is heated to the boiling point (to remove excess phosgene), and the solvent is then distilled off. The residue (70.7 g) consists of almost pure *N,N′*-di-n-butylallophanoyl chloride (yield 93%). Vacuum distillation of small quantities gives an analytically pure product, b.p. 98 °C/0.5 Torr; $n_D^{23} = 1.4662$ (cf. Section II, 2).

#### 2. *n-Butyl isocyanate from N,N′-di-n-butylallophanoyl chloride* [12]

11.7 g (0.05 mole) of *N,N′*-di-n-butylallophanoyl chloride in 235 g of *o*-dichlorobenzene is heated until the evolution of HCl stops (about 2 hours). Nitrogen preferably should be passed through the reaction mixture to remove the hydrogen chloride. Fractional distillation (to separate the product from the solvent) gives 9 g (91%) of n-butyl isocyanate, b.p. 115 °C (cf. Section II, 2).

#### 3. *N,N′-Di-n-butylchloroformamidine-N-carbonyl chloride* [13]

Phosgene is passed into a solution of 30.2 g (0.16 mole) of 1,3-di-n-butylthiourea in 600 ml of benzene until the exothermic reaction is complete (temperature 21.5–33.5 °C). After the excess phosgene has been removed with nitrogen, the solvent is distilled off *in vacuo*. The residue (39 g; 96.3%) consists of nearly pure *N,N′*-di-n-butylchloroformamidine-*N*-carbonyl chloride, which can be further purified by vacuum distillation of small quantities (b.p. 86 °C/0.5 Torr; $n_D^{23} = 1.4718$) (cf. Section II, 2).

#### 4. *p-Toluenesulfonyl isocyanate and n-butyl isocyanate from 1-p-toluenesulfonyl-3-n-butylurea*

270 g (1 mole) of 1-p-toluenesulfonyl-3-n-butylurea is introduced into 1350 ml of chlorobenzene. Traces of moisture are removed by azeotropic distillation, and 148.5 g (1.5 mole) of phosgene is passed into the solution over a period of about 2.5 hours at 80–100 °C. The solution is heated to boiling, nitrogen is passed through for 30 min, and the n-butyl isocyanate formed is distilled off with the solvent. Vacuum distillation of the residue yields 168.5 g (85.6%) of *p*-toluenesulfonyl isocyanate (b.p. 119–120 °C/4 Torr). The n-butyl isocyanate (b.p. 115 °C, yield 90%) can be separated from the solvent by fractional distillation of the solvent (cf. Section II, 3).

#### 5. *Benzenesulfonyl isocyanate*

78 g (0.5 mole) of benzenesulfonamide is dissolved in 588 ml of chlorobenzene, traces of moisture are removed by azeotropic distillation, and 9.9 g (0.1 mole) of n-butyl isocyanate is added as a catalyst at 75 °C. About 99 g (1 mole) of phosgene is then introduced over a period of 100 min at 129 to 130 °C. Nitrogen is passed through the solution for 30 min to remove excess phosgene, and the solvent, which contains the regenerated catalyst, is distilled off. Vacuum distillation of the residue gives 78 g (85.8%) of benzenesulfonyl isocyanate, b.p. 79–83 °C/0.7 Torr (cf. Section II, 3).

6. *p-Nitrobenzenesulfonyl isocyanate*

3.96 g (0.04 mole) of n-butyl isocyanate is added to a suspension of 20.2 g (0.1 mole) of *p*-nitrobenzenesulfonamide in 200 ml of *o*-dichlorobenzene. 46 g (0.46 mole) of phosgene are then introduced over a period of 46 min at 176–180 °C. The excess phosgene is removed with nitrogen, and the solvent, which contains the catalyst, is distilled off under vacuum. Vacuum distillation of the residue gives 18.5 g (81.1%) of *p*-nitrobenzenesulfonyl isocyanate, b.p. 137–143 °C/0.4 Torr; m.p. 70–73 °C (cf. Section II, 3).

7. *n-Butyl isocyanate and n-butylsulfinylamine (6), R = $C_4H_9$, from 1,3-di-n-butylurea and thionyl chloride*

6.0 g (0.05 mole) of thionyl chloride is introduced into a suspension of 8.6 g (0.05 mole) of 1,3-di-n-butylurea in 50 ml of carbon tetrachloride. The solution is refluxed for 4 hours, and the solvent is then distilled off over a Vigreux column. Distillation of the residue gives a mixture of 4.34 g (88%; determined by titration with di-n-butylamine) of n-butyl isocyanate, b.p. 115 °C, and 4.6 g (77%) of n-butylsulfinylamine, b.p. 116 °C ($\tilde{\nu}_{as}$NSO = 1235 $cm^{-1}$; $\tilde{\nu}_{s}$NSO = 1110 $cm^{-1}$), which cannot be separated by distillation (cf. Section II, 6).

8. *2,2,2-Trichloro-1,3-dimethyl-1,3-diaza-2-$P^V$-phosphetidinone (7), R = R' = $CH_3$* [21]

33.3 g (0.16 mole) of phosphorus pentachloride is introduced into a suspension of 13.2 g (0.15 mole) of 1,3-dimethylurea in 150 ml of carbon tetrachloride. The mixture is refluxed for 1 hour, and after removal of the hydrogen chloride with nitrogen (20 min), the solvent is distilled off. Vacuum distillation of the residue gives 24.1 g (71.9%) of 2,2,2-trichloro-1,3-dimethyl-1,3-diaza-2-$P^V$-phosphetidinone, b.p. 78–79 °C/1.5 Torr (cf. Section II, 5).

9. *p-Toluenesulfonyltrichlorophosphazene (8'), R = $CH_3$–$C_6H_4$, and n-butyl isocyanate from 1-p-toluenesulfonyl-3-n-butylurea and phosphorus pentachloride* [21]

2.7 g (0.01 mole) of 1-*p*-toluenesulfonyl-3-n-butylurea and 2.1 g (0.01 mole) of phosphorus pentachloride in 40 ml of carbon tetrachloride are refluxed for 60 min. Removal of the solvent, which contains 0.8 g (80.8%) of n-butyl isocyanate (determined by titration with di-n-butylamine) and crystallization of the residue from carbon tetrachloride yields 2.35 g (77%) of *p*-toluenesulfonyltrichlorophosphazene, m.p. 88 to 90 °C (cf. Section II, 6).

10. *Di-t-butylparabanic acid (9), R = R' = tert-$C_4H_9$* [21]

6.35 g (0.05 mole) of oxalyl chloride is added dropwise to an ice-cooled solution of 8.6 g (0.05 mole) of 1,3-di-t-butylurea in 86 ml of 1,2-dichloroethane. The mixture is stirred for 30 min at room temperature and then refluxed for 30 min. Removal of the solvent by distillation yields 10.8 g (95.6%) of 1,3-di-t-butylparabanic acid, m.p. 88–89 °C. Recrystallization from ethanol gives white needles, m.p. 95 °C (cf. Section II, 7).

11. *2-Imidazolidinone-1-carbonyl chloride (10), R = H* [11]

Phosgene (*ca.* 0.22 mole) and a solution of 17.2 g (0.2 mole) of 2-imidazolidinone in 220 ml of hot (75–80 °C) 1,2-dichloroethane are added simultaneously to 100 ml of 1,2-dichloroethane at 75–80 °C. After removal of excess phosgene by means of nitrogen, the mixture is filtered. When the filtrate is cooled, 25.6 g (86%) of 2-imidazolidinone-1-carbonyl chloride, m.p. 155–157 °C, separate out in form of colorless crystals. A further 1.6 g of product, m.p. 150–153 °C, can be obtained by concentration of the solution (cf. Section III, 1).

12. *Ethylene diisocyanate* [12]

50.5 g (0.5 mole) of triethylamine is added dropwise to a suspension of 78 g (0.525 mole) of 2-imidazolidinone-1-carbonyl chloride *(10)*, R = H, in 1500 ml of benzene. When the mixture has been allowed to stand for 30 min, 66.1 g (96%) of triethylammonium chloride can be filtered off. Approximately 10 g of phosgene is passed into the filtrate at 70–75 °C to remove any traces of amine. A further 1.3 g of triethylammonium chlorid is filtered off, and the solvent is removed by distillation. Vacuum distillation of the residue gives 38.6 g (66%) of ethylene diisocyanate, b.p. 77–70 °C/16 Torr; $n_D^{23}$ = 1.4472 (cf. Section III, 1).

13. *p-Isocyanatobenzenesulfonyl isocyanate (12), R = NCO, R' = X = H*

27.1 g (0.1 mole) of *N*-sulfanilyl-*N'*-n-butylurea is added in parts to a stirred, ice-cooled solution of 19.8 g (0.2 mole) of phosgene in 270 ml of chlorobenzene at 2 °C. The mixture is slowly heated to boiling with introduction of phosgene. After a further 90 minutes, the addition of phosgene is stopped, and excess phosgene is removed with nitrogen. After filtration, the solvent, which contains 6.8 g (68.7%) of n-butyl isocyanate, is distilled off. Vacuum distillation of the residue gives 14.4 g (64.3%) of *p*-isocyanatobenzenesulfonyl isocyanate, b.p. 115–120 °C/0.4 Torr, m.p. 40–44 °C (cf. Section III, 2).

14. *Di-o-tolylcarbodiimide*

22.5 g (0.22 mole) of phosgene in 100 ml of chlorobenzene at 48 °C is introduced into a suspension of 56.3 g (0.22 mole) of di-*o*-tolylthiourea in 460 ml of chlorobenzene over a period of 37 min. The mixture is heated to boiling, the excess phosgene is removed by means of nitrogen, and the solvent is distilled off. Vacuum distillation of the residue yields 40.7 g (83.4%) di-*o*-tolylcarbodiimide, b.p. 146–149 °C/0.7 Torr (cf. Section IV,1).

15. *N-p-Toluenesulfonyl-N'-n-butylchloroformamidine (13), R = $CH_3$–$C_6H_4$, R' = $C_4H_9$*

A solution of 7 g (0.07 mole) of phosgene in 50 ml of carbon tetrachloride is added dropwise to a stirred solution of 20 g (0.07 mole) of 1-*p*-toluenesulfonyl-3-n-butylthiourea in 150 ml of carbon tetrachloride. The solution is stirred for 90 min at room temperature, and 17.9 g (88.6%) of *N*-p-toluenesulfonyl-*N'*-n-butylchloroformamidine, m.p. 90–95 °C, separate as crystals (cf. Section IV, 2).

16. *Methanesulfonyl-n-butylcarbodiimide (14), R = $CH_3$, R' = $C_4H_9$*

5 g (0.05 mole) of phosgene in 40 ml of chlorobenzene is added dropwise to a suspension of 10.5 g (0.05 mole) of 1-methanesulfonyl-3-n-butylthiourea in 65 ml of chlorobenzene at 5 °C. The solution is stirred for 1 hour at room temperature and then heated to boiling, and the unchanged phosgene is removed by means of nitrogen. Removal of the solvent by distillation, followed by vacuum distillation of the residue, gives 7.0 g (79.5%) of methanesulfonyl-n-butylcarbodiimide, b.p. 103–105 °C/0.3 Torr; $n_D^{24.5}$ = 1.4798 (cf. Section IV, 2).

17. *3-Phenyl-4-p-toluenesulfonylimino-1,3-thiazetidin-2-one*

A solution of 2.8 g (0.028 mole) of phosgene in 35 ml of chlorobenzene is added dropwise to a suspension of 8.5 g (0.023 mole) of 1-*p*-toluenesulfonyl-3-phenylthiourea in

50 ml of chlorobenzene. The mixture is stirred for 1 hour, and the solvent is then distilled off *in vacuo*. Recrystallization of the residue [9 g (97.3%), m.p. 128–131 °C] from ethyl acetate yields analytically pure 3-phenyl-4-*p*-toluenesulfonyl-imino-1,3-thiazetidin-2-one, m.p. 139 °C (cf. Section IV, 2).

18. *2-Phenylimino-3-phenyl-1,3-thiazolidine-4,5-dione (15), $R = R' = C_6H_5$*

3.81 g (0.033 mole) of oxalyl chloride is added dropwise to a stirred, ice-cooled suspension of 6.84 g (0.03 mole) of 1,3-diphenylthiourea in 70 ml of 1,2-dichloroethane. The mixture is refluxed for 45 minutes, and the solvent is then distilled off. Recrystallization of the residue [8.1 g (96.5%), m.p. 124 to 125 °C] from carbon tetrachloride yields 6.49 g (76.5%) of 2-phenyl-imino-3-phenyl-1,3-thiazolidine-4,5-dione, m.p. 129–130 °C (cf. Section IV, 3).

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# Some Recent Developments in the Chemistry of Transition Metal Oxocations

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*The range of stability of transition metal oxocations in aqueous solution is discussed. Species with a metal-oxygen bond of order higher than unity are particularly interesting. Bond orders can sometimes be determined from bond lengths and angles, but generally only by infrared spectroscopy. – The frequency range of the metal-oxygen stretching vibration, previously assumed as about 900–1100 $cm^{-1}$, must according to these investigations be extended at least to 780 $cm^{-1}$ if all multiple bonds, particularly those in trans-dioxo complexes, are to be included. Broad bands down to 650 $cm^{-1}$ are ascribed to metal-oxygen bridges. – The existence of cations such as $ZrO^{2+}$ and $VO_2^+$, or of the "well-known" titanyl ion, $TiO^{2+}$, has never been proved. In many cases polynuclear, oxygen-bridged oxometal species must be assumed.*

## Introduction

Of recent theoretical and experimental interest is the general subject of multiple bonds. In the field of metal-oxygen multiple bonds it appears that the experimental science is still well ahead of the theoretical development, and so the former will be the main subject of this review.

No element appears to form multiple bonds with so many other elements as does oxygen. It is well known that oxygen can form multiple bonds with all non-metals, except fluorine and the lighter noble gases, with all metalloids, and apparently with almost all metals to which it bonds covalently [*].

This discussion is limited to oxometal species $MO_x^{n+}$ (where M = transition element; x = 1, 2, or 3; and n = 0–5), which are part of a complex. The other ligands may be strongly or weakly attached to M, while the oxygen is strongly bound and persistent during exchange of the other ligands. Excluded from consideration are the large number of $MO_4^{n-}$ species having only oxygen as ligand, as these have recently been discussed elsewhere [1–3]; the many binary (and most often non-stoichiometric) oxides of the transition metals; and the species $M_2O^{n+}$ [which appear to be quite well established for M = Ti(IV), Cr(III), Fe(III), Mo(V), Re(IV), Ru(IV), Rh(III), and Os(IV)], as in these the oxygen is always bridging, not terminal. The latter species are probably all linear and they are assumed to involve strong M–O–M π-bonding. Theoretical treatments of such entities have appeared [4–10].

Some of the experimental criteria most generally used to establish a bond order greater than one are:

[*] Whatever this may really mean; we exclude here the few ionic oxides such as $Li_2O$, CaO, $La_2O_3$, *etc.*, in which the oxygen is divalent but the bonding is more simply and satisfactory treated electrostatically.

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(a) If the bond length is found to be shorter (by at least a few tenths of an Ångstrom unit) than the calculated or an experimentally determined single bond distance; this is the best and most direct evidence.

(b) If the bond angle implies a higher bond order, for example if in an M–O–M unit it exceeds the tetrahedral angle by at least several degrees;

(c) If the bond stretching frequency is considerably higher than is found (or predicted) for a single bond between the same atoms.

This last method is more often relied upon because of its experimental simplicity. Often it provides the only experimental evidence on the multiplicity of a metal-oxygen bond [11–13].

Table 1. Approximate correlation between dominant species in aqueous solutions attaching to a metal ion of formal charge Q, in various pH ranges (after *Jørgensen* [14]).

| | Q | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| pH | +1 | +2 | +3 | +4 | +5 | +6 | +7 | +8 |
| –1 | $H_2O$ | $H_2O$ | $H_2O$ ↓ | $H_2O$ ↓ | $OH^-$ | $OH^-$ ↓ | $OH^-$ ↓ | $O_2^-$ |
| 7 | $H_2O$ | $H_2O$ ↓ | $OH^-$ | $OH^-$ ↓ | $OH^-$ ↓ | $O^{2-}$ | $O^{2-}$ | $O^{2-}$ |
| 15 | $H_2O$ | $OH^-$ | $OH^-$ | $O^{2-}$ | $O^{2-}$ | $O^{2-}$ | $O^{2-}$ | $O^{2-}$ |

Briefly let us consider where we should expect and where we actually find metal oxocations. We might begin by examination of Table 1, which has been patterned after a similar one given by *Jørgensen* [14] and is based on a large number of studies on solutions. It shows the approximate pH intervals in which $H_2O$, $OH^-$, and $O^{2-}$ are the common ligands to central ions oxidation states varying from +1 to +8. Although only qualitative, this table does suggest $O^{2-}$ to be a ligand toward metal ions (in solution) in high oxidation states (+4 to +8), and that the lower the oxidation state the higher must be the pH to prevent this ion from attaching a proton to form $OH^-$.

However, this interpretation of the table suffers from several obvious defects. It does not reflect the important contribution of cationic radius, r, and effective nuclear charge $Z_{eff}$; thus $Z_{eff}/r$ should be considered and not simply the formal charge Q. Also, because it represents an electrostatic picture it does not take into consideration what orbitals of the metal ion may be available for covalent bonding, certainly an important factor as the ionic charge increases and the ionic radius decreases. Further, it does not take into account the differences in covalent bonding capacity among $H_2O$, $OH^-$, and $O^{2-}$, *i.e.* their increasing π-bonding (really π-antibonding) capacities. *Jørgensen*'s [15] optical electronegativities of metal ions are possible measures of this tendency (*i.e.* the tendency for the metal ion to attract π-bonding electrons from oxygen). Finally, in the large intermediate pH ranges both $H_2O$ and $OH^-$ or $OH^-$ and $O^{2-}$ can co-exist as ligands. Indeed, a most remarkable fact is the co-existence within the same coordination sphere of both $H_2O$ and $O^{2-}$. This has been confirmed for $[VO(H_2O)_5]^{2+}$ [13, 16] and $[MO_2(H_2O)_x]^{2+}$ (M = U, Np, Pu, Am) [13, 17]. These are metal ions which have both their σ- and π-antibonding subshells empty, the latter being ideally suited, therefore, to accomodate strongly nucleophilic [*] oxide π-electrons. It is not sur-

Table 2. Mononuclear [a] oxocations of transition metals [b], according to periodic group, number of d-electrons, and oxidation number.

| IVb | Vb | | VIb | | |
|---|---|---|---|---|---|
| $d^0$ +4 | $d^0$ +5 | $d^1$ +4 | $d^0$ +6 | $d^1$ +5 | $d^2$ +4 |
| $TiO^{2+}$ | $VO^{3+}$, $VO_2^+$ | $VO^{2+}$ | $CrO^{4+}$, $CrO_2^{2+}$ | $CrO^{3+}$ | |
| $ZrO^{2+}$ | $NbO^{3+}$, $NbO_2^+$ | | $MoO^{4+}$, $MoO_2^{2+}$ | $MoO^{3+}$, $MoO_2^+$ | $MoO_2^0$ |
| $HfO^{2+}$ | $TaO^{3+}$, $TaO_2^+$ | | $WO^{4+}$, $WO_2^{2+}$ | $WO^{3+}$, $WO_2^+$ | |
| $(ThO^{2+})$ | $(PaO^{3+})$, $(PaO_2^+)$ | | | | |

| VIIb | | | | VIIIb | | | | 5f | |
|---|---|---|---|---|---|---|---|---|---|
| $d^0$ +7 | $d^1$ +6 | $d^2$ +5 | $d^3$ +4 | $d^0$ +8 | $d^1$ +7 | $d^2$ +6 | $d^4$ +4 | $f^{0-3}$ +6 | $f^{1-4}$ +5 |
| $MnO_3^+$ | | | $(MnO^{2+})$ | | | | | $UO_2^{2+}$ | $(UO_2^+)$ |
| $TcO_3^+$ | $TcO^{4+}$ | $TcO^{3+}$ | | | | $RuO^{4+}$, $RuO_2^{2+}$ | $RuO^{2+}$ | $NpO_2^{2+}$, $PuO_2^{2+}$ | $NpO_2^+$, $(PuO_2^+)$ |
| $ReO^{5+}$, $ReO_2^{3+}$, $ReO_3^+$ | $ReO^{4+}$, $ReO_2^{2+}$ | $ReO^{3+}$, $ReO_2^+$ | $ReO_2^0$ | $OsO_3^{2+}$ | $OsO^{5+}$ | $OsO^{4+}$, $OsO_2^{2+}$ | $(PtO^{2+})$ | $AmO_2^{2+}$ | $AmO_2^+$ |

[a] Several of the species listed, notably those of molybdenum and titanium, have been shown to be dimeric or polymeric with oxygen-bridged chains (see text and Figure 2).

[b] The underlined species are relatively common and well-established, at least in the solid state; those in parentheses are unstable or of doubtful existence.

[*] It would seem desirable to have a simple semantic way to distinguish nucleophilic groups according to whether their electrons seek to form a σ-bond or π-bond. The author suggests the terms σ-nucleophilicity and π-nucleophilicity.


[11] *C. G. Barraclough, J. Lewis,* and *R. S. Nyholm,* J. chem. Soc. (London) *1959*, 3552.

[12] *J. Selbin,* J. chem. Educat. *41*, 86 (1964).

[13] *J. Selbin,* Österr. Chemiker-Ztg. *65*, 275 (1964).

[14] See [6], p. 15.

[15] *C. K. Jørgensen,* Solid State Physics *13*, 375 (1962); Advances chem. Physics *5*, 33 (1963).

[16] *J. Selbin,* Chem. Reviews *65*, 153 (1965); Coord. Chem. Rev., in press.

[17] *E. Rabinowitch* and *R. L. Belford* in: International Series of Monographs on Nuclear Energy, Chemistry Division. Vol. 1. Spectroscopy and Photochemistry of Uranyl Compounds. Macmillan, New York 1964.

prising, therefore, that the largest number of complexes have been prepared with the stable ions $UO_2^{2+}$ and $VO^{2+}$.

The requirement that the metal ion possess empty, stable $\pi$-bonding ($\pi$-antibonding) orbitals is pointed up in Table 2, in which are listed oxometal entities according to periodic group number, number of d-electrons, and formal oxidation state. Not all these have been unambiguously established as mononuclear, and many of them are much less common than once believed [12, 13].

Theoretical treatments of bonding and electronic structure in oxocation complexes have appeared for $VO^{2+}$ [18, 19], $UO_2^{2+}$ [17, 20–24], $CrO^{3+}$ [25], and with somewhat less rigor for certain other species $MO^{n+}$, $MO_2^{n+}$ [7–9]. There is not a great deal of agreement among the several workers in the field, and this seems especially true for vanadyl [16] (*vide infra*).

The remainder of this paper will be devoted to a systematic and critical survey of some of the recent experimental developments in oxocation chemistry by periodic group. However, no pretense of exhaustiveness is made; the material selected simply reflects the author's interests and his opinions of what are the most interesting, fruitful, or active of the experimental studies in this area.

## I. Oxocomplexes of Group IVb Elements

### 1. Titanium

There are very few unambiguously established examples of true $MO^{2+}$ species (M = Ti, Zr, Hf, Th), and it may be concluded that these metals, $d^0$ in their quadrivalent state, have a much greater tendency to form either mononuclear hydroxo species, $M(OH)_x^{(4-x)+}$, or chains or rings involving bridging by oxygen or hydroxyl ions.

In spite of the continual reporting in the literature of "titanyl" ions, $TiO^{2+}$, in aqueous solutions, there has never appeared conclusive or even strong evidence to support this mononuclear formulation. The situation with regard to the solid state is somewhat more definitive. Although there is no direct X-ray evidence for a mononuclear entity in any oxotitanium compound, the Ti–O distance in the sulfate, $TiOSO_4(H_2O)$, which consists of (Ti–O–Ti–O) chains, is 1.80 Å [26]. This value is very close to the Ti–O distance of 1.78 Å in $[Ti(C_5H_5)Cl_2]_2O$ [27], which clearly contains the linear, and hence surely multiply-bonded, Ti=O=Ti unit. (The sum of the ionic radii, $Ti^{4+}$ and $O^{2-}$, is 0.60 + 1.45 = 2.05 Å, and the sum of the covalent radii is not very different.) The broad infrared absorption bands centered about 920 and 800 $cm^{-1}$ [11], observed for the sulfate, are probably correctly assigned to metal-oxygen vibrations of bonds with order greater than one, but less than two. Broad bands are found near and below 900 $cm^{-1}$ in the spectra of $TiOF_2(H_2O)$ and $TiOF_2$ [28]; $TiOCl_2$, $TiOCl_2(2C_5H_5N)$ [29]; $TiOI_2$ [30]; some Ti oxide alkoxides [31]; $[TiO(C_2O_4)_2]^{2-}$ [11, 32]; and in products of the reaction of $TiCl_4$ with dioxane or acetonitrile [33].

The assignment [34] of a band at 1149 $cm^{-1}$ in $TiO(OH)_2$ to Ti=O is most likely incorrect. A more probable origin for this band is $\delta$ (Ti–O–H). In fact, on the basis of infrared data alone, mononuclear titanyl species are rare. The most likely compounds, and their possible Ti=O stretching frequencies in $cm^{-1}$, are TiO(β-diketone)$_2$, 1020–1035 [35, 36]; $TiOCl_2 \cdot 2POCl_3$, 1078 [27]; and TiO(phthalocyanine), 965 [37], 978 [38], 972 [39]. An absorption band at 975 $cm^{-1}$, believed to be due to a Ti=O double bond, is observed for $[(C_2H_5)_4N)]_2TiOCl_4$ [38a].

### 2. Zirconium and Hafnium

There are two recent surveys of zirconium chemistry [40, 41]. Both agree that the bulk of the literature on the solution chemistry of Zr(IV) contains no evidence for zirconyl ions, $ZrO^{2+}$. Definitely established instead are such species as $[Zr_4(OH)_8]^{8+}$(aq) and other hydroxo- or oxo-bridged polymeric species, which depend critically upon solution conditions, *viz.* pH, age, temperature, *etc.*

After examining Zr–O bond distances in eighteen solid compounds, *Clearfield* [41] concluded that "the existence of zirconium-oxygen multiple bonds has not been unequivocally demonstrated". This conclusion is based on the very slight deviations in observed bond distances (2,20 Å) from the sum of ionic or covalent radii (2,22 Å). However, recent infrared studies on a series of

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[19] *T. R. Ortolano*, *J. Selbin*, and *S. P. McGlynn*, J. chem. Physics *41*, 262 (1964).

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[22] *M. E. Dyatkina*, *V. P. Markov*, *I. V. Tsapkina*, u. *Yu. N. Mikhailov*, Zh. neorg. Khim. *6*, 575 (1961).

[23] *R. L. Belford* and *G. Belford*, J. chem. Physics *34*, 1330 (1961).

[24] *M. E. Dyatkina* and *Yu. N. Mikhailov*, Komplekan Soedin Urana, Akad. Nauk SSSR obshch. neorg. Khim. *1964*, 341; Chem. Abstr. *62*, 45 (1965).

[25] *H. B. Gray* and *C. R. Hare*, Inorg. Chem. *1*, 363 (1962).

[26] *G. Lundgren*, Ark. Kemi *10*, 397 (1957).

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[28] *Yu. Ya. Kharitonov* and *Yu. A. Buslaev*, Izvest. Akad. Nauk SSSR, Ser. khim. *3*, 365 (1962).

[29] *K. Dehnicke*, Z. anorg. allg. Chem. *309*, 266 (1961).

[30] *K. Dehnicke*, Angew. Chem. *76*, 578 (1964), Angew. Chem. internat. Edit. *3*, 646 (1964); Z. anorg. allg. Chem. *338*, 279 (1965).

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[36] *M. Cox*, personal communication.

[37] *A. B. P. Lever*, personal communication.

[38] *R. Taube*, Z. Chem. *3*, 194 (1963).

[38a] *A. Feltz*, Z. anorg. allg. Chem. *334*, 242 (1965).

[39] *B. P. Block* and *E. G. Meloni*, Inorg. Chem. *4*, 111 (1965).

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[41] *A. Clearfield*, Rev. pure appl. Chem. *14*, 91 (1964).

"zirconyl" (and "hafnyl") fluorides prepared by thermal decomposition of $ZrF_4 \cdot 3H_2O$ [42], and on the isothiocyanato complexes $ZrO(NCS)_2 \cdot MNCS \cdot 2H_2O$ (where M = K, Rb, Cs, $NH_4$, or pyridinium) [42], have been interpreted as evidence for the existence of the zirconyl entity in such species.

Attempts by the present author [43] to duplicate the work with the fluorides were unsuccessful; the isothiocyanato work was successfully repeated [43] with M = Cs and $(CH_3)_4N$, and strong sharp bands at 916 and 920 $cm^{-1}$ in the respective compounds are tentatively assigned to Zr=O. If these isothiocyanato complexes do turn out to possess this elusive group, it is likely that the analogous hafnium complexes [44] do also.

*Dehnicke* and *Meyer* [45] report a band at 877 $cm^{-1}$ in $ZrOCl_2$ and one at 1083 $cm^{-1}$ in $ZrOCl_2 \cdot 2POCl_3$ which they claim arise from a Zr=O vibration, but neither of these assignments appears to be firmly based. The absence of a Zr=O group has been deduced from infrared data in oxalato, sulfato, and peroxo complexes of zirconium [46] and trichloroacetates of both zirconium and hafnium [47]. A band at 900 $cm^{-1}$ found in $ZrO(C_2O_4) \cdot 1.5H_2O$, but absent from the spectrum of $Zr(C_2O_4)_2$, is attributed to Zr=O, as is a narrow band at 1017 $cm^{-1}$ in $ZrO(NO_3)_2 \cdot 2H_2O$ [48].

Although a few thoryl, $ThO^{2+}$, formulations have been offered, for example ThOX (where X = $F_2$, $Cl_2$, S, Se, Te), no evidence has appeared to support such a mononuclear species.

Work on the crystal structures of some basic salts of Ce(IV), Th(IV), U(IV), Ti(IV), and Zr(IV) has been summarized by *Lundgren* [49] with the conclusion that no M(IV)-O bonds are short enough to be considered multiple bonds.

## II. Oxocomplexes of Group Vb

### 1. Vanadium

Oxocation chemistry in this periodic group is dominated by oxovanadium(IV), $VO^{2+}$. The author has recently surveyed preparative work, ESR, infrared, and visible-ultraviolet spectroscopy, X-ray diffraction, equilibrium, magnetic, and theoretical studies on this stable molecule-ion. With the exception of dioxouranium(VI), $UO_2^{2+}$, this is the most studied of the oxocations and the one for which we have the greatest number and variety of complexes.

Currently the $VO^{2+}$ ion is the center of a controversy over which theoretical model best describes its behavior and in particular its electronic or orbital structure. The apparent simplicity implicit in treating the $d^1$-system is illusory since there is very strong σ- and π-bonding between oxygen and vanadium, and the symmetry of its complexes is never higher than $C_{4v}$, but often lower. Several early (1957) attempts to treat this ion with a crystal field model [50–52] were shown (in 1962) to be inadequate by *Ballhausen* and *Gray* [18], who employed a modified self-consistent Wolfsberg-Helmholtz molecular orbital method in treating specifically the ion $[VO(H_2O)_5]^{2+}$. Their model and energy-level scheme was used by them and by others to interpret optical, ESR, and magnetic properties of $VO^{2+}$ complexes in general, and it was even extended to complexes of $CrO^{3+}$ and $MoO^{3+}$ (also $d^1$-systems) by *Gray* and *Hare* [25]. An analogous, but independent ligand field approach was applied to a generalized species $VOL_4^{n+}$ [53], yielding an energy scheme in approximate agreement with that of *Ballhausen* and *Gray*. Additional experimental work in the author's laboratory with vanadyl(IV) complexes [54,55] and, in particular, low-temperature studies [19,56] led to serious doubt in the universality, if not the specific validity, of the *Ballhausen-Gray* scheme, and a new energy scheme was tentatively proposed for vanadyl(IV) complexes [19]. Recent low-temperature studies [57,58] on vanadyl complexes suggest that none of the previously proposed schemes is acceptable.

Thus the problem of the origin of the visible and ultraviolet spectral bands is largely unsolved, and in its solution should be found important knowledge concerning the validity and usefulness of several modern theoretical approaches. Indeed *Piper* and *Wentworth* [58] are of the opinion that a simple electrostatic model is satisfactory for treating this and similar systems, whereas others, including this author, feel that covalent models must be employed. Additional low-temperature work now in progress, at 4 °K and 77 °K, including polarization spectra, as well as new ESR studies [59] are expected to clear up many of the present inconsistencies.

The mononuclear oxovanadium(V) species may be either $VO^{3+}$ or $VO_2^+$. The former is found more often in solid or liquid compounds such as $VOX_3$ (X = F, Cl, Br, OR, *etc.*) and in most complexes, such as $VO(OR)L_x$, whereas the dioxo ion is reported in relatively few compounds and is postulated in certain concentrated acid solutions.

When vanadate ($VO_4^{3-}$) solutions are acidified, extensive condensation probably gives decavanadate ions of the type $V_{10}O_{28}^{6-}$, $HV_{10}O_{28}^{5-}$, and $H_2V_{10}O_{28}^{4-}$ [60–63].

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[43] *J. Selbin* and *H. Pence*, unpublished work.

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[59] *D. Kivelson* and *S.-K. Lee*, J. chem. Physics *41*, 1869 (1964).

[60] *F. J. C. Rossotti* and *H. Rossotti*, Acta chem. scand. *10*, 957 (1956).

[61] *L. G. Sillen*, Quart. Rev. (chem. Soc., London) *13*, 146 (1959).

[62] *L. Newman* and *K. P. Quinlan*, J. Amer. chem. Soc. *81*, 547 (1959).

[63] *A. W. Naumann* and *C. J. Hallada*, Inorg. Chem. *3*, 70 (1964).

Upon further acidification a mononuclear cation is formed, but whether that species is $VO_2^+$ is not certain [1, 63–65].

However, several complexes are presumed to contain this elusive dioxo species. Thus $VO_2ClO_4$ (aqueous solution) is said to form $VO_2L_2$ below pH 4, and VO(OH)L above this value, where L = pyridine-2-carboxyl [66]. The same authors report that $VO_2^+$ absorbs at 730 mμ (13,700 $cm^{-1}$). In concentrated $HNO_3$ vanadium(v) is thought to exist as either $VO(NO_3)_3$ or $VO_2(NO_3)$ [67]. A brick-red powder, unstable in moist air, reported to have the formula $VO_2NO_3$ has been prepared [68] by reaction of liquid $N_2O_4$ with metallic vanadium. Infrared data indicate an ionic nitrate (1380 $cm^{-1}$, vs; 820 $cm^{-1}$, vw) and vanadium-oxygen multiple bonding (1020–1000 $cm^{-1}$). However, like the analogous Nb and Ta compounds [69] this nitrate is probably polymeric. Other reports of $VO_2^+$ complexes, for example with EDTA [70] or oxalate [71], do not convincingly demonstrate the presence of this particular ion. Thus the $VO_2^+$ species has never been unambiguously demonstrated either in a solid or in solution. In fact the existence of many complexes containing the $VO(OH)^{2+}$ unit suggests that the $VO_2^+$ species is very readily protonated. However, it is possible that protonation occurs only in the presence of ligands which transfer sufficient charge onto the vanadium to lower its electronegativity so far that it cannot remain multiply bonded to two oxygen atoms.

The $VO^{3+}$ entity is very common in anionic and neutral complexes as well as in covalent molecules. That strong oxygen-metal π-bonding occurs in $VOCl_3$ is reflected in its low dipole moment in $CCl_4$ solution of 0.31 D [72] (which implies a very low V–O bond moment), as well as in the high V–O stretching frequency of 1035 $cm^{-1}$ [73], a value exceeded only by the 1060 $cm^{-1}$ recorded for $VOF_3$ [74]. The value for $VOBr_3$ is lower, 1020 $cm^{-1}$ [75], reflecting probably more the increased mass against which the oxygen vibrates than a weakening of the V–O bond.

$VOCl_3$ reacts with a variety of molecules LH (for example: arenes) to form addition compounds of the types $VOCl_3 \cdot 2LH$ and $VOCl_3 \cdot LH$ [76,77]; or to give complexes of the type $VOCl \cdot L_x$ (x = 1 or 2) [78]; or $VOL_3$ [78–80], where L denotes either a mono- or bidentate ligand such as mono- and di-phenols and monocarboxylic acids.

Another common type of complex is of the general formula $VO(OR)L_x$, where usually x is 2, L is a bidentate ligand (*e.g.* salicylaldoxime), and R is most often H, but may also be alkyl.

*Dutta* and *Lahiry* [81] have prepared and characterized vanadium(IV) and vanadium(v) complexes with unusual bidentate ligands such as quinaldinic acid and its derivatives, hydroxamic acids, hydroxyphenyltriazines, benzimidazoles, benzotriazoles, and oxines. Most of these have the general formula $VO(OH)L_x$. Representative V–O stretching frequencies for the V(v) complexes are: $[VO(OH)Q_2] \cdot 2H_2O$, 939 $cm^{-1}$; $[VO(OH)B_2]$ 968 $cm^{-1}$ (QH = quinaldinic acid; BH = benzhydroxamic acid) which are comparable with the value for the 8-hydroxyquinoline complex $[VO(OH)(oxine)_2]$ of 952 $cm^{-1}$ [82].

### 2. Niobium and Tantalum

There are very few oxometal species of quadrivalent niobium and tantalum (and protactinium). The compounds $NbOCl_2$ [83], $NbOI_2$ [84], and $TaOCl_2$ [83] are the only Nb(Ta)(IV) compounds even formulated as having the oxometal entity. A number of non-oxo Nb(IV) compounds have been recently prepared [85,86], but attempts to obtain the ion $[NbOCl_5]^{3-}$ failed [85b] even though compounds $(RH)_2Nb(OR')Cl_5$ (R = organic amine, R' = alkyl) were readily prepared. Recently dioxo compounds $MNbO_2F$ (perovskites) with M = Li, Na, K, have been described [87] in which there are almost certainly Nb–O–Nb–O linkages with substantial ionic character.

In the quinquevalent state there are several compounds containing the $MO^{3+}$ group, and a few perhaps containing the $MO_2^+$ entity [12]. Examples of compounds formulated as having the latter grouping are $NbO_2Cl$, $K[NbO_2(C_2O_4)]$, $(NbO_2)_2(S_4O_{13})$ [12], $Nb(Ta)O_2NO_3$ [69],

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[83] *H. Schäfer*, *E. Sibbing*, and *R. Gerken*, Z. anorg. allgem. Chem. *307*, 163 (1961); *H. Schäfer* and *F. Liedmeier*, Z. anorg. allgem. Chem. *329*, 225 (1964).

[84] *H. Schäfer* and *R. Gerken*, Z. anorg. allgem. Chem. *317*, 105 (1962).

[85a] *R. A. D. Wenthworth* and *C. H. Brubaker*, Inorg. Chem. *1*, 971 (1962).

[85b] *R. A. D. Wenthworth* and *C. H. Brubaker*, Inorg. Chem. *2*, 551 (1963).

[86] *R. E. McCarley* and *B. A. Torp*, Inorg. Chem. *2*, 540 (1963).

[87] *W. Rüdorff* and *D. Krug*, Z. anorg. allgem. Chem. *329*, 211 (1964).

$NbO_2F$ and $NbO_2I$ [88]. Little is known about the structure of these dioxometal compounds; they are most likely polymeric.

Recent reports of $MO^{3+}$ (M = Nb, Ta) compounds include $M'_3[MO(C_2O_4)_3]\cdot xH_2O$, (M' = Na, K, $NH_4$) [89–91]; $[NbOF_5]^{2-}$ [92] and $[MOF_6]^{3-}$ [92–94b], with Nb=O stretching frequencies of 927 and 922 $cm^{-1}$, respectively; $[NbOCl_5]^{2-}$ [96–98]; $MO(SO_3F)_3$ [99]; $NbOCl_3\cdot 2(CH_3)_2SO$ [100] and $MCl\cdot NbOCl_3$ (M = Na, K) [101]; $NbO(NO_3)_3$ (prepared by reaction of $NbCl_5$ with $N_2O_4$); 906 $cm^{-1}$ band assigned to Nb=O [92]; $[NbOCl_2(acac)]_x$, the low frequency (850–800 $cm^{-1}$) and broadness [102] of the infrared bands suggesting that Nb–O–Nb bridging rather than a terminal Nb=O bond is present in the molecule. The possible existence of $PaOF_5^{2-}$ in HF solutions has been reported [95].

In sum, is appears that niobium-oxygen multiple bonds occur in several monooxo compounds, the stretching frequencies of which are found around 900–925 $cm^{-1}$. Lower frequency bands, particularly if they are broad, in the range 850–750 $cm^{-1}$ are indicative of the bond order lower than two found in Nb–O–Nb chains.

## III. Oxocomplexes of Group VIb Elements

There are more possibilities for oxometal species with this family than with the previous two, and indeed more varieties are observed [12].

### 1. Chromium

In the quinquevalent state the chromium species $CrO^{3+}$ is found in very few, but well studied, compounds. For $CrOCl_3$ [103] and the complexes $K_2[CrOCl_5]$ and [isoquinolinium][$CrOCl_4$], magnetic moments of 1.80, 1.92, and 1.82 B.M., respectively, have been recorded [104]. The pentachloro-complex has been studied by ESR [105], visible-ultraviolet [25], and infrared [11, 106] spectroscopy. The Cr=O frequency in $K_2CrOCl_5$ is 950 $cm^{-1}$ [11, 106]. A species believed to be $[CrOF_5]^{2-}$ has also been examined by ESR [105] and magnetic, spectral, and conductivity measurements have been made on Cr(v) species in $H_2SO_4$ solutions [107].

At least two compounds of sexivalent chromium appear to contain the $CrO^{4+}$ group, *viz.* $CrOF_4$ [108] and $CrO(O_2)_2(C_5H_5N)$ [109]. X-ray structure determination on the latter complex reveals a very short Cr–O distance of 1.57 Å, compared to 1.794 for a Cr-(peroxo-O) length [109]. X-ray data on Cr–O distances are available for the following compounds: $K_3CrO_8$ (1.87, 1.97); $CrO_3$ (1.80); $(NH_4)_2CrO_4$ (1.60, 1.98); $(NH_4)_2Cr_2O_7$ (1.63, 1.91) [109]; $CrO(O_2)$(*o*-phen) (1.56, 1.83) [109a].

The much more common dioxo species $CrO_2^{2+}$ is found in $CrO_2X_2$ [12, 109b] (X = F, Cl, Br, $ClO_4$, $NO_3$, $N_3$, $CH_3COO$, NCO, NCS, $BO_2$, $SO_3F$, $^1/_2S_2O_7$), and in $CrO_2ClN_3$ [110].

The Cr=O stretching frequencies are expected in the range 950–1020 $cm^{-1}$, although few data are available [12].

### 2. Molybdenum

After uranium and vanadium, molybdenum has most likely yielded the largest number of oxo complexes. Many of these have been tabulated by the author [12], and a recent review [110a] is devoted entirely to oxo-species of Mo(v) and Mo(vi).

Some compounds of Mo(iv) have been formulated as oxometal species, *e.g.* $MoO_2(acacH)_2$, supposedly containing neutral acetylacetone, and analogous complexes with other neutral diketones [111]; $MoOCl_2$ [112], which has the same X-ray powder pattern as the analogous Nb and Ta compounds [83]; and $[Mo_3O_4(C_2O_4)_4]^{2-}$ [113]. However it seems that only in the first-mentioned of these is a terminal Mo=O bond likely, and even for this there is scant evidence.


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At present there is great interest in two problems of oxomolybdenum chemistry: the nature of Mo(v) species in acidic aqueous solutions, and the structural units in the solid state.

From spectrophotometric [114–117], magnetic [118–120], and potentiometric [114] studies of Mo(v) species in hydrochloric acid, it has been concluded that in concentrated HCl (>10 M) the predominant species is monomeric and paramagnetic (1 unpaired electron) $[MoOCl_5]^{2-}$; at intermediate HCl concentrations (2–10 M) two (or more) dimeric forms, one paramagnetic, one diamagnetic, exist in equilibrium; and at low HCl concentrations (<2 M) diamagnetic species predominate, but their nature is not known. The results of a recent spectrophotometric study of Mo(v) and Mo(vi) in HBr solutions [121] have been interpreted in

Table 3. Recently prepared and characterized Mo(v) oxocomplexes.

| Complex | Ref. | Complex | Ref. |
|---|---|---|---|
| | | $MoO^{3+}$-Derivatives | |
| $[MoOCl_5]^{2-}$<br>965 ± 20 [a] | [35, 122] | $[MoOCl(oxine)_2]$<br>935 [b] | [126, 127] |
| $[MoOBr_5]^{2-}$ | [121, 122] | $[MoOF(oxine)_2]$<br>938 | [35] |
| $[MoO(NCS)_5]^{2-}$ | [123, 124] | $[MoOBr(oxine)_2]$<br>933 | [35] |
| $[MoO(OH)_3]$<br>977, 895; 757, 714 | [35, 125] | $[MoO(OH)(acac)_2]\cdot 4\,H_2O$ | [126, 127] |
| $[MoOCl_3(bipy)]$<br>979 | [125] | $MoO(OH)_2Br_2\cdot 4\,H_2O$ | [121] |
| $[MoO(OH)_2Cl_3]^{2-}$ | [128] | $[MoOCl_3L_2]$ [c]<br>965 ± 3 | [129] |
| | | $Mo_2O_3^{4+}$-Derivatives | |
| $[Mo_2O_3(NCS)_8]^{4-}$ | [130] | $[Mo_2O_3Cl_4(o\text{-phen})_2]$ | [126, 127] |
| $[Mo_2O_3Cl_4(bipy)_2]$<br>966 | [125] | $[Mo_2O_3(oxine)_4]H_2O$ | [126, 127] |
| $[Mo_2O_3(acac)_4]$ | [131] | $[Mo_2O_3(C_2H_5OCS_2)_4]$<br>946, 760, 765 [d] | [133] |
| $[Mo_2O_3(H_2N\text{-}CS\text{-}NH_2)_8]X_4$<br>X = Cl, Br | [132] | | |
| | | $Mo_2O_2^{6+}$-Derivatives | |
| $[Mo_2O_2Cl_8]^{2-}$<br>975 ± 5 | [35, 122] | $[Mo_2O_2(CN)_8]^{2-}$<br>929 ± 1 | [35] |
| $[Mo_2O_2Br_8]^{2-}$<br>985 ± 10 | [35, 121, 122] | $[Mo_2O_2Cl_6(L)]$<br>L = *o*-phen: 975; bipy: 969<br>8-$NH_2$Q: 966 | [35] |
| | | $Mo_2O_4^{2+}$-Derivatives | |
| $Na_2[Mo_2O_4(EDTA)_2]\cdot H_2O$<br>959 | [138] | $(C_5H_5NH)_2[Mo_2O_4Cl_4(CH_3OH)_2]$ | [137] |
| $[Mo_2O_4(NCS)_4]^{2-}$ | [127, 130, 133] | $[Mo_2O_4Cl_2(bipy)_2]$<br>952 | [125] |
| $[Mo_2O_4(NCS)_4]^{2-}$<br>950 ± 4 | [35, 123] | $[Mo_2O_4(C_2O_4)_2]^{2-}$<br>983 ± 2 | [35, 139] |
| $[Mo_2O_4(C_2O_4)_2(H_2O)_2]^{2-}$<br>980, 725 [e] | [126, 135, 136] | $(C_5H_5NH)_4[Mo_2O_4(NCS)_6]$ | [134] |

[a] Values below certain complexes are IR frequencies in $cm^{-1}$. The values above 900 $cm^{-1}$ are due to multiple bond Mo—O terminal vibrations, those below 800 $cm^{-1}$ to Mo—O—Mo bridge vibrations.

[b] Abbreviations: bipy = 2,2'-bipyridyl; oxine = 8-hydroxyquinoline anion; acac = acetylacetone anion; *o*-phen = *o*-phenanthroline; EDTA = ethylenediaminetetraacetate anion; 8-$NH_2$Q = 8-aminoquinoline.

[c] L = $(C_6H_5)_3PO$, $(C_6H_5)_3AsO$, $(CH_3)_2SO$.

[d] See text for discussion of this complex.

[e] This is really a Mo(vi) complex [136] and should be formulated $[Mo_2O_5(C_2O_4)_2(H_2O)_2]^{2-}$. See text.


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terms of four dimeric Mo(v) species in aqueous HBr in the concentration range 1.0–8.6 M. At the highest HBr concentration the predominant form is believed to be $[(MoOBr_4)_2]^{2-}$ and no spectral evidence was obtained for $[MoOBr_5]^{2-}$. This is somewhat surprising in view of the fact that salts of $[MoOBr_5]^{2-}$ can be isolated from aqueous HBr solutions [121, 122]. Salts of $[MOX_4]^-$ (M = Mo or W, X = Cl or Br) which is present most likely as bridged dimers, $[M_2O_2X_8]^{2-}$, have been obtained from solutions in $SO_2$ [122].

This brings us to another current problem, *viz.*, the nature of the species of oxomolybdenum(v) in the solid state. Apparently at least four oxo-species can occur in the solid state: $MoO^{3+}$, $Mo_2O_2^{6+}$, $Mo_2O_3^{4+}$, and $Mo_2O_4^{2+}$ (see Fig. 1). The latter two are singly bridged and doubly bridged, respectively, by oxygen. In Table 3 are listed some of the recently prepared and characterized oxo complexes of Mo(v) according to the probable structure [*] of the oxocation.

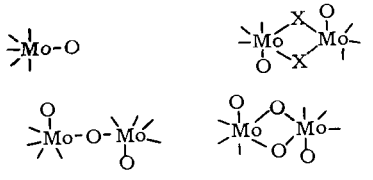

Fig. 1. Possible structures of Mo(v) oxocation species. The strokes simply denote a coordination number of 6.

Recent X-ray structure determination of a xanthate complex, $[Mo_2O_3(C_2H_5OCS_2)_4]$, has revealed a linear Mo–O–Mo bridge, a short M–O bond length of 1.64 Å, and a bridge Mo–O bond length of 1.86 Å [133].

However, the band assignment [133] of 1236 $cm^{-1}$ to Mo=O and either 1046 or 946 $cm^{-1}$ to Mo–O–Mo seems in error. On the basis of the data from Table 2, it would be preferable to assign the 946 $cm^{-1}$ band to Mo=O and bands at about 760 and 765 $cm^{-1}$(shoulder) to Mo–O–Mo. The compound originally formulated as a Mo(v) oxalato complex, $K_2[Mo_2O_4(C_2O_4)_2(H_2O)_2]$ probably is a molybdenum(vi) complex [136], $K_2[Mo_2O_5(C_2O_4)_2(H_2O)_2]$, with bond lengths Mo=O of 1.69 Å, Mo–O (bridging) 1.88, Mo–O (of oxalate) 2.19 and 2.09, and Mo–O (of $H_2O$) 2.33 Å. However, the high value found for the Mo=O stretching frequency, 980$cm^{-1}$, in the compound [126] $[Mo_2O_4(C_2O_4)_2(H_2O)_2]^{2-}$ suggests that there are in reality two nearly identical oxalato complexes, which differ only in the oxidation state of the Mo and in the Mo:O ratio.

The Mo=O frequency in a Mo(vi) complex usually is lower than in a Mo(v) complex by 50–80 $cm^{-1}$. The infrared data available on the $Mo_2O_2^{6+}$ dimers (Table 3) support the bridged structure shown in Figure 1, rather than a structure involving oxygen bridges, since the Mo–O frequencies are all too high to have arisen from the latter. It appears that a coordination number of six is maintained in all series of complexes. The preparation and properties of $MoOCl_3$ have been reported recently [140–142] and the Mo=O stretching frequency has been found as 1020 [141] and 1010 [142] $cm^{-1}$.

Fewer and generally less stable complexes arise with Mo(vi). Compounds derived from $MoO^{4+}$ are few [12], as are those derived from $MoO_3$; the largest number of compounds of Mo(vi) seems to be those of $MoO_2^{2+}$ [12]. Recent work includes a new preparation of $MoOCl_4$ [143], with a value of 990 $cm^{-1}$ recorded [142] for the M=O frequency; preparation [144] and X-ray structure study [145] of $MoO_3$(diethylenetriamine), revealing three mutually *cis* oxygen atoms in an octahedral structure with Mo–O distances of 1.74 Å [145] and only one strong infrared band, at 835 $cm^{-1}$, in the expected region [144]; also an X-ray study of $NaNH_4[MoO_3(C_2O_4)]\cdot 2H_2O$ [146], which consists of infinite Mo–O–Mo–O bent and unsymmterical chains, each Mo being surrounded by a distorted octahedron comprising two terminal oxo oxygens at 1.82 and 1.85 Å, and two oxalato oxygens, in addition to the two bridging oxygens.

The Mo=O stretching frequencies in Mo(vi) compounds (there are as yet few data on the dioxo species) fall in the range 900 ± 10 $cm^{-1}$. That this is lower than the range 960 ± 30 $cm^{-1}$ found for Mo(v) species is due mainly to the presence of two multiply bonded oxygens on the same Mo(vi) atom, which leads to a


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mutual lowering of the bond strength and bond order of each oxygen. No Mo(v) compounds are known for sure to have two multiply bonded terminal oxygens, and there are certainly no spectral data to support such species.

### 3. Tungsten

The compounds of W(v) that have been prepared seem quite analogous to the corresponding Mo(v) compounds[12]. For example, $K_2[WO(NCS)_5]$ has been examined by ESR[124], and $M_2[WOX_5]$ and $M[WOX_4]$ (X = Cl, Br, M = K, Rb, Cs, $(CH_3)_4N$) have been studied magnetically and spectrally[122], $Rb_2[WOCl_5]$ showing a W=O band at 970 $cm^{-1}$.

A large number of compounds of W(VI) have been synthesized by reaction of $WOCl_4$ with primary mono- and diamines, substituted phenols, aromatic secondary and tertiary amines, organic acids, *etc.*[147]. The infrared spectrum of $WOCl_4$ shows a strong W=O absorption at 1020 $cm^{-1}$ in the gas phase (1018 $cm^{-1}$ in $SOCl_2$ and 1025 $cm^{-1}$ in $CS_2$)[142]. In the crystalline state $WOCl_4$ and $WOBr_4$ absorb at 882 and 833 $cm^{-1}$, respectively, owing no doubt to a polymeric chain structure[142].

## IV. Oxocomplexes of Group VIIb Elements

With the exception of $MnO_3F$, the $MnO_3^+$ ion in solution, $MnO(C_5H_5N)$phthalocyanine[12], and some oxohalides of Tc, such as $TcO_3X$ (X = F, Cl), $TcOX_3$ (X = Cl, Br), $TcOX_4$ (X = F, Cl)[148], only oxocompounds of rhenium are known in this group[12].

### 1. Rhenium

Rhenium has an extraordinary capacity for forming multiple bonds to oxygen (and also nitrogen); it forms oxo species in the oxidation states +5, +6, +7, and +4, with the number of examples known decreasing sharply in that order. It is possible to find anionic, neutral, and even cationic complexes of rhenium in the oxidation state +5[12]. The bulk of the oxo complexes derive from this oxidation state[149–156b].

Octahedral Re(v) complexes with only one terminal oxygen show Re=O absorptions in the range 930 to 1015 $cm^{-1}$[149,151,154,156b], where, for example, a 978 $cm^{-1}$ frequency[149] corresponds to an X-ray determined Re=O bond length of 1.60 Å[157]. Re(v) complexes with two terminal oxygens per rhenium, most probably in *trans* positions to each other, show O=Re=O bands at 780–830 $cm^{-1}$; the low values derive from anionic complexes such as $[ReO_2(CN)_4]^{-3}$ (780 $cm^{-1}$) and the higher values from cationic complexes such as $[ReO_2(ethylenediamine)_2]^+$ and $[ReO_2(C_5H_5N)_4]^+$. The lower Re=O stretching frequencies of the dioxo compounds is expected from the very strong *trans* effect that a multiply bonded oxygen should show. This effect also explains the observed lowering of the Re=O frequency in a series of complexes $ReOXY_2(R_3P)_2$ as more strongly *trans*-affecting ligands X in the O=Re–X grouping are substituted[151]. (X = Cl, Br, I, Y = Cl, Br, $OCH_3$, $OC_2H_5$, R = $C_6H_5$, $C_2H_5$).

In the dimers $[ReO_2(RCOO)]_2$ it seems possible that the bands at about 934 $cm^{-1}$ are due to terminal Re=O bonds and that there is also bridging by two oxygens as in the $Mo_2O_4^{4+}$ species, although this possibility requires penta- or tetra-coordinated rhenium depending on whether the RCOO group occupies one or two coordination positions. The complexes $[ReOCl(RCOO)]_2$ have similar Re=O frequencies (about 940 $cm^{-1}$) which suggests double chloride bridging, leaving two terminal Re=O groups.

No infrared frequencies are known for oxorhenium(IV) compounds, but those obtained for Re(VII) compounds are: $ReO_3Cl$, 960 $cm^{-1}$ (bond length 1.76 Å); $Re_2O_7$, 910 $cm^{-1}$; and $KReO_4$, 913 $cm^{-1}$.

## V. Oxocomplexes of Group VIIIb Elements

No oxocomplexes of iron, cobalt, nickel, rhodium, palladium, iridium, or platinum of the types considered here appear to exist, with the possible exception of $PtOF_4$[158], about which little is known.

### 1. Ruthenium

There are very few oxometal compounds of ruthenium[12], and none of them have been investigated with the purpose of definitely establishing the existence of a Ru=O multiple bond. For example, $Cs_2[RuO_2Cl_4]$ was prepared in pure form and some of its properties determined[159], but nothing definitive about the $RuO_2^{2+}$ entity is known. However, it should be a relatively stable species, the oxygens in the octahedral

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$[RuO_2Cl_4]^{2-}$ ion should be *trans*, and the metal-oxygen vibrations should occur around the 780–830 $cm^{-1}$ region, judging from the data on the analogous osmium(VI) species, $Cs_2[OsO_2Cl_4]$.

### 2. Osmium

The oxometal chemistry of osmium is relatively rich, a few +8, one +7, and many +6 compounds being known [12]. Osmium and rhenium possess the greatest tendency among the metals to form multiple bonds also with nitrogen. Recently infrared data on ten dioxo complexes have been tabulated [160]. In complexes of the types $[OsO_2X_4]^{n+}$ and $[OsO_2X_2Y_2]^{n+}$ one can arrange the X and Y ligands according to the effect on the antisymmetric stretching frequency of the *trans* dioxo species as follows:

| Ligand | $2\,OH^-$ $2\,C_2O_4^{2-}$ | $<4\,OH^-$ | $<4\,HN_3$ | $<2\,C_2O_4^{2-}$ | $<4\,CN^-$ | $<4\,Cl^-$ | $<4\,OCH_3^-$ | $\approx 2\,OH^-$ $2\,NO_2^-$ | $<2\,NO_3^-$ $2\,NO_2^-$ |
|---|---|---|---|---|---|---|---|---|---|
| $\tilde{\nu}_{as}$ (O·M=O) | 796 | 800 | 808 | 824 | 830 | 837 | 840 | 840 | 871 $cm^{-1}$ |

Crystal structure data on $K_2[OsO_2(OH)_4]$ and $K_2[OsO_2(CN)_4]$ reveal Os=O bond lengths of 1.77 and 1.75 Å, respectively [12], and the *trans* positioning of the oxygens is verified.

A discussion of the molecular orbitals and bonding in $OsO_2^{2+}$ complexes [161] has drawn a distinction between the $UO_2^{2+}$ and $OsO_2^{2+}$ groups, from which it is suggested that because of the vacant f-orbitals of uranium, the former can form a triple bond whereas the Os–O bond can only have a multiplicity of two. This may account in large measure for the higher (by 50–100 $cm^{-1}$) antisymmetric stretching frequencies observed for $UO_2^{2+}$ complexes.

Finally, there has recently appeared a review article [161a] on osmium and its compounds.

## VI. Oxocomplexes of Elements with 5f-Electrons

Oxocations in this group include the very stable $UO_2^{2+}$, $NpO_2^{2+}$, $NpO_2^+$, $PuO_2^{2+}$, $AmO_2^{2+}$, and $AmO_2^+$, redox-unstable $UO_2^+$ and $PuO_2^+$, and perhaps $UO^{2+}$ and $PuO^{2+}$. More complexes of $UO_2^{2+}$ have been prepared and characterized than for all other oxocations combined. For over a century and a half uranyl complexes have been investigated, and many hundreds of papers dealing with $UO_2^{2+}$ complexes have appeared in recent years. A book, published in 1964, but containing relatively little information obtained after 1960, deals specifically and thoroughly with the spectroscopy and photochemistry of $UO_2^{2+}$ compounds [17].

There is general agreement that the $O{=}U{=}O^{2+}$ entity is linear with very short bonds (1.60–1.92 Å), that the bond orders are between two and three, and that coordination by other ligands occurs in the equatorial plane with four, five, or six ligands. It is most interesting that five ligands in the equatorial plane is the arrangement found at least as often as four or six, giving the uranium a total coordination number of seven [162]. The linear $UO^{2+}$ species is expected to show three fundamental vibrations, $\nu_1$, symmetric stretching, $\nu_2$, bending, and $\nu_3$, antisymmetric stretching. All three bands have been observed in the infrared, not unusual since crystal and solution distortions can cause $\nu_1$ to be IR-allowed. The $\nu_3$ vibration is generally observed as a very strong band in the 900–1000 $cm^{-1}$ region; $\nu_1$ may be found, with lower intensity, in the 780–900 $cm^{-1}$ region; and $\nu_2$ has been observed a few times in the 210–280 $cm^{-1}$ region [17, 21, 163–168].

Infrared-spectroscopic studies of the transuranium ions yielded the data collected in Table 4 [169, 170]. The decrease of over 100 $cm^{-1}$ from $MO_2^{2+}$ to $MO_2^+$ (for M = Np, Am) must be due primarily to a weakening of the M–O $\pi$-bond by virtue of the presence of an additional electron on the quinquevalent metal ion. This result supports the idea that oxometal bonds will in general be weakened by other ligands capable of transferring charge onto the metal ion. The decrease in frequency of $\nu_3$ from solution to solid state must reflect both the stronger ligand character of acetate over water and the tighter binding in a rigid crystalline lattice.

Table 4. Infrared absorption maxima (in $cm^{-1}$) of some uranium and transuranium oxocations.

| fn | in aqueous $HClO_4$ [169] | $\tilde{\nu}_3$ | Solid [170] | $\tilde{\nu}_3$ | $\tilde{\nu}_1$ [a] |
|---|---|---|---|---|---|
| $f^0$ | $UO_2(ClO_4)_2$ | 965 | $NaUO_2(CH_3CO_2)_3$ | 931 | 856 |
| $f^1$ | $NpO_2(ClO_4)_2$ | 969 | $NaNpO_2(CH_3CO_2)_3$ | 934 | 844 |
| $f^2$ | $PuO_2(ClO_4)_2$ | 962 | $NaPuO_2(CH_3CO_2)_3$ | 930 | 818 |
| $f^3$ | $AmO_2(ClO_4)_2$ [b] | 939 | $NaAmO_2(CH_3CO_2)_3$ | 914 | 749 |
| $f^2$ | $NpO_2ClO_4$ | 824 | | | |
| $f^4$ | $AmO_2ClO_4$ | 832 | | | |

[a] Observable only in thick layers.
[b] In $NaClO_4$ solution.

Recently some non-hygroscopic, thermally unstable formate complexes of U(IV) were prepared [171] and


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[171] *B. Sahoo* and *D. Patnaik*, Current Sci. (India) *27*, 243 (1958).

formulated as follows: $UO(HCOO)_2 \cdot NH_4(HCOO)$, 2 $UO(HCOO)_2 \cdot H_2O$. An acetate complex was also isolated and formulated as 2 $UO(CH_3COO)_2 \cdot NH_4(CH_3COO)$. Earlier formulations of U(IV) oxo species have included a nitrate, sulfate, formate, and halides [171]. However, for none of these compounds is any real evidence presented for a mononuclear $UO^{2+}$ entity. A recent infrared study [172] of compounds obtained by thermal decomposition of $UCl_3(OH) \cdot 6H_2O$ failed to yield conclusive evidence for a terminal U=O bond. Bands observed in the 720–735 $cm^{-1}$ region are assumed to arise from O–U–O bridge stretching vibrations, which implies bond orders greater than one, but lower than two. A band at 960 $cm^{-1}$ was found in one of the compounds at a position where a species such as $U{=}O^{2+}$ might absorb, but this band could also be due to a U–O–H segment of the structure. In sum, no firm evidence has been published (to this author's knowledge) which supports the $UO^{2+}$ (or $PuO^{2+}$) species.

## VII. Appendix

Recent work on oxocations of molybdenum has included structural and ESR studies as well as the preparation of new complexes. X-ray structure analysis of $\{[MoO(C_2O_4)H_2O]_2O_2\}^{2-}$ reveals two octahedrally coordinated Mo atoms sharing an edge, terminal Mo=O bond lengths of 1.70 Å, and bridge bond lengths of 1.88 and 1.93 Å [173]. *Cotton* and *Wing* [174] have discussed metal-oxygen multiple bonds, especially those involving molybdenum, considering specifically the relationships among bond lengths, stretching force constants, and stretching frequencies.

The new complexes of Mo(v) include: $MoCl_3 \cdot 2RCN$ (R = $CH_3$, $C_2H_5$, $C_3H_7$); Mo=O stretching frequency 980 $cm^{-1}$; $MoOCl_3 \cdot A$ (A = *o*-phenanthroline, bipyridyl), $\nu_{Mo=O}$ = 975 $cm^{-1}$; $MoOCl_3 \cdot 2P(C_6H_5)_3$, $\nu_{Mo=O}$ = 950 $cm^{-1}$ [175]; $MoOCl_3 \cdot 2R$ (R = tetrahydrofuran, tetrahydropyran), bands at 1000, 985 and at 995, 985 $cm^{-1}$, respectively); $MoOCl_3 \cdot R^1$ ($R^1$ = 1,4-dioxane, 1,4-oxathiane, ethylene glycol dimethyl ether, dimethyl sulfide, diethyl sulfide, di-n-propyl sulfide) [176].

The ESR spectra of $d^1$ Mo(v) complexes are being studied increasingly [177–180]; recently [180] it was reported that $g_{\|} > g_{\perp}$ in $MOX_n^{3-n}$ (M = Mo, W), which is the opposite of what is normally the case.

Chemical and structural studies of oxo-complexes of Re(v) are increasing rapidly [156a–e, 181–184] so that the oxocation complexes of Re(v) are now among the most thoroughly investigated of the oxometal compounds.

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German version: Angew. Chem. *78*, 736 (1966)

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# COMMUNICATIONS

## The Structure of Fulminic Acid, HCNO

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The structure of fulminic acid was hitherto not known with certainty [1]. *H. Wieland* [2] showed that the free acid exists and can be distilled with ether. We have found that the compound, which is liberated from aqueous sodium fulminate by dilute $H_2SO_4$ [2a] and can be sublimed unchanged bellow *ca.* −20 °C/$10^{-4}$ mm, is sufficiently stable in the gaseous state for its IR spectrum to be measured at room temperature. This spectrum [3] indicates that gaseous fulminic acid has the structure of a "formonitrile" oxide, a structure which explains the polymerization and addition reactions of fulminic acid [1]. The spectrum contains a C–H stretching vibration at 3335 $cm^{-1}$ (parallel band); for the form CNOH, however, the O–H stretching vibration is expected at 3600 $cm^{-1}$ [4]. The pseudosymmetric and asymmetric CNO stretching vibrations were found at 1251 and 2190 $cm^{-1}$ (parallel bands). In the region 1000–1400 $cm^{-1}$, the IR spectrum of the form CNOH, however, should contain, besides the $\nu_s$(CNO) band, a second, intense absorption (the NOH bending vibration) [4]. Further, the band at 1250 $cm^{-1}$ is not shifted on deuteration of the compound. The CNO bending vibration at 538 $cm^{-1}$ is a typical perpendicular band with a marked Q branch.

The molecule HCNO may be considered as pseudo-dinitrogen oxide. In fact, the corresponding IR frequencies of HCNO and $N_2O$ show considerable analogy (see table), so that the ground state of fulminic acid can be described approximately by the formulae:

$$H\text{-}C{\equiv}\overset{\oplus}{N}\text{-}\overset{\ominus}{O} \longleftrightarrow H\text{-}\overset{\ominus}{C}{=}\overset{\oplus}{N}{=}O$$

| | $\nu_1$ ($cm^{-1}$) | $\nu_2$ ($cm^{-1}$) | $\nu_3$ ($cm^{-1}$) |
|---|---|---|---|
| $N_2O$ [5] | 1285 | 589 | 2224 |
| HCNO | 1251 | 538 | 2190 |

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[1] Cf. *R. Huisgen*, Angew. Chem. *75*, 612 (1963); Angew. Chem. internat. Edit. *2*, 574 (1963).

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[2a] HCN is formed as a byproduct. Cf., however, *H. Wieland*: Die Knallsäure. Samml. chem., chem.-techn. Vortr. *14*, 385 (1909).

[3] The IR spectra were measured on a Perkin-Elmer spectrophotometer model 21 with LiF and NaCl prisms, and on a Beckman IR 12 instrument, with 1-m gas cuvettes.

[4] Compare, *e.g.*, the corresponding IR frequencies of formaldehyde oxime: *S. Califano* and *W. Lüttke*, Z. physik. Chem., N.F. *6*, 83 (1956).

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## Stimulation of RNA Polymerase in Liver Nuclei by Cortisol in vitro

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The RNA polymerase in cell nuclei is stimulated by hormones *in vivo* [1]. We have now found that cortisol stimulates RNA polymerase in cell nuclei also *in vitro*; the effect appears within a few minutes. Isolated and purified rat liver nuclei were incubated for 1–15 min with cortisol at 37 °C. From these the DNA-dependent RNA polymerase was isolated as Weiss complex [2]. The activity of the RNA polymerase was measured in a system [1c] that synthesises RNA *in vitro*. This system consists of 0.25 mole each of ATP, GTP, and CTP; 0.1 μCi of $^{14}$C–UTP (spec. act. 145 mCi/mmole), creatine phosphate 2.5 μmole, creatine-phosphokinase 5 μg, 2-mercaptoethanol 3 μmole, $MnSO_4$ 2 μmole, and tris[(hydroxymethyl)amino]methane 12 μmole; final volume 0.15 ml; pH 7.9; the enzyme preparation was added in quantities containing 50–100 μg of DNA; incubation time 4 min.

| System | μμmoles of $^{14}$C–UTP incorporated into RNA/(mg of DNA/min) |
|---|---|
| Controls | 89.7 + 7 |
| Nuclei incubated with 20 γ of cortisol/ml, 1 min | 112 +10 ($p$ <0.01) [a] |
| Controls | 136.9 ± 9 |
| Nuclei incubated with 20 γ of cortisol/ml, 5 min | 214 ± 26 ($p$ <0.02) |
| Controls | 67.5 ± 13 |
| Nuclei incubated with 20 γ of cortisol/ml, 10 min | 93 ± 8.9 ($p$ <0.05) |
| Nuclei incubated with 20 γ of pregnanediol/ml, 10 min | 69.3 ± 12 |

[a] $p$ values according to Fisher's t-test, based on 4–6 individual determinations. Cf. *R. A. Fisher* and *F. Yates*: Statistical Tables for Biological Agriculture and Medical Research. Edinburgh 1949.

The rapid increase in enzyme activity (within a few minutes) is explained by assuming that cortisol increases the matrix activity of DNA, perhaps in the sense of a derepression as envisaged by *Jacob* and *Monod* [3].

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German version: Angew. Chem. *78*, 748 (1966)

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## Synthesis of Derivatives of 1,4-Diaza-3,6-diboracyclohexane and 1,4-Diaza-2-boracyclopentane by Reaction of Hydrogen Cyanide with Alkylboranes

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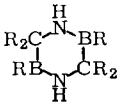
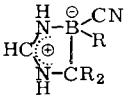
When hydrogen cyanide is passed into triethyl- or tri-n-butylborane (molar proportions 6:1) at room temperature, a colorless oil is obtained that can be partially distilled in a high vacuum. Compound *(1)* crystallizes from the lower-boiling fraction [90–100 °C/0.01 mm Hg for *(1a)*, 120–135 °C/0.01 mm Hg for *(1b)*], and compound *(2)* is obtained when the higher-boiling fraction [85–100 °C/$10^{-3}$ mm Hg for *(2a)*, 160–180 °C/$10^{-3}$ mm Hg for *(2b)*] is rubbed with benzene/chloroform.



*(1)*



*(2)*

*(1a)*, R = $C_2H_5$; m.p. 65 °C; 5 %
*(1b)*, R = n-$C_4H_9$; m.p. 71 °C; 14 %
*(2a)*, R = $C_2H_5$; m.p. 118 °C; 10 %
*(2b)*, R = n-$C_4H_9$; m.p. 121 °C; 2 %

All the products are colorless and stable in air. The 1,4-diaza-3,6-diboracyclohexane derivatives *(1a)* and *(1b)* [1] are readily soluble in nonpolar solvents but sparingly so in polar solvents; the 1,4-diaza-2-boracylopentane derivatives *(2a)* and *(2b)* show the opposite behavior.

The structure of the ethyl derivative *(1b)* follows from degradation by chromyl trichloroacetate [2] to di-n-butyl ketone (52 %), ammonia (12 %), and some 1-butanol, as well as from the spectra: $^{11}$B-NMR [in $CHCl_3$, external standard $BF_3 \cdot (C_2H_5)_2O$], −44 ± 2 ppm [3]; $^1$H-NMR (in $CCl_4$, internal standard tetramethylsilane), τ = 6.4 (2 NH).

Compound *(2a)* dissolves in aqueous acid with loss of 1 mole of HCN. After quantitative precipitation of the HCN as AgCN, oxidation with alkaline hydrogen peroxide yields diethyl ketone (47 %), ethanol (32 %), and ammonia (45 %). Oxidation by air gave some ethylboric acid. – The structure of compound *(2a)* is confirmed also by the spectra: $^{11}$B-NMR [in $CH_3OH$, external standard $BF_3 \cdot (C_2H_5)_2O$], 6.5 ppm; $^1$H-NMR (in $CD_3COCD_3$, tetramethylsilane as internal standard), multiplet at τ = 2.1–2.5 (1 NH and 1 CH), τ = 2.6–3.0 (1 NH), multiplet at τ = 9.4–10.0 (B–$CH_2$–$CH_3$); IR (in KBr), 3410 and 3300 $cm^{-1}$ vs ($\nu_{NH}$), 2180 $cm^{-1}$ m ($\nu_{C\equiv N}$), 1618 $cm^{-1}$ vs ($\nu_{\overset{\oplus}{C}=N}$ [4]. The molecular weight was confirmed by mass spectrometry, the chief fragment having mass 152 = molecular mass (179) – HCN (27) [5].

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[*] Extract from the Dissertation, Universität Erlangen-Nürnberg 1966.

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[3] We thank Prof. *H. Nöth* and *H. Vahrenkamp*, Munich, for measuring and interpreting the $^{11}$B-NMR spectra.

[4] vs = very strong; m = medium.

[5] We thank Dr. *D. Henneberg* and Dr. *P. Binger*, Mülheim/Ruhr, for measuring the mass spectrum.

## Vinylogous Guanidinium and ω,ω-Diaminoacrylamidinium Salts

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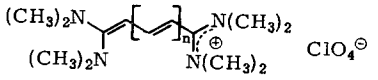
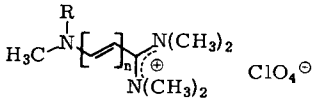
Polymethiniminium salts of types *(1)* and *(2)* can be considered as vinylogous ω,ω-diaminoacrylamidinium and guanidinium salts, respectively.



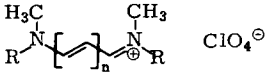
*(1a)*, n = 0; *(1b)*, n = 1; *(1c)*, n = 2; *(1d)*, n = 3



*(2a)*, n = 0, R = $CH_3$;
*(2b)*, n = 1, R = $CH_3$;
*(2c)*, n = 1, R = $C_6H_5$

We have prepared some representatives of the series *(1)* and *(2)* by using the strong nucleophilic base 1,1-bisdimethylaminoethylene *(3)*[1]. This base readily removes methylaniline from the vinylogous formamidinium salts *(4b)* and

$[(CH_3)_2N]_2C{=}CH_2$ *(3)*



R = $C_6H_5$: *(4a)*, n = 0; *(4b)*, n = 1; *(4c)*, n = 2
R = $CH_3$: *(5a)*, n = 2; *(5b)*, n = 3; *(5c)*, n = 4

*(4c)* with double substitution. One mole of the salt *(4b)* and 2 moles of the base *(3)* at 20 °C afford immediately a deep-red solution, from which 7,7-bisdimethylamino-*N,N,N',N'*-tetramethyl-2,4,6-heptatrienamidinium perchlorate *(1c)* crystallizes in 94 % yield on addition of ether 15 min later. This product forms green, shiny leaflets of m.p. 159 °C (from $CH_2Cl_2$/ether), $\lambda_{max}$ = 530 mμ (log ε = 5.20); cf. *(5b)*, 519 mμ (5.30)[2].

Similarly the salt *(4c)* and the base *(3)* afford 9,9-bisdimethylamino-*N,N,N',N'*-tetramethyl-2,4,6,8-nonatetraenamidinium perchlorate *(1d)* in 90 % yield as blue, shiny leaflets of m.p. 138 °C (decomp.) (from $CH_2Cl_2$/ether), $\lambda_{max}$ = 629 mμ (log ε = 5.31); cf. *(5c)*, 625 mμ (5.47)[2].

Compounds *(1c)* and *(1d)* were purified by chromatography in $CH_2Cl_2$ on $Al_2O_3$ (activity III, neutral).

Compound *(4a)* reacts with the base *(3)* in $CH_2Cl_2$ at 20 °C (or in pyridine at 110 °C) giving a 97 % yield of 3-(*N*-methylanilino)-*N,N,N',N'*-tetramethylacrylamidinium perchlorate *(2c)* only. Yellow 5,5-bisdimethylamino-*N,N,N',N'*-tetramethyl-2,4-pentadienamidinium perchlorate *(1b)* is formed only in traces, whereas the reaction of salts *(4b)* and *(4c)* with the base *(3)* (even in a molar ratio of 1:1) cannot be kept at the intermediate stage of vinylogues of compound *(2c)*. Compound *(2c)* forms pale yellow needles of m.p. 113.5 °C (from 2-propanol), $\lambda_{max}$ = 331 mμ (log ε = 4.65). We finally obtained the pentamethine *(1b)* from 1 mole of diethoxycarbonium fluoroborate[3] and 2 moles of *(3)* in $CH_2Cl_2$ at −60 °C, with subsequent conversion into the perchlorate. In this reaction 3-dimethylamino-*N,N,N',N'*-tetramethylacrylamidinium perchlorate *(2b)* is also formed as a result of loss of dimethylamine from *(3)* through the resulting ethanol. Compound *(2b)* could be completely separated by chromatography in $CH_2Cl_2$ on $Al_2O_3$ (activity III, neutral). Compound *(1b)* forms yellow leaflets of m.p. 167 °C (from 2-propanol), $\lambda_{max}$ = 435 mμ (log ε = 5.02); cf. *(5a)*, 416 mμ (5.08)[2].

After treatment of 1 mole of the dimethylformamide-dimethyl sulfate adduct[4] with 1 mole of base *(3)* in $CH_2Cl_2$ at −10 °C we isolated the pure compound *(2b)* in 71 % yield as perchlorate, which formed colorless leaflets, moderately soluble in water, m.p. 128 °C (from 2-propanol), $\lambda_{max}$ = 317 mμ (log ε = 4.62). Treating the tetramethylurea-dimethyl sulfate adduct[5] with base *(3)* under the same conditions afforded, not the trimethine *(1a)*, but tetramethylammonium perchlorate in moderate yield. Attempts to prepare hexamethylguanidinium perchlorate *(2a)* from the tetramethylurea-dimethyl sulfate adduct or *C*-chloro-*N,N,N',N'*-tetramethylamidinium chloride[6] and dimethylamine also failed.

The cations *(1b)*–*(1d)* are strongly basic, being protonated in the carbon chain even by water with decolorization and formation of bis-amidinium ions.

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[2] *S. S. Malhotra* and *M. C. Whiting*, J. chem. Soc. (London) *1960*, 3812.

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[4] *H. Bredereck, F. Effenberger*, and *G. Simchen*, Chem. Ber. *96*, 1350 (1963).

[5] *H. Bredereck, F. Effenberger*, and *H. P. Bayerlin*, Chem. Ber. *97*, 1834 (1964).

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## Synthesis of Isocyanates by Fragmentation of Sulfonylureas

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We have found a new method of preparing isocyanates in the pyrolysis of 1,3-disubstituted sulfonylureas *(1)*. The sulfonamides formed at the same time react with the isocyanates only very sluggishly or not at all.

The sulfonylureas needed are accessible easily and quantitatively from sulfonyl isocyanates *(2)* and amines. The regenerated sulfonamides *(3)* can be readily reconverted into sulfonyl isocyanates by treatment with phosgene[1].

$$\underset{(2)}{RSO_2NCO} + R'NH_2 \rightarrow \underset{(1)}{RSO_2NHCONHR'}$$

$$\underset{(1)}{RSO_2NHCONHR'} \xrightarrow{\Delta} \underset{(3)}{RSO_2NH_2} + R'NCO$$

$$\underset{(3)}{RSO_2NH_2} + COCl_2 \rightarrow \underset{(2)}{RSO_2NCO} + 2\,HCl$$

Sulfonylureas can be stored in the solid state, so that the isocyanates can be prepared as required by heating sulfonylureas in a distillation apparatus. If the alkyl group is primary, it is advantageous to use a high-boiling solvent such as *o*-dichlorobenzene, 1,2,4-trichlorobenzene, or 2-chloronaphthalene.

| Isocyanate [a] | B.p. (°C/mm Hg) | Yield (%) |
|---|---|---|
| $(CH_3)CH{-}NCO$ | 76/760 | 75 |
| $(CH_3)_3C_2{-}NCO$ | 84–85/760 | 92.5 |
| $C_2H_5O{-}CH_2{-}CH_2{-}NCO$ | 140–142/760 | 43 |
| $CH_3O{-}(CH_2)_3{-}NCO$ | 146–148/760 | 35.1 |
| $CH_2{=}CH{-}CH_2{-}NCO$ [b] | 85–87/760 | 59 |
| $C_6H_{11}{-}NCO$ | 150–155/760 | 88 |
| $C_6H_5{-}NCO$ | 160–162/760 | 58.2 |
| $2\text{-}ClC_6H_4{-}NCO$ | 105/25 | 55.2 |

[a] Prepared from *p*-toluenesulfonylureas.
[b] In 1-chloronaphthalene as solvent.

Since isolation of the sulfonylureas is not essential, the amines can also be converted directly into isocyanates by reaction with arenesulfonyl isocyanates.

*Experimental*:

98.5 g (0.5 mole) of *p*-toluenesulfonyl isocyanate is dropped into a solution of 36.5 g (0.5 mole) of t-butylamine in 500 ml of *o*-dichlorobenzene. When the mixture is heated at 160–180 °C, 38 g (77 %) of t-butyl isocyanate (b.p. 84–85 °C) distils off.

The method described above is particularly suitable for preparation of isocyanates that can react further with hydrogen chloride. For example, ethoxyethyl isocyanate cannot be prepared by treatment of the amine with phosgene directly [2], but is accessible in 43 % yield by our method.

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[1] *H. Ulrich*, Chem. Reviews *65*, 369 (1965).

[2] *W. Sicfken*, Liebigs Ann. Chem. *562*, 75 (1949).

## The Stereochemistry of Pentaaryl Derivatives of Phosphorus, Arsenic, and Antimony

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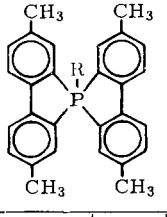
Penta-*p*-tolyl-phosphorane, -arsenic, and -antimony (which can be synthesized by the tosylimine method [1]) at room temperature give only one methyl-proton signal in the $^1$H-NMR spectrum ($CS_2$ solutions), namely at $\delta$ = 2.15, 2.27, and 2.24 ppm, respectively. The singlet for the methyl group in the spectrum of penta-*p*-tolylphosphorane remains unchanged even when the solution is cooled to −60 °C [2]. The equivalence of the five tolyl groups thus demonstrated is compatible neither with the trigonal-bipyramidal structure *(1)* (which has been proved for crystalline pentaphenylphosphorane [3]) nor with the tetragonal-pyramidal structure *(2)* (which is present in solid pentaphenylantimony [4]), since two ligand positions can be differentiated in structures of each of these two types.

The experimental results are, however, intelligible if one assumes that the pentacoordinated molecule in solution undergoes rapid transformation between the structures *(1)* and *(2)*, so that the differentiable ligand positions become averaged [5].

*(1)* *(2)* *(1)*

Further information can be obtained from the series of spirocyclic phosphoranes of type *(3)* [3], whose $^1$H-NMR spectra, measured for $CS_2$ solutions at room temperature, show characteristic differences for the methyl-proton resonances according to the size of the group R.

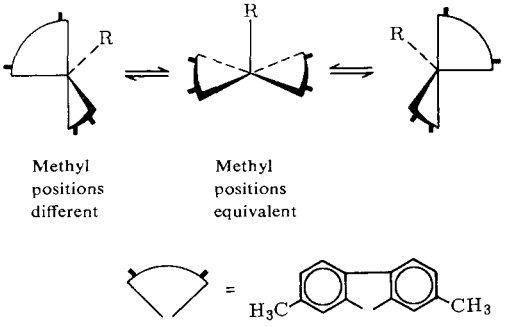


*(3)*

| R: | Phenyl | 2-Naphthyl | 2-Biphenylyl | 1-Naphthyl | 9-Anthryl |
|---|---|---|---|---|---|
| Nature of signal | Sharp | Sharp | Diffuse [a] | Sharp | Sharp |
| No. of signals | 1 | 1 | — | 2 | 2 |
| $\delta$ [ppm] | 2.14 | 2.09 | 1.85–2.35 | 1.97/2.08 | 1.87/2.10 |

[a] Split into four singlets at −60 °C.

Thus here also rapid intramolecular exchange of positions occurs which is slowed down with increasing bulkiness of the group R until finally, with the 1-naphthyl and the 9-anthryl derivative, the trigonal-bipyramidal structures achieve such a long life that two discrete methyl signals appear in the $^1$H-NMR spectrum, one for the axial and another for the equatorial position of the methyl group. In spirophosphoranes the tetragonal-pyramidal form probably has the character of a transition state [6].




Received: June 6th, 1966 [Z 258 IE]
German version: Angew. Chem. 78, 749 (1966)

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[2] Pentamethylantimony also gives only a single methyl-proton signal down to −100 °C: *E. L. Muetterties*, *W. Mahler*, *R. Schmutzler*, and *K. J. Packer*, Inorg. Chem. *3*, 1302 (1964).

[3] *P. J. Wheatly*, J. chem. Soc. (London) *1964*, 2206.

[4] *P. J. Wheatly*, J. chem. Soc. (London) *1964*, 3718.

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## Conversion of Isocyanates into Isothiocyanates by Reaction with *O,O'*-Diethyl Hydrogen Dithiophosphate

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We have found that the exothermic reaction of *O,O'*-diethyl hydrogen dithiophosphate *(1)* with aliphatic or aromatic mono- or di-isocyanates leads exclusively to the *N*-alkyl or *N*-aryl derivatives [1] *(2)* of *S*-carbamoyl *O,O'*-diethyl dithiophosphate only if the temperature is kept below 40 °C. At higher temperatures the compounds *(2)* decompose to isothiocyanates and a mixture of sulfur-containing polyphosphoric acids, *O,O',O''*-triethyl thiophosphate, triethyl phosphate, and numerous unidentified products in small quantities. The structures of the products *(2)* were proved by elemental analysis and IR spectroscopy.

*Leber* [2], who studied the thermal decomposition of compound *(2)*, R = $C_6H_5$, found some diphenylurea but apparently did not recognize the isothiocyanates. Under our conditions we did not find dissociation of compounds *(2)* back to *(1)* and isocyanates, though *Leber* observed this in $CH_2Cl_2$ solution. Alkyl derivatives of *(2)* are less stable thermally than the aromatic analogues; thus, compound *(2)*, R = butyl, decomposes at 50 °C, whereas *(2)*, R = phenyl, decomposes appreciably only at 70 °C. Compounds of series *(2)* are stable at room temperature.

We have exploited the decomposition of compounds *(2)* for the conversion of isocyanates into the corresponding isothiocyanates on a preparative scale and in most cases have obtained yields between 50 and 75 %.

$$RNCO + HSPS(OC_2H_5)_2 \rightarrow \underset{(1)}{RNHCO-SPS(OC_2H_5)_2} \xrightarrow{\Delta} \underset{(2)}{RNCS}$$

| R | (2), M.p. (°C) | (2), $n_D^{25}$ | (2), Yield (%) | RNCS Yield (%) |
|---|---|---|---|---|
| $C_2H_5$– | liquid | 1.5125 | 98.5 | 57 |
| i-$C_3H_7$– | 70.5–71.5 | | 98 | 68.5 |
| n-$C_4H_9$– | liquid | | 97 | 73.5 |
| –$(CH_2)_6$– | 65–66 | | 97 | 31 |
| OCN–$(CH_2)_6$– | liquid | | 94.5 | – |
| $C_6H_5$– | 56 | | 95 | 69.5 |
| *m*-$CH_3$–$C_6H_4$– | 45–46 | | 99 | 61 |
| *o*-Cl–$C_6H_4$ | liquid | 1.5815 | 100 | 44 |
| *p*-Cl–$C_6H_4$– | 69–70 | | 74 | 54 |
| 3,4-$Cl_2C_6H_3$– | 76–77 | | 96 | 73.5 |
| *m*-$NO_2$–$C_6H_4$– | 80–81 | | 85.5 | 48 |
| 4-Methyl-1,3-phenylene | 115–117 | | 100 | 70.5 |

*Example of Synthesis*:

112.8 g (0.604 mole) of *O,O'*-diethyl hydrogen dithiophosphate is added dropwise to 60 g (0.604 mole) of n-butyl isocyanate with stirring, the temperature being kept at 20 to 25 °C by use of a cooling bath. At the end of the reaction the *S*-butylcarbamoyl *O,O'*-diethyl dithiophosphate (a straw-colored oil) is heated for 2 hours at 125–130 °C. Then, after cooling, the solution is set aside for several hours, and the upper layer is decanted, extracted with ice-water, dried with anhydrous sodium sulfate, and distilled through a 90 cm spinning-band column. Yield: 51 g of n-butyl isothiocyanate.

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[1] We did not obtain the *N*-phenyl derivative, but merely its decomposition products, under the conditions described by *A. N. Pudovik* and *A. V. Kuznetsova*, Ž. obšč. Chim. *25*, 1369 (1955); *Houben-Weyl*: Methoden der Organischen Chemie. Thieme Verlag, Stuttgart 1955, Vol. 12/2, pp. 689, 823–824.

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## Preparation and X-Ray Investigation of Higher Uranium Nitrides

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Nitrides of uranium have been repeatedly studied in recent years because of the importance of the mononitride as reactor fuel, yet there is no generally accepted opinion about the composition of the various nitrides that can be obtained from metallic uranium (produced from $UH_3$) and nitrogen at 1 atm pressure.

Between 470 and 1000 °C we have obtained the following nitrides $UN_x$:

| Temp. (°C) | 470 | 510 | 580 | 700 | 770 | 830 | 930 | 1000 |
|---|---|---|---|---|---|---|---|---|
| $x$ | 1.74 | 1.76 | 1.68 | 1.67 | 1.64 | 1.63 | 1.58 | 1.55 |

The proportions of nitrogen given are accurate within 1 %. The time for nitrogen uptake was 62 hr at 470 °C, 42 hr at 510 °C, and less than 30 min at 1000 °C. To prevent further nitridation during cooling, the nitrides were either quenched at the end of the reaction time or were cooled slowly under helium.

Decomposition of the $UN_{1.74}$ in a stream of hydrogen (100 ml/min) at 800 °C gave $UN_{1.62}$ after 2 hr, $UN_{1.60}$ after 4 hr, $UN_{1.58}$ after 6 hr, and $UN_{1.45}$ after 20 hr. The nitrogen content fell rapidly as far as $UN_{1.62}$ (the composition of this material corresponds approximately to an equilibrium at 1 atm $N_2$ pressure). Further decomposition as far as $UN_{1.45}$ occurs more slowly and at an almost constant rate. $UN_{1.74}$ is decomposed to pure uranium mononitride within 1.5 hr in an $H_2$ stream at 1200 °C. We found the lattice constant of UN (NaCl type) to be $a = 4.890 \pm 0.002$ Å, in agreement with data in the literature.

The lattice constants of the nitrides $UN_x$ obtained by direct nitridation or by decompositon in an $H_2$ stream decreased linearly with increasing nitrogen content from $10.700 \pm 0.003$ Å for $UN_{1.50}$ to $10.628 \pm 0.008$ Å for $UN_{1.76}$[1]; the wider limit of error is due to increase, at high glancing angle, in the width of the lines and in the background with increasing nitrogen content.

| $x$ | 1.45 [2] | 1.55 | 1.58 | 1.60 | 1.62 | 1.64 | 1.67 | 1.71 [3] | 1.76 |
|---|---|---|---|---|---|---|---|---|---|
| $a$ (Å) | 10.700 | 10.692 | 10.680 | 10.675 | 10.665 | 10.662 | 10.650 | 10.645 | 10.628 |

*Rundle et al.*[4] give lattice constants of $10.700 \pm 0.005$ Å for $UN_{1.50}$ and $10.601 \pm 0.005$ Å (recalculated from kX units) for $UN_{1.75}$.

All the nitrides prepared by us with $x \geq 1.50$ had the body-centered cubic $Mn_2O_3$ structure. The continuous decrease in intensity of the weak diffraction lines characteristic of this structure type that occurred on transition from $UN_{1.50}$ to $UN_{1.76}$ indicates a one-phase transition from the $Mn_2O_3$ structure to the face-centered cubic $CaF_2$ structure of $UN_2$, as was assumed also by *Rundle et al.*[4]. We assume that in this process the nitrogen is taken into the $UN_{1.50}$ lattice statistically. At $UN_{1.76}$ the number of weak lines has been reduced to five[5].

We found no indication in the diffraction patterns for the existence of discrete, stable phases such as have been demonstrated for the $PrO_{1.50}$–$PrO_{2.0}$ system[6].

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German version: Angew. Chem. *78*, 750 (1966)

[1] The values were obtained by extrapolation against $\cos^2\Theta$ (camera diameter 57.3 mm, asymmetrical film position).

[2] The diffraction diagram for this nitride showed some weak lines due to UN as well as the lines due to $UN_{1.50}$.

[3] We obtained this nitride by treatment in an $H_2$ stream for 5 hr at 500 °C.

[4] *R. E. Rundle, N. C. Baenzinger, A. S. Wilson*, and *R. A. McDonald*, J. Amer. chem. Soc. *70*, 99 (1948).

[5] For further details of the transition from the $Mn_2O_3$ type to the $CaF_2$ type see *G. Brauer* and *H. Gradinger*, Z. anorg. allg. Chem. *276*, 209 (1954).

[6] Cf., for instance, *B. G. Hyde, E. E. Garver, U. E. Kuntz*, and *L. Eyring*, J. physic. Chem. *69*, 1667 (1965); *J. M. Honig, A. F. Clifford*, and *P. A. Faeth*, Inorg. Chem. *2*, 791 (1963); *L. Eyring* and *N. C. Baenziger*, J. appl. Physics *33*, 428 (1962).

## An Organometallic Compound with Two-coordinated Fluorine Atoms

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An X-ray structure analysis[1] recently carried out on the compound $K[(C_2H_5)_3Al$–$F$–$Al(C_2H_5)_3]$ confirmed the suggestion by *Ziegler et al.*[2] that a two-coordinated fluorine atom occurs in the anions of this complex organoaluminum fluoride. Surprisingly, however, it was found that the Al–F–Al bridge is linear. This may be taken as evidence for sp-

hybridized fluorine atoms in strong (p → d)π-interaction with the aluminum atoms. We have now synthesized an electroneutral compound containing the isoelectronic system Si–F–Al and find similarly remarkable bonding relations.

Fluorotrimethylsilane reacts at about 0 °C quickly and completely with an equivalent amount of triethylaluminum, forming a colorless mobile liquid of m.p. −81 to −79 °C. Fluorotrimethylsilane can no longer be removed from this substance at −25 °C in a vacuum. Clearly, under these conditions, the two components undergo complex formation:

$$2\,(CH_3)_3SiF + [Al(C_2H_5)_3]_2 \rightarrow 2\,(CH_3)_3Si{-}F{-}Al(C_2H_5)_3 \qquad (1)$$

The resulting triethylaluminum-fluorotrimethylsilane *(1)* is stable even at room temperature. Its structure follows from the $^1$H-NMR spectrum, which contains a doublet for the Si-bound methyl groups with $\delta = -10.5$ Hz as well as the triplet ($\delta = -46.5$ Hz)[3] and the quartet ($\delta = +20.3$ Hz) with $J(H{-}C{-}C{-}H) = 7.2$ Hz for the ethyl groups. The relative areas of the signal groups are 9:9:6. The doublet signal is accompanied by $^1H{-}C{-}^{29}Si$ satellites, with $J(^1H{-}C{-}^{29}Si) = 7.05$ Hz. It is, however, noteworthy that the coupling constant $J(^1H{-}C{-}Si{-}^{19}F)$ of 9.4 Hz is almost 30 % greater than that of free fluorotrimethylsilane (J = 7.35 Hz)[4]. This indicates an increased s-character of the fluorine orbitals concerned in the Si–F linkage, as is to be expected on hybridization of the fluorine atom in the direction of increasing sp-character. Since the coupling constants $J(^1H{-}^{13}C)$ and $J(^1H{-}C{-}^{29}Si)$ are only very slightly changed on complex formation[4], the increase in $J(^1H{-}C{-}Si{-}^{19}F)$ is to be attributed mainly to changes in the Si–F linkage.

Compound *(1)* should therefore show angle widening at the fluorine atom, corresponding at least to that of the oxygen atom of the isosteric hexaalkyldisiloxanes $R_3Si{-}O{-}SiR_3$ (140 °) or even that in the anions $[R_3Al{-}F{-}AlR_3]^-$ (180 °).

Compound *(1)* decomposes above 30 to 35 °C into ethyltrimethylsilane and fluorodiethylaluminum[5]. These two products can be isolated almost quantitatively (98.8 and 93.5 %, respectively) by distillation. Trimethylaluminum-ether adduct does not react with fluorotrimethylsilane.

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[1] *G. Natta, G. Allegra, G. Perego,* and *A. Zambelli,* J. Amer. chem. Soc. *83,* 5033 (1961).

[2] *K. Ziegler, R. Köster, H. Lehmkuhl,* and *K. Reinert,* Liebigs Ann. Chem. *629,* 33 (1960).

[3] Measured for the pure substance with a 5 % solution of tetramethylsilane in $CCl_4$ as external standard; Varian-A-60, 60 MHz.

[4] *H. Schmidbaur,* J. Amer. chem. Soc. *85,* 2336 (1963).

[5] *A. W. Laubengayer* and *G. F. Lengnick,* Inorg. Chem. *5,* 503 (1966).

## Triorganosilyl Hypochlorites

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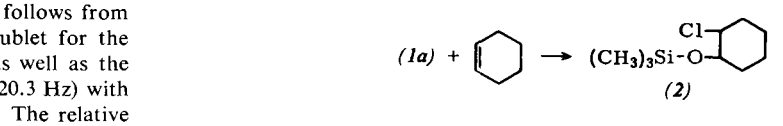
According to *Berry*[1], bistriorganosilyl peroxides are formed by the action of chlorine on sodium triorganosilanolates. Repetition of this work showed that the hitherto unknown triorgaonsilyl hypochlorites, and not silyl peroxides, are formed. On treatment of sodium trimethylsilanolate at −5 to 0 °C, or sodium triphenylsilanolate at −20 °C, with the calculated amount of chlorine in dry $CCl_4$, trimethyl- *(1a)* or triphenylsilyl hypochlorite *(1b)*, respectively, was produced in more than 80 % yield:

$$R_3Si{-}O{-}Na + Cl_2 \rightarrow R_3Si{-}O{-}Cl + NaCl$$

*(1a)*, R = $CH_3$
*(1b)*, R = $C_6H_5$

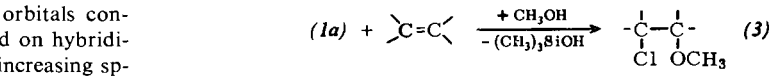
A $CCl_4$ solution of product *(1a)* showed a sharp UV absorption band at 260 mμ characteristic of the hypochlorite group, but this band from *(1b)* was overlaid by the broad, fine-structure bands of the phenyl groups.

Compounds *(1a)* and *(1b)* have not yet been isolated in the pure state, since they decompose even in solution in the dark at 0 °C, with chlorination of the organic substituents on the silicon, and they have strong chlorinating action in general. They undergo electrophilic addition to olefins: *(1a)* and cyclohexene (molar ratio 1:1) in boiling $CCl_4$ containing catalytic amounts of *p*-toluenesulfonic acid give 1-chloro-2-(trimethylsiloxy)cyclohexane *(2)* (yield *ca.* 15 %), which can also be obtained from cyclohexene oxide and chloro(trimethyl)silane[2]. Appreciably better yields of product *(2)*




*(2)*

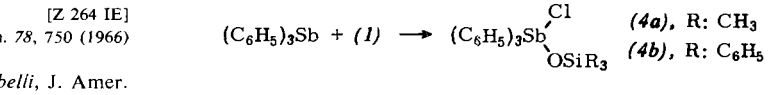
were obtained when *ca.* 1 mole of trimethylsilanol were added. In the presence of methanol, compound *(1a)* reacts with olefins analogously to t-butyl hypochlorite[3], yielding methyl β-chloro-ethers *(3)*: with 1-heptene it gives 1-




*(3)*

chloro-2-methoxyheptane, and with cyclohexene 1-chloro-2-methoxycyclohexane.

Compounds *(1a)* and *(1b)* liberate an equivalent amount of iodine from iodide solutions. Electrophilic addition to triorgano derivatives of elements of Group 5, which is fast even at 0 °C and gives good yields, is particularly suited for detection of hypochlorites. Thus the stibinoheterosiloxanes *(4a)* (m.p. 89–90 °C, from pentane; yield 70 %) and *(4b)* (m.p. > 200 °C (decomp.), from benzene/pentane; yield 84 %) were obtained from *(1a)* and *(1b)*, respectively, and $Sb(C_6H_5)_3$. The arsenic compounds analogous to *(4)* were obtained on use of triphenylarsine.




*(4a)*, R: $CH_3$
*(4b)*, R: $C_6H_5$

Received: June 20th, 1966 [Z 265 IE]
German version: Angew. Chem. 78, 751 (1966)

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## Trifluoromethanesulfonylpentacarbonylmanganese

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Trifluoromethanesulfonyl chloride *(1)*[1] and the strong Lewis base $[Mn(CO)_5]^\ominus$ *(2)* (molar ratio 1:1) in tetrahydrofuran at −60 °C react according to eq. (a), giving a deep

$$\underset{(1)}{CF_3SO_2Cl} + \underset{(2)}{[Mn(CO)_5]^\ominus} \rightarrow \underset{(3)}{CF_3SO_2Mn(CO)_5} + Cl^\ominus \qquad (a)$$

orange-yellow substance that is stable in air, soluble in most organic solvents, and diamagnetic and melts between 50 and 53 °C. On the basis of elemental analysis and its IR spectrum it is considered to be trifluoromethanesulfonyl-

pentacarbonylmanganese *(3)*. $ClMn(CO)_5$ is always obtained as by-product and can be separated from *(3)* by virtue of its insolubility in diethyl ether.

If, in place of the chloride *(1)*, $FSO_2Cl$, whose fluorine atom is still more electronegative than the $CF_3$ group, is used, then fission to $SO_2$, $F^{\ominus}$, and $Cl^{\oplus}$ occurs in presence of the carbonyl *(2)*; $Cl^{\oplus}$ and *(2)* give $ClMn(CO)_5$ quantitatively.

The IR spectrum of compound *(3)* (in $CH_2Cl_2$), in accord with the pseudo-$C_{4v}$ symmetry, includes four CO absorption bands at very short wavelength: 2158(vs) ($A_1$), 2100(s) ($B_1$), 2045 and 2041(vs) (E), and 2028(m-s) $cm^{-1}$ ($A_1$). The lowering of symmetry causes the IR-forbidden $B_1$ vibration to become active. Because of the electron-attracting $CF_3$ group, the S-O stretching vibrations of compound *(3)* are shifted towards short wavelengths compared to those of $CH_3SO_2Mn(CO)_5$ [2], but quite considerably to longer wavelengths in comparison with the chloride *(1)*, since the Mn atom provides sufficient d-electrons for metal-sulfur back-donation: $\nu_{as}$ = 1217.5(m-s), $\nu_s$ = 1098(m) $cm^{-1}$. This corresponds to a noteworthy weakening of the $(p_\pi-d_\pi)O-S$ bond and simultaneously a strengthening of the bonds to the terminal CO groups. The C–F frequencies appear at 1204(m) and 1154(m) $cm^{-1}$. The weak absorption of the solid in KBr at 807 $cm^{-1}$ can be assigned to the symmetrical stretching vibration of the C–S bond. In the UV spectrum compound *(3)* shows an intense absorption maximum at 280 mμ.

Received: June 21st, 1966 [Z 266 IE]
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## Separation of Conformational Isomers of a Nitrosamine

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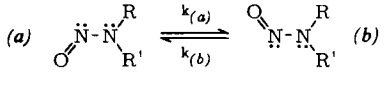
The planar conformations *(a)* and *(b)* of nitrosamines are favored by mesomerism. If R and R′ are different, conformational isomers may arise, but their existence has been indicated merely in equilibrium [1]. Reorientation of the nitroso group in *(1)* requires a free energy of activation of about 23 kcal/mole [2]. This corresponds to the limiting value of $\Delta G^{\ddagger}$, above which *(a)* and *(b)* should be stable in solution at room temperature [3].




*(1)*, R: R′: $CH_3$
*(2)*, R: = $CH_2-C_6H_5$, R′: 2,6-$(CH_3)_2C_6H_3$
*(3)*, R: $CH_2-C_6H_5$, R′: $CH(CH_3)_2$

We have succeeded in separating the isomers of compound *(2)* by two-fold preparative thin-layer chromatography at 6 °C on silica gel (Merck $HF_{254}$) with benzene as the solvent. The mixture of *(2a)* and *(2b)*, m.p. 57–80 °C, was prepared by nitrosation of *N*-benzyl-2,6-dimethylaniline.

The isomers were identified by their $^1$H-NMR spectra in $CCl_4$:

| | τ($CH_2$) | τ($CH_3$) | $R_F$ | M.p. (°C) |
|---|---|---|---|---|
| *(2a)* | 4.59 | 8.36 | 0.4 | 62–63.5 |
| *(2b)* | 5.09 | 8.11 | 0.6 | 86.5–88 |

The nitrosamine structures are also in accord with the infrared spectra, which are similar for both isomers. Elemental analyses and molecular weights correspond to formula *(2)*. The compounds are stable in the solid state. In $CCl_4$ at 36.5 °C an equilibrium mixture [37.5 % of *(2a)*] is formed, starting either from *(2a)* or from *(2b)*, with a half-life of 86 min. Thence can be calculated the rate constants $k_{(2a)} = 8.6 \times 10^{-5}$ and $k_{(2b)} = 5.2 \times 10^{-5}$ $sec.^{-1}$, and $\Delta G^{\ddagger}_{(2a)} = 23.9 \pm 0.2$ and $\Delta G^{\ddagger}_{(2b)} = 24.2 \pm 0.2$ kcal/mole.

Compound *(3a)* can be enriched by crystallization to 75 % purity, and *(3b)* to about 94 % purity [4]. Complete separation was not yet achieved; nor was it achieved for several similar nitrosamines, because they equilibrate somewhat more easily than *(2)*, *e.g.* $\Delta G^{\ddagger}_{(3a)} = 22.3$ and $\Delta G^{\ddagger}_{(3b)} = 23.2$ kcal/mole. Comparison of these values with those for *(2)* shows that the 2,6-dimethylphenyl group contributes little to the conformational stability of compounds *(2a)* and *(2b)*.

Enrichment of rotational isomers that are stabilized by partial double bonds has hitherto been possible only for a thioformamide [5], for mesitylenecarboxamides [6], and for 2,6-dimethylphenylformamides [7]; some rotational isomers of mesitylenethiocarboxamides [4] have been completely separated. It is uncertain whether interconversion of nitrosamines occurs by internal rotation, as inversion on the nitroso-nitrogen atom is possible also.

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## A New Principle of Biosynthesis involving Secoanthraquinones [1]

By Prof. B. Franck and F. Hüper

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and Doz. D. Gröger and Dr. D. Erge

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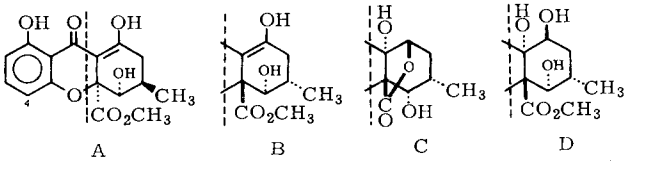
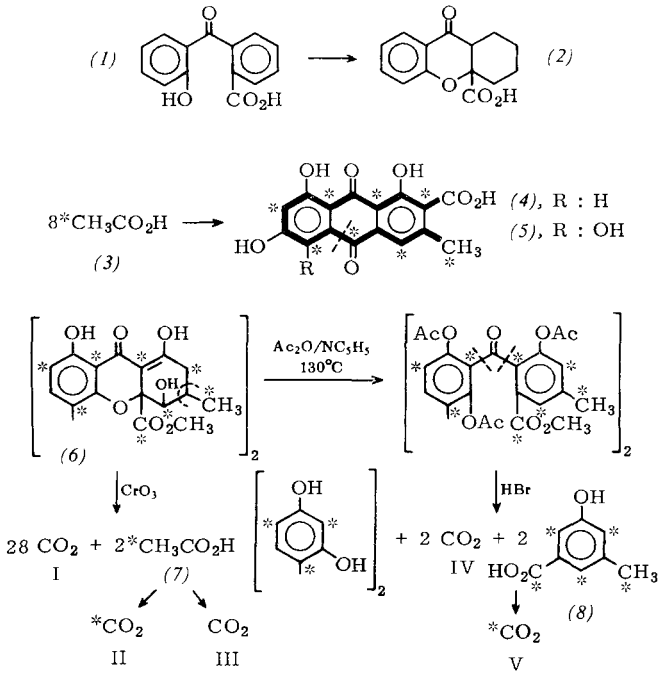
A new principle of biosynthesis can be recognized in the ten ergot dyes (ergochromes) whose structures have recently been elucidated [1–4]. These constitute an unusually complete group of natural products; they comprise all ten dimer combinations of the four monomeric xanthones A to D, the monomers being linked at positions 4,4′ or 2,2′.




The occurrence of the ergochromes in ergot [2, 3] concurrently with the hydroxyanthraquinones *(4)* and *(5)* [5,6], as well as model experiments [7], made it seem possible that the ergochromes are formed from anthraquinones by way of seco-

anthraquinones, in the steps: (a) oxidative fission of the anthraquinone to benzophenonecarboxylic acids of type *(1)*, similar to the Baeyer-Villiger oxidation; and (b) ring closure to xanthone derivatives *(2)* [7].

In agreement with this hypothesis we have found that ergochrome AB *(6)*, as well as the anthraquinones [8], are formed from acetic acid units, the C atoms of the acetic acid being arranged in the ergochrome in accord with the biosynthetic route *(3)* → *(4)* → *(6)*. For the study of this biosynthetic route it is noteworthy that the ergot fungus *Claviceps purpurea* forms the same anthraquinones and ergochromes in liquid cultures [9] as on rye plants – this is generally not the case for ergot alkaloids.




A total of 29 mg of $^{14}CH_3CO_2Na$ (spec. activity 1.41 mCi/mmole) was fed to ten 17-day-old 200 ml liquid cultures of the fungus. The mycelium harvested after a further 17 days yielded 200 mg of ergochrome AB *(6)* [3] after dilution with inactive ergochrome AB; it had a specific activity of $2.495 \times 10^{-3}$ mCi/mmole. By the degradations shown in the formula scheme the activities of the C atoms in the Kuhn-Roth acetic acid *(7)* and in the carbonyl and carboxyl groups of ergochrome AB, which are of particular interest for this investigation, were determined singly, those of others in groups. The number of labeled atoms thus found agreed with that required by our biosynthetic scheme within experimental error (see Table). The distribution of activity in the ergochrome AB obtained after feeding of $CH_3{}^{14}CO_2Na$ also agreed with our biosynthetic scheme.

Measured activities of the degradation products of ergochrome AB *(6)*.

| Substance | Spec. activity (mCi/mmole)×10⁶ | Labeled C atoms per molecule | |
|---|---|---|---|
| | | theor. | found [10] |
| *(6)* | 2500 | 16 | 16.0 |
| I | 72.5 | 0.5 | 0.47 |
| II | 132 | 1 | 0.85 |
| *(7)* | 132 | 1 | 0.85 |
| III | 0.1 | 0 | 0.01 |
| IV | 12.7 | 0 | 0.08 |
| V | 96.0 | 1 | 0.62 |
| *(8)* | 680 | 5 | 4.4 |

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[1] Part 15 of Ergot Dyes. – Parts 12–14: *B. Franck, G. Baumann, E. M. Gottschalk, U. Ohnsorge*, and *F. Hüper*, Chem. Ber., in press.

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[10] The values found were referred to the activity of ergochrome AB *(6)* with 16 radioactive carbon atoms without allowance for a possible radioactivity of the $CH_3O$ groups.

## *N*-Trimethylsilyl-substituted Sulfurous Diamides and Monoimides; *N*-Alkyl-*N'*-phenyl(sulfur diimides)

By Dr. O. J. Scherer and P. Hornig

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Lithium *N*-alkyltrimethylsilylamides [1] add to *N*-sulfinylaniline (molar ratio 1:1) in ice-cooled petroleum ether giving the *N*-lithium derivatives *(1)* of *N'*-(trimethylsilyl)-sulfurous diamides (*ca.* 70 % yield). These products are sensitive to air and insoluble in petroleum ether, but excellently soluble in diethyl ether.

$$(CH_3)_3Si\text{-}\overset{R}{N}\text{-}Li + C_6H_5\text{-}N{=}S{=}O \longrightarrow C_6H_5\text{-}\overset{Li\,O\,Si(CH_3)_3}{N\text{-}S\text{-}N}\text{-}R$$

R : $CH_3$, $C_2H_5$, *(1)*

The compounds *(1)* react *inter alia* with $(CH_3)_3SnCl$ and $AlCl_3$. With $(CH_3)_3SiCl$ (molar ratio 1:1) in petroleum ether at 20 °C they afford in *ca.* 60 % yields the sulfurous diamides

$$(1) + (CH_3)_3SiCl \xrightarrow{-LiCl} C_6H_5\text{-}\overset{(CH_3)_3Si\,O\,Si(CH_3)_3}{N\text{-}S\text{-}N}\text{-}R$$

*(2)*

*(2)* [*(2a)*: R = $CH_3$, m.p. 27–29 °C; *(2b)*: R = $C_2H_5$, m.p. 25–27 °C], whose $^1H$–NMR signals have the calculated relative areas [*(2a)*: calc. 9:9:5:3, found 9:9:5.2:2.8; *(2b)*: calc. 9:9:5:5, found 9:9:5.1:4.9].

Attempts to distil compounds *(2)* led to loss of hexamethyldisiloxane above 100 °C. The sulfur diimides *(3)* formed could be isolated nearly pure and were identified by $^1H$–NMR spectroscopy. The lithium derivatives *(1)* and $AlCl_3$ (molar ratio 3:1) in petroleum ether give *ca.* 50 % yields of *N*-alkyl-*N'*-phenyl(sulfur diimides) *(3)* [*(3a)*: R = $CH_3$, b.p. 52 to 54 °/0.1 mm; *(3b)*: R = $C_2H_5$, b.p. 65–67 °/0.1 mm] as orange liquids which give the expected $^1H$–NMR signals

$$(1) + {}^1/_3\,AlCl_3 \xrightarrow{-LiCl} C_6H_5{-}N{=}S{=}N{-}R + {}^1/_3\,Al[OSi(CH_3)_3]_3$$

*(3)*

with the expected relative areas [*(3a)*: $\tau$ = 6.44 ($CH_3$), $\tau$ = 2.03 (m) ($C_6H_5$), rel. areas 5:3; *(3b)*: $\tau$ = 8.70 (t) and 6.08 (q) ($C_2H_5$), $\tau$ = 2.88 (m) ($C_6H_5$), rel. areas 1:1].

We have synthesized the first *N*-silylated sulfinylamine (sulfurous monoimide), using tris(trimethylsilyl)amine and thionyl chloride (molar ratio 1:1) without a solvent with $AlCl_3$ as catalyst at *ca.* 70 °C, obtaining *N*-(trimethylsilyl)-sulfinylamine *(4)* in *ca.* 50 % yield as a colorless liquid (b.p. 108–110 °C/760 mm; m.p. < –78 °C), which is sensitive to

hydrolysis and gives in its $^1$H–NMR spectrum a sharp signal at $\tau = 9.64$ [$J^{13}$C–H = 120.5 Hz, $J^{29}$Si–C–H = 7.2 Hz; Varian A60 (60 MHz), 5 % solution in $CCl_4$, TMS as internal standard].

$$[(CH_3)_3Si]_3N + SOCl_2 \xrightarrow{70\,^\circ C} (CH_3)_3Si{-}N{=}S{=}O + 2\ (CH_3)_3SiCl$$

*(4)*

In the IR spectrum the two characteristic bands $\tilde{\nu}_{as}$(NSO) = 1297 and $\tilde{\nu}_s$(NSO) = 1122 cm$^{-1}$ are easily assigned [$(CH_3)_3C$–N=S=O (b.p. 98–99 °/760 mm), prepared for the first time from t-butylamine and thionyl chloride, gives wave numbers $\tilde{\nu}_{as}$(NSO = 1250, $\tilde{\nu}_s$(NSO) = 1095 cm$^{-1}$].

The formulae of *(2)*, *(3)*, and *(4)* are confirmed by elemental analyses and molecular-weight determinations.

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## Metabolism of Thiodan® in Insects

By Dr. K. Ballschmiter and Priv.-Doz. G. Tölg[1]

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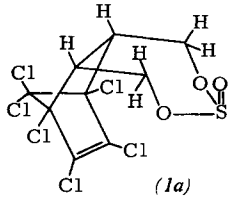
So far, the sulfate *(2)*[2] is the sole identified metabolite of the insecticide Thiodan® (1,2,3,4,7,7-hexachlorobicyclo[2.2.1] hept-2-ene-5,6-bismethylene sulfite) *(1a)* + *(1b)*, in houseflies (*Musca domestica*)[3].

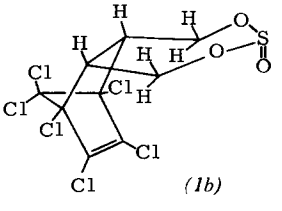
We have studied the metabolism of the male imagos of the locust (*Pachytilus migratorius migratorioides*) and have found that after peroral, cutaneous, and subcutaneous application ($LD_{50}$ = 5–10 µg/g[3]) Thiodan *(1a)* + *(1b)* is excreted, partly unchanged, in the feces.

The metabolites *(2)* to *(5)* were identified in the following way[4]. The possible products of assumed hydrolytic, oxidative, and conjugative detoxication reactions of Thiodan were mostly available or were synthesized, and chromatographic data of the metabolites were compared with those of the synthetic compounds. The reference material and the metabolite were considered identical if, after a preliminary separation by thin-layer chromatography, they gave identical retention times on gas chromatography on columns containing various polar liquids (see table).

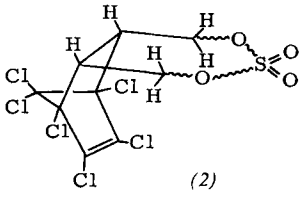
The configuration of the hydroxyl group in compound *(4)* is uncertain.



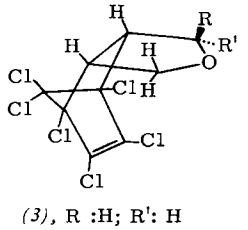
*(1a)*



*(1b)*



*(2)*



*(3)*, R :H; R': H
*(4)*, R: OH; R' = H
*(5)*, R+R' : O

| | M.p. (°C) | Ref. | Relative retention times | | |
|---|---|---|---|---|---|
| | | | Col. 1 | Col. 2 | Col. 3 |
| *(1a)* | 108–110 | [2, 5] | 1 | 1 | 1 |
| *(1b)* | 209–211 | [2, 5] | 2.16 | 2.70 | 1.34 |
| *(2)* | 180–181 | [2] | 4.83 | 6.02 | 1.70 |
| *(3)* | 224–226 | [2, 5] | 0.34 | 0.47 | 0.43 |
| *(4)* | 234–235 | [4] | 0.73 | 1.09 | 0.67 |
| *(5)* | 260–263 | [6] | 1.71 | 2.31 | 0.71 |

Column 1: 2 % Fluoro silicone rubber (QF-1) on Anakrom ABS; 110–120 mesh; Duran glass 50; int. diam. 2.5 mm, length 1 m; 180 °C; retention time *(1a)* 3.82 min.
Column 2: 2 % Nitrile silicone rubber (XE-60) on Anakrom ABS; 110–120 mesh; Duran glass 50; int. diam. 2.5 mm, length 1 m; 210 °C; retention time *(1a)* 2.92 min.
Column 3: 5 % Methyl silicone rubber (SE-30) on Diatoport PAW; 60–80 mesh; Duran glass 50; int. diam. 4 mm, length 1 m; 225 °C; retention time *(1a)* 13.1 min.

In the thin-layer chromatography on aluminum oxide H (Merck) and silica gel HR (Merck) the substances *(1)* to *(5)* were detected in nanogram quantities by fluorescence indicators[7] such as *N,N,N',N'*-tetraethylbenzidine, *N,N*-dimethylaminofluoranthene, 9-methylcarbazole, and 3-aminopyrene. Picogram quantities were detected by electron-capture detectors[8] after gas-chromatographic separation, so that experiments could be made with single imagos. [F + M Scientific Gas chromatograph model 700 with electron-capture detector; carrier gas, argon + 5 % of methane; and Varian Aerograph model 205 B with two electron-capture detectors; carrier gas, purified nitrogen].

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[1] The Deutsche Forschungsgemeinschaft, Verband der chemischen Industrie, and Farbwerke Hoechst AG. supported this work financially. We thank the Studienstiftung des deutschen Volkes for a Promotionsstipendium (*K. B.*).

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## Preparation of Organocarboranes by Hydroboration of Alkyl-1-alkynylboranes

By Dr. R. Köster, H.-J. Horstschäfer, and Dr. P. Binger

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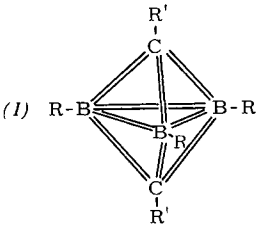
Hydroboration of non-complexed dialkyl-1-alkynylboranes[1,2] by alkyldiboranes is particularly useful for preparation of carboranes alkylated both on boron and on carbon. For instance, 1 mole of diethyl-1-propynylborane and 2 moles of diethylborane afford pentaethyldicarbaclovopentaborane-(5) *(1a)* (b.p. 84–86 °C/9 mm, m.p. –61.5 °C), whose IR, Raman, and $^1$H- and $^{11}$B-NMR spectra indicate a trigonal-bipyramidal structure in which the two carbon atoms occupy the apices. This product is accompanied by small amounts of higher-boiling organocarboranes with up to five boron atoms in the skeleton.

*(1)*



*(1a)*, R = R' : $C_2H_5$
*(1b)*, R : $C_3H_7$, R' : $C_2H_5$

For the preparation of 1,5-diethyl-2,3,4-tripropyl-1,5-dicarbaclovopentaborane(5) *(1b)*, a solution of "tetrapropyldiborane" (63 g) (containing 1.051 % of hydride H corresponding to 0.662 mole b H[3]) in tripropylborane (275 g) is dropped, with stirring and cooling in ice-water, during 2–3 hr into 42.4 g (0.31 mole) of dipropyl-1-propynylborane (b.p. 50 °C/10 mm, m.p. −63 °C), the mixture becoming slightly warm.

Distillation (up to *ca.* 50 °C/10 mm) removes tripropylborane and "tetrapropyldiborane"; then one obtains 19 g (52 %) of *(1b)* (b.p. 117–118 °C/10 mm; molecular weight 244, determined by mass spectrometry). Alongside *(1b)*, *ca.* 15 % of a second substance is disclosed by gas chromatography; it is probably a *B*-monoisopropyl derivative. Distillation of the residue affords a further 2 g of yellow viscous material (b.p. 70–100 °C/$10^{-3}$ mm), which contains compounds for which mass spectrometry yields molecular weights of 258, 272, and 286, as well as 254, 268, and 282 (up to 5 boron atoms). There remains 5.1 g of highly viscous red residue (18.4 wt.-% of B).

Use of "methyldiboranes" leads with diethyl-1-propynylborane to a series of homologous compounds with molecular weights of 160, 174, 188, and 202.

Compounds with $B_3C$ groups, which disproportionate to $C_2B_3$ carboranes, are indicated as intermediate products by the following equations:

$$R_2B{-}C{\equiv}CR'' \xrightarrow{R_2BH} (R_2B)_2C{=}CHR'' \xrightarrow{R_2BH} (R_2B)_3C{-}CH_2R''$$

$$2\,(R_2B)_3C{-}CH_2R'' \rightarrow 3\,BR_3 + C_2(CH_2R'')_2B_3R_3$$

Triborylated alkanes, $(R_2B)_2CH{-}CH(BR_2)R''$, which may also be formed by hydroboration of $R_2B{-}C{\equiv}CR''$ with alkyldiboranes, can form organocarboranes only after isomerization at higher temperatures:

$$(R_2B)_2CH{-}CH(BR_2)R'' \xrightarrow{>100\,^\circ C} (R_2B)_3C{-}CH_2R''$$

Therefore further carboranes are obtained when the hydroboration mixture is heated. The yields of $C_2B_3$ carboranes are highest when "tetraalkyldiboranes" are used in trialkylborane solution. The hydroboration mixture then consists chiefly of dialkylboron hydrides and thus selective addition of BH is possible[3]. In the present case preferential formation of 1,1,1-triborylated alkanes results.

Organocarboranes can also be obtained by hydroboration of alkyldi-1-alkynylboranes with alkyldiboranes. From isobutyldi-1-propynylborane and "tetraethyldiborane" we obtained two alkylated $C_2B_3$ carboranes with molecular weights 202 *(1a)* and 230 [B-monoisobutyl derivative of *(1)*].

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## The Electronic Effect of Phosphorus in *para*-Phosphorus-substituted Anisoles

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The O–$C_{arom.}$ stretching frequency of alkyl aryl ethers is influenced by the substituents on the aryl ring[1]. The relevant IR bands of *p*-P-substituted anisoles *(1)* to *(4)* should thus provide information about the electronic effect of phosphorus when present as a phosphine, phosphine oxide, phosphine sulfide, or phosphonium group.

$(p\text{-}CH_3O{-}C_6H_4)_nP(C_6H_5)_{3-n}$ *(1)*

$(p\text{-}CH_3O{-}C_6H_4)_nP(X)(C_6H_5)_{3-n}$ *(2)*: X = O; *(3)*: X = S

$(p\text{-}CH_3O{-}C_6H_4)_n\overset{\oplus}{P}(CH_3)(C_6H_5)_{3-n}\ Hal^{\ominus}$ *(4)*

In the alkyl aryl ethers *(1)–(4)*, the values of $\tilde{\nu}$(O–$C_{arom.}$) (see table) exhibit, in general, the same relationships as the half-neutralization potentials of analogously substituted dimethylanilines[2], but there are the following differences. In the anisole series phosphorus as a phosphine group is a "weaker" substituent than as a phosphine oxide group, even when $n = 2$ or 3; the three methoxyphosphines show the same dependence on $n$ as do the phosphine oxides *(2)* and the analogous *p*-(dimethylamino)phenylphosphine chalcogenides[2]. However, in the sulfide series *(3)*, $\tilde{\nu}$(O–$C_{arom.}$) is independent of $n$; in the phosphonium series *(4)* it increases with increasing $n$.

In principle, substituent constants can be obtained from $\tilde{\nu}$(O–$C_{arom.}$), but it is not clear whether $\sigma$ or $\sigma'$ should be used[3]. The values of $\tilde{\nu}$(O–$C_{arom.}$) for the substituted anisoles listed in the top part of the table were plotted against $\sigma$ and $\sigma'$, respectively; in both cases "satisfactory"[3] linear equations [(a) to (d)] were obtained, and thence the Hammett constants given in the table for the phosphorus-containing groups.

The results show that here also phosphorus in all types of compound behaves as an electron acceptor. The $\sigma'$ values generally resemble those for the dimethylaniline series[2]; in three out of four cases $\sigma$ is greater than the Hammett constants derived from the $pK_a'$ values of similarly substituted benzoic acids[4,5].

$\tilde{\nu} = 27.785\,\sigma + 1243.38$ (a) $r = 0.978$, $s = \pm 2.4\ cm^{-1}$

$\sigma = 0.0360\,\tilde{\nu} - 44.750$ (b) $r = 0.978$, $s = \pm 0.09$ σ-unit

$\tilde{\nu} = 19.798\,\sigma' + 1243.09$ (c) $r = 0.973$, $s = \pm 2.5\ cm^{-1}$

$\sigma' = 0.0505\,\tilde{\nu} - 62.789$ (d) $r = 0.973$, $s = \pm 0.12$ σ-unit

| Compound [a] | $\tilde{\nu}$(O–$C_{arom.}$) ($cm^{-1}$, in KBr) | σ [b] [c] | σ′ [b] [d] |
|---|---|---|---|
| Ar–$OCH_3$ | 1236 | −0.268 | −0.268 |
| Ar–$CONH_2$ | 1256 | – | +0.627 |
| Ar–$SO_2NH_2$ | 1257 | +0.621 | – |
| Ar–$COOCH_3$ | 1258 | +0.522 | +0.636 |
| Ar–$COCH_3$ | 1260 | +0.516 | +0.874 |
| Ar–CN | 1260 | +0.628 | +1.000 |
| Ar–COOH | 1261 | (+0.265 [e]) | +0.728 |
| Ar–$NO_2$ | 1267 | +0.778 | +1.270 |
| Ar–$P(C_6H_5)_2$ | 1251 | +0.29 (0.19) | +0.39 (0.32) |
| Ar–$P(O)(C_6H_5)_2$ | 1263 | +0.72 (0.50) | +0.99 (0.88) |
| Ar–$P(S)(C_6H_5)_2$ | 1261 | +0.65 (0.49) | +0.89 (0.73) |
| Ar–$P^{\oplus}(CH_3)(C_6H_5)_2Br^{\ominus}$ | 1263 | +0.72 (1.01) | +0.99 (1.09) |
| $Ar_2PC_6H_5$ | 1248 (broad) | +0.18 | +0.24 (0.86) |
| $Ar_2P(S)C_6H_5$ | 1261 | +0.65 | +0.89 (0.64) |
| $Ar_3P$ | 1247 | +0.14 | +0.19 (0.63) |
| $Ar_3PO$ | 1256 | +0.47 | +0.64 (0.60) |
| $Ar_3PS$ | 1261 | +0.65 | +0.89 (0.50) |
| $Ar_3P^{\oplus}CH_3I^{\ominus}$ | 1267 | +0.86 | +1.20(1.09[f]) |

[a] Ar = $p$-$CH_3O{-}C_6H_4{-}$.
[b] For phosphorus-free substituents taken from [3].
σ(–$COOC_2H_5$) used for σ(–$COOCH_3$).
[c] Values in parentheses are σ constants calculated from the $pK_a'$ values of the corresponding benzoic acids.
[d] The σ′ constants in parentheses are those calculated from the half-neutralization potentials of the dimethylanilines [2].
[e] Very uncertain value[3], not used for the evaluation of eqs. (a) and (b).
[f] Value for the group $>P^{\oplus}(C_2H_5){-}$.

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## 1,6-Methano[10]annulen-2-amine and -2-ol

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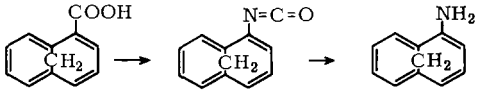
No amino or hydroxy derivative of 1,6-methano-[1] or 1,6-epoxy-[10]annulene[2], 1,2,8,9-tetradehydro[14]annulene[3], or dihydro-*trans*-15,16-dimethylpyrene[4] has yet been described.

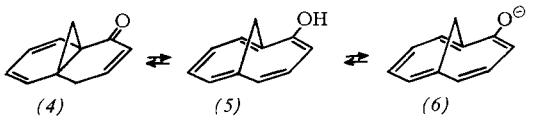
1,6-Methano[10]annulene-2-carboxylic acid[1] *(1)* and thionyl chloride give the acid chloride (b.p. 97–98 °C/0.02 mm Hg; yield 92 %), which in a Curtius reaction with sodium azide in boiling toluene affords the isocyanate *(2)* as a pale yellow liquid (b.p. 69–72 °C/0.01 mm Hg; 90 % yield), whose NMR spectrum (in $CCl_4$) contains a multiplet at $\tau = 2.2$–$3.5$ and an AB system with its center at $\tau = 10.6$ (proton ratio 7:2); the derived methylurethane has m.p. 145–146 °C.




*(1)* *(2)* *(3)*

Treating the isocyanate *(2)* with dilute NaOH (formation of the sodium carbamate) and then with dilute $H_2SO_4$ in amount equivalent to the alkali affords an orange-yellow, air-sensitive, basic substance (yield 85 %), b.p. 97–98 °C/0.07 mm Hg [UV spectrum in cyclohexane: $\lambda_{max} = 254$ ($\varepsilon = 32{,}000$), 270 (21,000)(sh), 342 (5500), and 415 mμ (1100)]. The NMR spectrum of this product in $CCl_4$ contains a multiplet at $\tau = 2.5$–$4.2$ (7 vinyl protons), a broad singlet at $\tau = 6.2$ (2 amino protons), and an AB system at $\tau = 10.0$ and 10.85 with $J_{AB} = 9.5$ Hz ($CH_2$ protons) and thus shows the presence of 1,6-methano[10]annulen-2-amine *(3)*, free from imino tautomers. The amine was characterized as hydrochloride and acetyl derivative (m.p. 204 °C), but attempts to diazotize it had no clear result.

When the aqueous solution of the hydrochloride of *(3)* is heated in the presence of toluene a keto-enol mixture is obtained from which the ketone can be crystallized (m.p. 26 °C). It can be concluded from the NMR spectrum of the ketone (Fig. 1) that the hydrolysis involved not only tautomerization but also cycloheptatriene-norcaradiene valence isomerization, because the AX system at $\tau = 7.9$ and $\tau = 9.8$ with $J_{AX} = 4.5$ Hz can be assigned unambiguously to $CH_2$ protons in a cyclopropane ring[5]. When it is further considered that the UV spectrum (in cyclohexane) with $\lambda_{max} = 215$ ($\varepsilon = 11{,}600$), 274 (2600), and 320 mμ (180) is to be interpreted as superposition of the absorption bands of a norcaradiene system[6] and an α,β-unsaturated carbonyl group (CO band at 1660 $cm^{-1}$), then the ketone must be tricyclo[4.4.1.$0^{1,6}$]undeca-3,7,9-trien-2-one *(4)*.




*(4)* *(5)* *(6)*

In the presence of catalytic amounts of acid or base the ketone *(4)* is equilibrated with the enol, which is proved to be 1,6-methano[10]annulen-2-ol by its NMR spectrum (Fig. 1). The ketone *(4)* is favored ($\approx$ 80 %) in the equilibrium mixture in benzene, but the enol *(5)* preponderates (97 %) in dimethyl sulfoxide. Catalytic amounts of HCl in methanol cause rapid etherification to 2-methoxy-1,6-methano[10]-annulene.

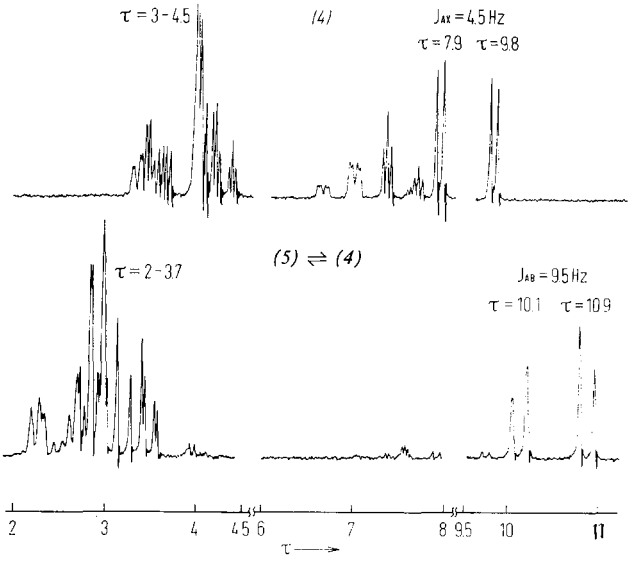



Fig. 1. NMR spectra [60 MHz; in $(CD_3)_2SO$] of the pure ketone *(4)* and of the enol-ketone mixture (97:3) obtained by equilibration with catalytic quantities of trimethylamine (OH absorption at $\tau$ — 0.1).

The ketone and the enol are converted by alkali into the intensely yellow anion *(6)* (NMR spectrum in $(CD_3)_2SO$: multiplet at $\tau = 2.3$–$4.5$ and AX system at $\tau = 9.35$ and 11.05 with $J_{AX} = 9$ Hz) which is sensitive to oxygen but from which a mixture of the tautomers can be regenerated by acidification[7].

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## 11-Methylene-1,6-methano[10]annulene and 1,6-Methano[10]annulen-11-ol

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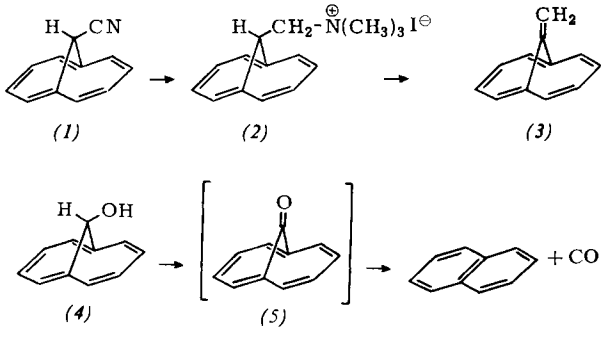
The possibility that 1,6-bridged [10]annulenes with a trigonal C-11 atom might have a $C_{10}$ perimeter[2] even more nearly planar than 1,6-methano[10]annulene[1] aroused our interest in 11-methylene-1,6-methano[10]annulene *(3)* and 1,6-methano[10]annulen-11-one *(5)*. The geometry of these

compounds prevents normal conjugation of the π-electron systems of the peripheral ten-membered ring and the bridge (orthogonal $p_z$-orbitals on C-11 and C-1 or C-6). It is still an open question whether the two chromophores influence each other in other ways.

The synthesis of compound *(3)* started with 11-cyano-1,6-methano[10]annulene *(1)*[3] [m.p. 100–101 °C; NMR spectrum in $CCl_4$: multiplet at $\tau$ = 2.4–3.0 and singlet at $\tau$ = 9.4 (proton ratio 8:1)]. With $LiAlH_4$ this gave 11-(1,6-methano-[10]annulene)methylamine (b.p. 87–90 °C/0.08 mm Hg; yield 82%; benzoyl derivative, m.p. 163–164 °C), which with $CH_3I$ yielded the methiodide *(2)* [m.p. 224–226 °C; yield 70%; NMR spectrum in $DCCl_3$: multiplet at $\tau$ = 2.3 to 3.1, singlet at $\tau$ = 7.0, doublet at $\tau$ = 7.8 with $J$ = 6 Hz, and broad triplet at $\tau$ = 10.2 with $J$ = 6 Hz (8:9:2:1)].




Although fragmentation to naphthalene, acetylene, and trimethylamine occurs on reaction of the methiodide *(2)* with potassium amide[4], a 4:1 (wt.-proportion) mixture of naphthalene and a pale yellow hydrocarbon $C_{12}H_{10}$ (m.p. 85 to 86 °C) is obtained on pyrolysis of the ammonium base derived from *(2)* at 100–140 °C/0.1–1 mm Hg.

The NMR spectrum of this compound $C_{12}H_{10}$ contains only an $A_2B_2$ system (as two identical $A_2B_2$ systems) at $\tau$ = 2.8 and a sharp singlet at $\tau$ = 6.8 (8:2); thus the compound is 11-methylene-1,6-methano[10]annulene *(3)*. The absorption of the olefinic bridge protons at unusually high field is to be expected for a structure *(3)*, since these protons should be strongly shielded by the 10π-electron system. The compound *(3)* has an UV spectrum that is almost superposable on that of 1,6-methano[10]annulene [$\lambda_{max}$ in cyclohexane = 258 (ε = 67,500), 300 mμ (6700), bands with 7 maxima between 360 and 410 mμ (ε between 130 and 190)], whence it follows that the geometries of the $C_{10}$ perimeters of the two compounds do not differ appreciably and that in compound *(3)* there is no noteworthy interaction between the π-electron systems of the perimeter and the bridge.

It was hoped to obtain the ketone *(5)* by conversion of 11-bromo-1,6-methano[10]annulene[5] into the alcohol *(4)* and subsequent oxidation. We succeeded in converting the bromide by silver acetate in boiling glacial acetic acid into 11-acetoxy-1,6-methano[10]annulene [m.p. 92–93 °C; yield 60%; NMR spectrum in $CCl_4$: multiplet at $\tau$ = 2.5–3.2, singlet at $\tau$ = 7.9, singlet at $\tau$ = 8.5 (8:1:3)] and thence, by $CH_3MgI$, into 1,6-methano[10]annulen-11-ol *(4)* [m.p. 71–72 °C; yield 50%; NMR spectrum in $CCl_4$: multiplet at $\tau$ = 2.5–3.2, singlet at $\tau$ = 8.6, broad singlet at $\tau$ = 9.9 (8:1:1)]. However, naphthalene (yield 80 and 75%, respectively) was always the sole product on oxidation of the alcohol *(4)* with $CrO_3$ or lead tetraacetate in pyridine; on use of aqueous chromic acid or of manganese dioxide in hexane the naphthalene was accompanied by α-naphthaldehyde [which is isomeric with *(5)*].

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[1] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964); *E. Vogel* and *W. A. Böll*, Angew. Chem. *76*, 784 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964).

[2] For the geometry of the 1,6-methano[10]annulene skeleton see the X-ray structure analysis of 1,6-methano[10]annulene-2-carboxylic acid by *M. Dobler* and *J. D. Dunitz*, Helv. chim. Acta *48*, 1429 (1965).

[3] Obtained by conversion of 11-bromotricyclo[4.4.1.$0^{1,6}$]-undeca-3,8-diene [5] by CuCN in DMF into 11-cyanotricyclo-[4.4.1.$0^{1,6}$]undeca-3,8-diene (m. p. 73–74 °C), and dehydrohalogenation by 15% methanolic KOH of the tetrabromo adduct of the nitrile.

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## Concerning the Existence of 2,3-Didehydro-1,6-methano[10]annulene

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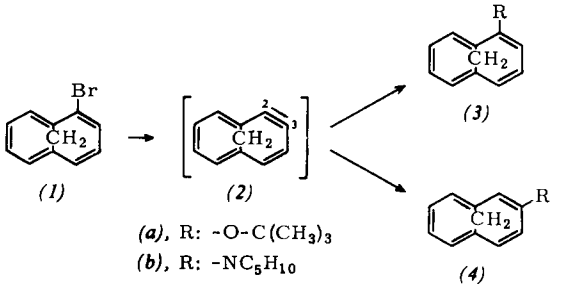
Numerous electrophilic reagents convert 1,6-methano[10]-annulene into substitution products where the substituent has entered only at the 2-position[1]. A possible route to 3-substituted derivatives appeared to be reaction of 2-bromo-1,6-methano[10]annulene *(1)* by way of the 2,3-didehydro compound *(2)*, which with nucleophiles should give a mixture of the position isomers *(3)* and *(4)*.




Metalation and base-catalysed deuterium exchange of 1,6-methano[10]annulene showed that the hydrogen on C-2 is appreciably more acidic than that on C-3[2], whence it was to be expected that the negative charge in the transition state resulting from addition of a nucleophile to *(2)* should be better stabilized on C-2 and that thus the 3-isomers should be formed preferentially[3].

When *(1)* was heated for 12 hr at 90 °C with potassium t-butoxide in dioxane containing 1 mole/l of t-butyl alcohol, a 5:95 mixture of 2- and 3-t-butoxy-1,6-methano[10]-annulene, *(3a)* and *(4a)*, was obtained in 40% yield.

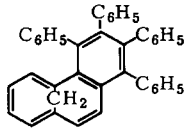
The structure of *(4a)* (m.p. 27 °C) follows from the UV spectrum [in cyclohexane, $\lambda_{max}$ = 262 (ε = 70000), 304 (6900), and 383 mμ (330)] and from the NMR spectrum (in $CCl_4$, multiplet at $\tau$ = 2.5–3.5, singlet at $\tau$ = 8.65, and AB system at $\tau$ = 10.43 and 10.57; $J_{AB}$ = 8.8 Hz; intensity ratio 7:9:2). Fine splitting of the AB doublets of the $CH_2$– protons into triplets ($J \approx$ 0.8 Hz), which is a consequence of stereospecific long-range coupling with the protons in positions 2 and 5, and 7 and 10, respectively, confirms the position of the t-butoxy group on C-3. The isomer *(3a)* (b.p. 76 to 78 °C/0.01 mm Hg) was synthesized independently by reaction of the Grignard compound from *(1)* with t-butyl perbenzoate[4] (yield 85%); it is differentiated from its isomer *(4a)* by its longer-wavelength UV absorption [$\lambda_{max}$ = 260 (ε = 49000), 316 (6000) and 403 mμ (470)] and by the larger NMR shift of the $CH_2$ protons forming the AB system ($\tau$ = 10.28 and 10.72; $J_{AB}$ = 9.4 Hz); fine splitting of the A part into triplets and of the B part into doublets ($J \approx$ 0.9 Hz) is as expected for substitution in position 2.

When the reaction of the bromide *(1)* with potassium t-butoxide at 90 °C was carried out in presence of piperidine (1 N in dioxane) in place of t-butyl alcohol, compounds

*(3b)* and *(4b)* were obtained in a total yield of 93 % and a ratio 6:94. Replacement of the $KOC(CH_3)_3$ by the stronger base lithium piperidide altered this ratio to 60:40. This reversal, and the marked dependence of the isomer ratio on temperature, piperidine concentration, and solvent, suggest that reaction by way of the dehydro compound *(2)* is in competition with direct exchange of substituents to give *(3b)*; this is being studied further.

The viscous reddish-yellow mixture (b.p. 114–116 °C/ 0.04 mm Hg) of isomers *(3b)* and *(4b)* was separated by column chromatography. The UV spectrum of *(3b)* [$\lambda_{max}$ = 255 ($\varepsilon$ = 31000), 275 (19500, sh), 353 (8200), and 410 mμ (1400, sh)] is very similar to that of 1,6-methano[10]annulene-2-amine[5], whereas that of *(4b)* is shifted towards shorter wavelengths. This observation and the fine splitting of the AB doublets in the NMR spectrum unambiguously prove the structure shown.

Experiments designed to trap the postulated intermediate 2,3-didehydro-1,6-methano[10]annulene *(2)* in Diels-Alder reactions[6] were successful on use of tetracyclone (tetraphenylcyclopentadienone): we obtained – again by dehydrohalogenation of *(1)* with potassium t-butoxide – a *ca.* 30 % yield of 1,2,3,4-tetraphenyl-7,12-methanobenz[10]annulene *(5)* (m.p. 258 °C).




*(5)*

Received: June 15th, 1966 [Z 267c IE]
German version: Angew. Chem. *78*, 755 (1966)

[1] *E. Vogel* and *W. A. Böll*, Angew. Chem. *76*, 784 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964); *E. Vogel, W. A. Böll,* and *M. Biskup*, Tetrahedron Letters *1966*, 1569. – Nitration is an exception.

[2] *W. A. Böll*, unpublished work.

[3] Compare similar relations with naphthalene. – *R. Huisgen* and *J. Sauer*, Angew. Chem. *72*, 91 (1960).

[4] *S. D. Lawesson* and *N. C. Yang*, J. Amer. chem. Soc. *81*, 4230 (1959).

[5] *E. Vogel, W. Schröck,* and *W. A. Böll*, Angew. Chem., in the press.

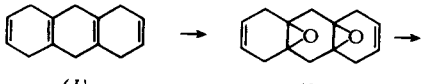
[6] For dehydrobenzene see *G. Wittig*, Angew. Chem. *77*, 752 (1965); Angew. Chem. internat. Edit. *4*, 731 (1965).

## 1,6:8,13-Diepoxy[14]annulene

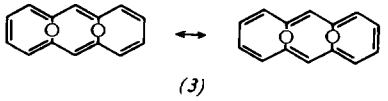
By Prof. E. Vogel, Dr. M. Biskup, A. Vogel, and Dr. H. Günther

Institut für Organische Chemie, Universität Köln (Germany)

We recently reported some experiments on the synthesis of bridged [14]annulenes[1] with an "anthracene perimeter". Whereas *anti*-1,6:8,13-dimethano[14]annulene has hitherto been obtained only as 7,14-dihydro derivative, the analogous 1,6:8,13-diepoxy[14]annulene *(3)* (probably the *syn*-form) can be prepared surprisingly easily.



*(1)* *(2)*



*(3)*

Treatment of 1,4,5,8,9,10-hexahydroanthracene *(1)*[1] with two equivalents of peracetic acid gives almost quantitatively 4a,9a:8a,10a - diepoxy - 1,4,5,8,9,10 - hexahydroanthracene *(2)*[2], the NMR spectrum of which indicates that it is a mixture (*ca.* 60:40) of *syn*- and *anti*-isomers, since the four central $CH_2$ protons give rise to an AB system (*syn*-form) as well as a singlet (*anti*-form). If compound *(2)* (*syn-anti*-isomer mixture) is allowed to react with two equivalents of *N*-bromosuccinimide in $CCl_4$ and the crude bromination product is treated with potassium t-butoxide in tetrahydrofuran, a carmine-red substance (leaflets from methanol) of m.p. 230 °C is formed in 5 % yield; it can be isolated readily by chromatography[*]. Analysis and the mass-spectrographic molecular weight ($M^+$ = 210) lead to the molecular formula $C_{14}H_{10}O_2$.

The NMR spectrum (Fig. 1a)[3] proves the compound to be 1,6:8,13-diepoxy[14]annulene *(3)* (*syn*- or *anti*-form). It shows a singlet at $\tau$ = 2.06 ppm (relative intensity 2) due to the protons H-7 and H-14 and an AA'BB' system ($\tau_A$ = 2.25 and $\tau_B$ = 2.40 ppm[4]; relative intensity 8) arising from the protons H-2 to H-5 and H-9 to H-12.

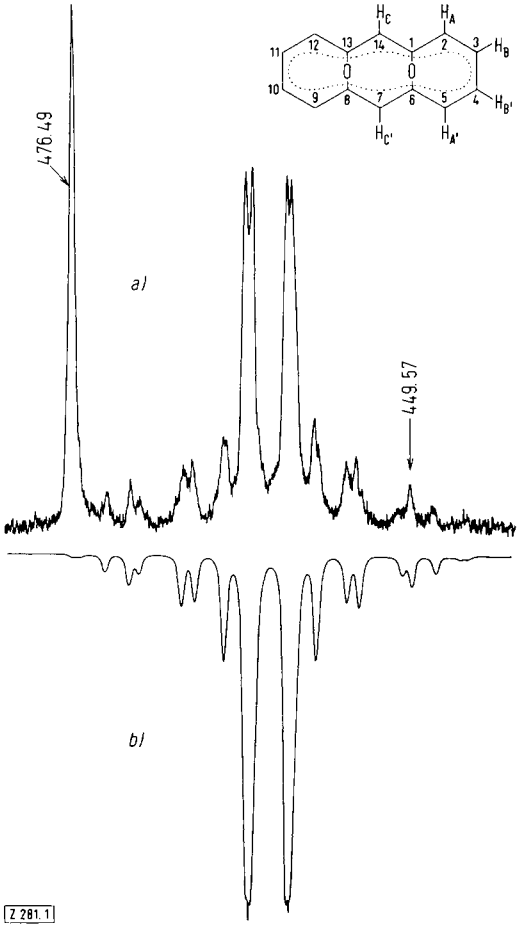



Fig. 1. a) Experimental NMR spectrum for compound *(3)* at 60 MHz (0.19 M in $CDCl_3$); values are in Hz relative to tetramethylsilane as internal standard.
b) Calculated AA'BB' system of protons H-2 to H-5 and H-9 to H-12.

The fact that H-2 to H-5 and H-9 to H-12 have identical NMR parameters (appearance of only one AA'BB' system) excludes an olefinic structure with fixed double bonds. A fluctuating structure is consistent with the symmetry of the spectrum, but does not account for the positions of the proton resonances, whose paramagnetic shift evidently is caused by a ring current due to the π-electrons. If 1,6-epoxy[10]annulene *(4)*[5] is taken as reference substance, calculations for *(3)* by the *Pople* point dipole model[6] give $\tau_C$ = 1.92, $\tau_A$ = 2.27, and $\tau_B$ = 2.65 ppm, in good agreement with experiment. Coupling parameters for *(3)* are identical with those for *(4)*[7], namely:

$$J_{AB} = 9.0;\ J_{BB'} = 9.2;\ J_{AB'} = 0.3;\ J_{AA'} = 1.1 \text{ Hz}.$$

The fact that the vicinal coupling constants $J_{AB}$ and $J_{BB'}$ are almost identical indicates that there is no appreciable alternation in the corresponding C–C bond lengths[8].

The UV spectrum is also compatible with structure *(3)*. It shows $\lambda_{max}$ = 306 ($\varepsilon$ = 169000), 345 (14400), 382 (8500), and 555 mμ (775), the last-mentioned band having fine structure (in cyclohexane).

The aromatic structure of *(3)* that follows from the spectra is manifested by the remarkable thermal stability of the compound and by its insensitivity to oxygen. Preliminary experiments suggest, moreover, that compound *(3)* is amenable to electrophilic substitution.

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[*] Column $Al_2O_3$, solvent $CCl_4/CH_2Cl_2$ (70:30).

[1] *E. Vogel, M. Biskup, A. Vogel, U. Haberland,* and *J. Eimer*, Angew. Chem. *78*, 642 (1966); Angew. Chem. internat. Edit. *5*, 603 (1966).

[2] According to *J. Runge*, J. prakt. Chem. [4] *31*, 280 (1966), the diepoxide *(2)* obtained from *(1)* and perbenzoic acid has the *anti*-configuration.

[3] Measured at 60 and 100 MHz on Varian A-6C-A and HA-100 NMR spectrometers and analysed with the computer program LAOCOON II [*S. Castellano* and *A. A. Bothner-By*, J. chem. Physics *41*, 3863 (1964)].

[4] Assignment of the resonances is not possible by analysis alone and was made in analogy to *(4)* [*F. Gerson, E. Heilbronner, W. A. Böll,* and *E. Vogel*, Helv. chim. Acta *48*, 1494 (1965)].

[5] *E. Vogel, M. Biskup, W. Pretzer,* and *W. A. Böll*, Angew. Chem. *76*, 785 (1964); Angew. Chem. internat. Edit. *3*, 642 (1964); *F. Sondheimer* and *A. Shani*, J. Amer. chem. Soc. *86*, 3168 (1964).

[6] *J. A. Pople*, J. chem. Physics *24*, 1111 (1956); for application to *(4)* see [7].

[7] *H. Günther*, Z. Naturforsch. *20b*, 948 (1965).

[8] X-Ray analysis of 1,6-methano[10]annulene-2-carboxylic acid [*M. Dobler* and *J. D. Dunitz*, Helv. chim. Acta *48*, 1429 (1965)] showed that the identity of vicinal coupling constants observed earlier [7] for 1,6-methano[10]annulene is due mainly to nearly equal C–C bond lengths.

## Isolation of Protease Inhibitors [1]

By Dr. H. Fritz, H. Schult, M. Neudecker, and Prof. E. Werle

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A 1:1 maleic anhydride-ethylene copolymer (mol. wt. range 13500–135000; type DX 840–21 EMA–M) in aqueous buffer solutions (0.2 M phosphate; pH 7.5) reacts with the ε-amino groups of the lysine residues in trypsin (EC 3.4.4.4) [1 g of EMA–M binds *ca.* 5 g of trypsin]; in the presence of hexamethylenediamine as crosslinking agent an insoluble trypsin-maleic acid-ethylene copolymer is formed[2]. The portion (*ca.* 20 %) of the trypsin covalently fixed on the insoluble carrier that retains its enzymatic acivity is subject to trypsin inhibitors such as Kunitz inhibitor from pancreas or soybean inhibitor[2].

We have used the trypsin resin for selective absorption, in the neutral pH region, of trypsin inhibitors from crude organ extracts. After all the accompanying materials have been washed out of the trypsin resin by 0.1 M triethanolamine buffer + 0.1 M NaCl (pH 7.8), the inhibitors are eluted by 0.2 M KCl/HCl buffer.

The previously characterized[1,3] trypsin inhibitors shown in the Table were isolated in pure form and high yield in one step from organ extracts that had been freed from protein with 3 % perchloric acid.

The inhibitor from pig pancreas was separated electrophoretically[*] into three fractions that were active as inhibitors[1,3]; the middle fraction was found to have the composition[3a] 4 Lys, 2 Arg, 4 Asp, 5 Thr, 6 Ser, 6 Glu, 5 Pro, 4 Gly, 1 Ala, 6 Cys½, 4 Val, 3 Ileu, 2 Leu, 2 Tyr. Absence of the amino acids tryptophan, methionine, and histidine is remarkable.

Inhibitors and enzymes isolated by means of a maleic anhydride-ethylene copolymer.

| Copolymer plus | Isolation from | Yield (%) of pure enzyme or inhibitor |
|---|---|---|
| Trypsin (EC 3.4.4.4) | Trypsin inhibitor from: | |
| | Pig pancreas | 90 |
| | Dog pancreas | 82 |
| | Ox pancreas | 95 |
| | Seminal vesicles of mice | 75 |
| Chymotrypsin (EC 3.4.4.5) | Kunitz inhibitor from ox pancreas | 90 |
| Kallikrein (EC 3.4.4.21) | Trypsin-kallikrein inhibitor from ox organs | 70 |
| Tryspin-kallikrein inhibitor Trasylol® | Trypsin | 95 |
| | Chymotrypsin | 90 |

In addition, the water-insoluble enzyme-maleic acid-ethylene copolymers of chymotrypsin (EC 3.4.4.5) and kallikrein (EC 3.4.4.21) were prepared. Use of the chymotrypsin or kallikrein resin led to the isolation, from ox pancreas extracts, of the Kunitz inhibitor, and subsequent use of the trypsin resin afforded the specific trypsin inhibitors remaining in the extract. There was quantitative separation of the two inhibitors, which have similar molecular weights [Kunitz inhibitor: $M$ = 6513; spec. trypsin inhibitor: $M$ = 6000 (from the amino acid composition), 6800 (by *Andrews'* molecular-sieve method[4])].

We have also used the process for purification of enzymes. The kallikrein inhibitor[5] bound to the copolymer adsorbs trypsin, chymotrypsin, or kallikrein specifically from protein-containing solutions. Trypsin and chymotrypsin were eluted in 90 to 95 % yield from the kallikrein inhibitor resin by acid buffer solutions such as 0.2 M KCl–HCl (pH 2).

The enzyme- and inhibitor-maleic acid-ethylene copolymers retain their specific activity on repeated use (tested for up to 60 operations) for isolation of inhibitors or enzymes provided the experiments are carried out at 4 to 8 °C.

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[*] Carrier, cellulose acetate sheets (275×310 mm) from Schleicher & Schüll; 0.01 M borate buffer (pH 8); 400 volts; 3 hr running time; apparatus, Elphorkammern from Bender & Hobein, Munich (Germany).

[1] Part 3. – Part 2: *H. Fritz, F. Woitinas,* and *E. Werle*, Z. physiol. Chem. *345*, 168 (1966).

[2] *Y. Levin, M. Pecht, L. Goldstein,* and *E. Katchalski*, Biochemistry *3*, 1905 (1964).

[3] *H. Fritz, G. Hartwich,* and *E. Werle*, Z. physiol. Chem. *354*, 150 (1966).

[3a] We thank Prof. *G. Braunitzer*, of the Max-Planck-Institut für Biochemie, Munich, for the analyses.

[4] *H. Fritz, I. Trautschold,* and *E. Werle*, Z. physiol. Chem. *342*, 253 (1965).

[5] *R. Vogel, I. Trautschold,* and *E. Werle*: Natürliche Proteinase-Inhibitoren. Thieme, Stuttgart 1966, in press; this inhibitor is identical with the Kunitz inhibitor.

## 5'-*O*-Methylthymidine

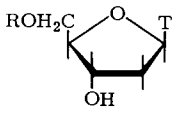
By Dr. G. Kowollik, K. Gaertner, and Dr. P. Langen

Institut für Biochemie der Deutschen Akademie der Wissenschaften zu Berlin, Berlin-Buch (Germany)

Direct nucleophilic replacement of a primary sulfonyloxy group by methoxy has hitherto been observed only for a few pentose[1] and hexose derivatives[2]. We have applied

to a deoxyribonucleoside the methods used in those cases (reaction of the sulfonyl derivative with $CH_3ONa/CH_3OH$ under reflux or in a closed vessel at 100 °C).

Under these conditions 5'-*O*-tosylthymidine *(1)* gives 5'-*O*-methylthymidine *(2)* (60 % yield) and thymidine *(3)* in a molar ratio of 7:3 to 8:2; the products *(2)* and *(3)* can be separated by partition chromatography on Hyflo Super-Cel[3] with ethyl acetate/propan-2-ol/water (12:1:6 v/v) as running solvent and are obtained analytically pure by recrystallization from 96 % ethanol. If 3'-*O*-acetyl-5'-*O*-methanesulfonylthymidine is used in place of *(1)*, the same products *(2)* and *(3)* result in the same amounts.




T: 1-Thymyl
*(1)*, R: p-$CH_3$-$C_6H_4$-$SO_2$-
*(2)*, R: $CH_3$
*(3)*, R: H

*(2)*: m.p. 170.5 °C; UV spectrum ($H_2O$), $\lambda_{max}$ = 265.5 mμ, $\lambda_{min}$ = 234.5 mμ, $\varepsilon_{max}$ = 9500; IR spectrum (KBr), 1090 $cm^{-1}$ ($OCH_3$); $R_F$ = 0.63 in butan-1-ol/water/conc. aq. $NH_3$ (86:14:15 v/v). 3'-*O*-Acetyl derivative: m.p. 154 °C; $R_F$ = 0.75.

In contrast to thymidine *(3)*, the ether *(2)* is not cleaved by uridine deoxyuridine phosphorylase (EC 2.4.2.3) or thymidine phosphorylase (EC 2.4.2.4) and does not inhibit the cleavage of thymidine by this enzyme.

Received: June 22nd, 1966 [Z 270 IE]
German version: Angew Chem. *78*, 752 (1966)

[1] *P. A. Levene* and *A. L. Raymond*, J. biol. Chemistry *102*, 331 (1933); *S. C. Williams* and *J. K. N. Jones*, Canad. J. Chem. *43*, 3440 (1965).

[2] *P. A. Levene* and *A. L. Raymond*, J. biol. Chemistry *97*, 751 (1932); *A. K. Mitra*, *D. H. Ball*, and *A. Long*, J. org. Chemistry *27*, 160 (1962).

[3] For operating technique see *G. Etzold* and *P. Langen*, Chem. Ber. *98*, 1988 (1965).

## Isopolyanions of Molybdenum(VI)

By Prof. O. Glemser and W. Höltje

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Universität Göttingen (Germany)

The chief products of aggregation of $MoO_4^{2-}$ caused by protons in aqueous solution were found by *Glemser et al.*[1] and by *Aveston et al.*[2] to be $MoO_7$ and $MoO_8$ complexes (at $p$ = 1.14 and 1.50, respectively[3]), whereas *Sasaki* and *Sillén*[4,5] arrived at a different reaction scheme in terms of species $Mo_7O_{24}^{6-}$ ($p$ = 1.14), $HMo_7O_{24}^{5-}$ ($p$ = 1.29), $H_2Mo_7O_{24}^{4-}$ ($p$ = 1.43), $H_3Mo_7O_{24}^{3-}$ ($p$ = 1.57), and a larger complex at $p$ = 1.79.

To clarify this discrepancy we have studied the chemical relaxation of acidified molybdate solutions ($10^{-2}$ M + 0.3 M $NaNO_3$) at acidifications[3] $p$ = 0.2, 0.6, 1.14, 1.31, 1.50, and 1.56, using the temperature-jump method[6]; ancillary measurement of pH-indicator equilbria with very short equilibration times (Chlorophenol Red, Methyl Red, Bromocresol Green, Bromochlorophenol Blue, Benzyl Orange) allowed spectrophotometric recording. The temperature jump was from 18 °C to 25 °C; the measuring cell was brought to thermal equilibrium before each experiment.

At $p$ = 0.2, 0.6, 1.14, 1.31, and 1.50 relaxation effects with only one time constant in the msec region were observed (*e.g.* for $[Mo]_t = 1.5\times10^{-2}$ at $p$ = 1.41, $1/\tau = 1.71\times10^3$ $sec^{-1}$, and at $p$ = 1.50, $1/\tau$ = 257 $sec^{-1}$). However, solutions with $p$ = 0 and $p$ = 1.56, and indicator control solutions without molybdate, gave no relaxation in the time interval 0.1 sec to 50 μsec.

The occurrence of a single relaxation time indicates an equilibrium between *two* species having different degrees of aggregation. If no relaxation signal is obtained, then either only a single species is present (limits of detection 3–5 %) or the equilibria are protolytic and therefore too rapidly established to be registered.

Since, at the concentrations used, the equilibria are almost entirely on the side of the polyanions, the scheme of *Sasaki* and *Sillén*, which involves only protonation stages between $p$ = 1.14 and 1.57, cannot be correct[7]. On the other hand, there is agreement with our earlier results[1]: aggregation occurs up to formation of the $Mo_8$ complexes at $p$ = 1.50; at higher $p$ values ($p$ = 1.56) only protolytic reactions occur.

The nature of the primary aggregation step was also studied by means of relaxation measurements (indicator: Chlorophenol Red). At not too high $H^+$ and Mo concentrations the observed extinction curves were characterized by a single time constant. At pH 5.50 the reciprocal of the relaxation times is related to the third power of the monomolybdate concentration (*e.g.* $[Mo_1] = 6.7\times10^{-3}$ M, $1/\tau$ = 12.2 $sec^{-1}$; $17.7\times10^{-3}$ M, 64.8 $sec^{-1}$); when the Mo concentration is kept constant ($1.0\times10^{-2}$ M), $1/\tau$ depends on the fifth power of $[H^+]$ (*e.g.* at pH 5.6, $1/\tau$ = 12.4 $sec^{-1}$; at pH 5.36, $1/\tau$ = 55.6 $sec^{-1}$). Thus the first polyanion to be formed on acidification of a $MoO_4^{2-}$ solution is a tetramolybdate[9], formation of which consumes six $H^+$ ions. Di- and trimolybdates do not exist in aqueous solution. Accordingly the overall equation is

$$4\,MoO_4^{2-} + 6H^+ \rightleftarrows [Mo_4O_{10}(OH)_6]^{2-}.$$

This formula for the new isopolymolybdate species[10] is also in agreement with the fact that all the hepta- and octamolybdates known so far[2] are built up from octahedral $MoO_6$ units. Moreover, in such fast reactions addition seems more probable than condensation[11].

Received: June 27th, 1966 [Z 276 IE]
German version: Angew. Chem. *78*, 756 (1966)

[1] *O. Glemser* and *W. Holznagel*, Abstracts VIIth Internat. Conf. on Coordination Chemistry, Stockholm 1962, p. 173; *O. Glemser*, *W. Holznagel*, and *S. I. Ali*, Z. Naturforsch. *20b*, 192 (1965).

[2] *J. Aveston*, *E. W. Anacker*, and *J. S. Johnson*, Inorg. Chem. *3*, 735 (1964).

[3] "Acidification", $p$, denotes the quotient of the $H^{\oplus}$ and total molybdate concentrations used, *i.e.* $p = [H^{\oplus}]_t/[Mo]_t$; at higher $MoO_4^{2-}$ concentrations ($\geq 10^{-2}$ M), where the polyanions are formed almost quantitatively, $p$ is identical with the "degree of acidity", $Z = [H^+]_t - [H^+]/[Mo]_t$, that is often used [4].

[4] *Y. Sasaki*, *I. Lindqvist*, and *L. G. Sillén*, J. inorg. nuclear Chem. *9*, 93 (1959).

[5] *Y. Sasaki* and *L. G. Sillén*, Acta chem. scand. *18*, 1014 (1964).

[6] *M. Eigen* and *L. de Maeyer* in *S. L. Friess*, *E. S. Lewis*, and *A. Weissberger*: Techniques of Organic Chemistry. Interscience Publishers, New York 1963, Vol. VIII, Part II, Chapter XVIII. We thank Prof. *M. Eigen* and Dr. *H. Diebler*, Göttingen, for valuable support.

[7] By the same method, *Sasaki* (Abstracts VIIth Internat. Conf. on Coordination Chemistry, Stockholm 1962, p. 171) found tungstates $H_nW_6O_{21}^{(6-n)-}$ (n = 1, 2, 3, or 4) in equilibrated polytungstate solutions of degree of acidity $Z > 1.4$, although under these conditions 12-fold aggregation must predominate [1, 8].

[8] *O. Glemser*, *W. Holznagel*, *W. Hölte*, and *E. Schwarzmann*, Z. Naturforsch. *20b*, 725 (1965).

[9] *G. Schwarzenbach* and *J. Meier*, J. inorg. nuclear Chem. *8*, 302 (1958), and *G. Schwarzenbach*, *G. Geier*, and *J. Littler*, Helv. chim. Acta *45*, 2601 (1962), found a similar intermediate $W_4$ species in the system $H^+/WO_4^{2-}$.

[10] The species $Mo_4O_{13}^{2-}$ described in the literature can only be an octamolybdate [1].

[11] *D. L. Kepert*, Progr. inorg. Chem. *4*, 199 (1962).

## Synthesis of *C*-Methyl Branched Uracil Nucleosides

By Doz. F. W. Lichtenthaler and H. Zinke

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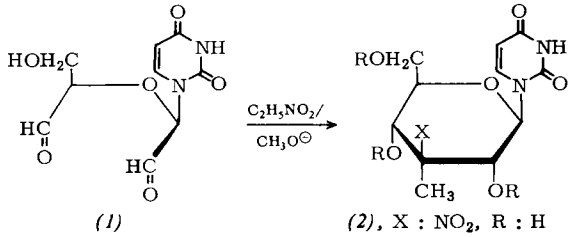
Extension of the reaction whereby "nucleoside dialdehydes" are cyclized by nitromethane[1,2] to nitromethane homologues[3] would be expected to produce branched nucleosides of pharmacological interest.

2-*O*-[(*R*)-Formyl-(1-uracilyl)methyl]-(*R*)-glyceraldehyde ("uridine dialdehyde") *(1)*, obtained by oxidation of uridine with periodate, is converted by nitromethane/sodium methoxide in methanol into a crystalline mixture of isomers (yield 79.7 % based on uridine), from which 1-(3′-deoxy-3′-*C*-methyl-3′-nitro-β-D-glucopyranosyl)uracil *(2)*, m.p. 226 to 240 °C (decomp.), $[\alpha]_D^{20} = +25.5°$ ($H_2O$), can be separated as main product by fractional crystallization. Acetylation of this product in acidic solution gives the tri-*O*-acetate *(3)*, m.p. 228 °C, $[\alpha]_D^{20} = -8°$ ($CHCl_3$); hydrogenation in presence of Raney nickel gives 1-(3′-amino-3′-deoxy-3′-*C*-methyl-β-D-glucopyranosyl)uracil *(4)* as monohydrate, m.p. 146–148 °C, $[\alpha]_D^{20} = +39°$ ($H_2O$). With acetic anhydride/methanol the amine affords the acetamido compound *(5)*, m.p. 248–250 °C (decomp.), $[\alpha]_D^{20} = +72°$ ($H_2O$), which is converted by further acetylation into the tetraacetate *(6)*, m.p. 133 °C, $[\alpha]_D^{20} = +21°$ ($CHCl_3$).




*(1)*

*(2)*, X : $NO_2$, R : H
*(3)*, X : $NO_2$, R : Ac
*(4)*, X : $NH_2$, R : Ac
*(5)*, X : NHAc, R : H
*(6)*, X : NHAc, R : Ac

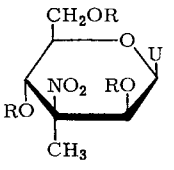
The 3′-*C*-methyl-D-*gluco*-configuration of the nitro compound *(2)* and the derived products *(3)* to *(6)* follow from NMR spectroscopic data:

1. In $(CD_3)_2SO$ the nitro-compound *(2)* gives a 1 H doublet at $\tau = 4.02$ with $J = 6$ Hz, which proves the diaxial arrangement of the 1′- and 2′-protons and thus the equatorial orientation of the 2′-hydroxyl group[5].

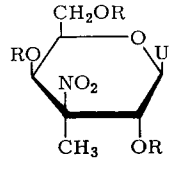
2. The NMR spectrum of the nitro acetate *(3)* in $CDCl_3$ contains around $\tau = 8$ two signals with the intensity ratio 2:1 that indicate equatorial acetoxy groups at positions 2′ and 4′ ($\tau = 7.93$; 6 H) as well as the primary 6′-acetoxy group ($\tau = 8.02$; 3 H). The signals (in $CDCl_3$) of the acetoxy groups of the tetraacetate *(6)* must be interpreted analogously: 6′-OAc at $\tau = 7.99$, equatorial 2′- and 4′-OAc at $\tau = 7.90$ and 7.93.

3. The configuration at the tertiary C-3′ can be determined by comparison of the acetamido and acetoxy signals with those of analogous compounds[6]. The 3 H singlet at $\tau = 8.15$ in the $CDCl_3$ spectrum of the tetraacetate *(6)* is thus due to an equatorial 3′-acetamido group. The corresponding orientation is to be assumed for the nitro group in *(2)*.

Fractional crystallization, from water, of the mixture remaining after separation of the main product yields two further nitrohexosyluracil isomers: *(7)*, m.p. 186–190 °C, $[\alpha]_D^{20} = +121°$ (methanol), and *(8)*, m.p. 157–160 °C, $[\alpha]_D^{20} = +50°$ (methanol), as monohydrates in low yield; on acetylation in acidic solution these afford tri-*O*-acetates *(9)*, m.p. 106–109 °C, $[\alpha]_D^{20} = +124°$ ($CHCl_3$), and *(10)*, m.p. 107 to 110 °C, $[\alpha]_D^{20} = +24°$ ($CHCl_3$), respectively. According to their NMR spectra compounds *(7)* and *(9)* have the D-*manno*- and compounds *(8)* and *(10)* the D-*galacto*-configuration.




U: 1-Uracilyl




*(7)*, R : H
*(9)*, R : $CH_3CO$

*(8)*, R : H
*(10)*, R : $CH_3CO$

In the present case our total yields of isomer mixture (79.7 %) exclude the epimerization at C-5 observed by *Baer*[4c] for nitroethane cyclization of 2-*O*-[(*S*)-formyl(methoxy)methyl]-(*R*)-glyceraldehyde.

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[2] *K. A. Watanabe, J. Beranek, H. A. Friedman*, and *J. J. Fox*, J. org. Chemistry *30*, 2735 (1965); *J. Beranek, H. A. Friedman, K. A. Watanabe*, and *J. J. Fox*, J. heterocyclic Chem. *2*, 188 (1965); *F. W. Lichtenthaler* and *H. P. Albrecht*, Chem. Ber. *99*, 575 (1966).

[3] Cyclizations with nitroethane have already been carried out with aliphatic dialdehydes [4a] and with dialdehydes derived from methylglycosides [4b, 4c].

[4a] *F. W. Lichtenthaler, H. Leinert*, and *H. K. Yahya*, Z. Naturforsch., in press.

[4b] *S. W. Gunner, W. G. Overend*, and *N. R. Williams*, Chem. and Ind. *1964*, 1523.

[4c] *H. H. Baer* and *G. U. Rao*, Liebigs Ann. Chem. *686*, 210 (1965).

[5] Cf. *L. D. Hall*, Tetrahedron Letters *1964*, 1458.

[6] *P. Emig*, Diploma Thesis, Technische Hochschule Darmstadt, 1966; *F. W. Lichtenthaler* and *P. Emig*, unpublished.

# CONFERENCE REPORTS

## Preparative and Kinetic Aspects of Radiation Chemistry

The Nuclear, Radio, and Radiation Chemistry Section of the Gesellschaft Deutscher Chemiker and the Hahn-Meitner-Institut für Kernforschung, Berlin, held a symposium from April 5th to 7th in Berlin (Germany), on the chemical effects of energetic radiation. The following is a selection of the abstracts of papers read.

### γ-Radiolysis of Liquid Ammonia in the Presence of *p*-Nitrophenol

*M. Dobó* and *D. Schulte-Frohlinde*, Karlsruhe (Germany)

On γ-irradiation of *p*-nitrophenol in liquid ammonia, *p*-aminophenol, 2-amino-4-nitrophenol, hydrazine, nitrogen,

and hydrogen are formed by reactions of the radiolysis products of $NH_3$ with one another or with the trapping agent. The 2-amino-4-nitrophenol is produced by addition of the $\cdot NH_2$ radical to *p*-nitrophenol, with subsequent dehydrogenation of the cyclohexadienyl radicals formed. It is remarkable that this introduction of an amino group into an aromatic compound by way of a free radical occurs selectively.

Aminophenol arises from the action of $\cdot H$ and $e^{\ominus}$ on nitrophenol through intermediate stages. Hydrogen and hydrazine are formed from ammonia even if the nitrophenol concentration is high (*ca.* 1 mole/l); the precursors of these products are thus not trapped by nitrophenol. At dosages greater than $3\times10^{20}$ eV/ml the $N_2H_4$ concentration becomes stationary, *i.e.* hydrazine is formed as rapidly as it is degraded to nitrogen.

For a study of the kinetics $G_{2\text{-amino-4-nitrophenol}}$, $G_{\text{hydrogen}}$, and $G_{\text{nitrogen}}$ were measured in relation to dosage and to the concentration of *p*-nitrophenol. At concentrations exceeding 1.0 mole/l $G_{2\text{-amino-4-nitrophenol}}$ is constant ($G \approx 1.80$). If it is assumed that in this region each amino radical that is formed is recovered in the 2-amino-4-nitrophenol and that one nitrogen molecule is formed from two molecules of hydrazine (for which there is some evidence), then the following stoichiometry results for the γ-radiolysis of liquid ammonia in the presence of *p*-nitrophenol:

$$3.0\ NH_3 \xrightarrow[100\ eV]{\gamma} 1.8\ \cdot NH_2 + 1.74\ (H\cdot + e^{\ominus}) + 0.5\ 8N_2H_4 + 0.61\ H_2$$

## Labeling of Aromatic Halides by Radiation-Induced Isotopic Exchange

*H. Elias*, Darmstadt (Germany)

Aliphatic halides RX are in general easily labeled by homogeneous, nucleophilic isotopic exchange in solution:

$$R{-}X + {}^*X^- \rightleftarrows R{-}{}^*X + X^- \qquad (1)$$

or by heterogeneous isotopic exchange in gas chromatography columns[1]:

$$R{-}X_{\text{mob. phase}} + [(Butyl)_4N]\ {}^*X_{\text{stat. phase}} \rightleftarrows R{-}{}^*X_{\text{mob. phase}} + [(Butyl)_4N]\ X_{\text{stat. phase}} \qquad (2)$$

Both methods fail for aromatic halides such as $C_6H_5I$, $C_6H_5Br$, and $C_6H_5Cl$ in which there is no group next to the halogen that favors substitution.

On radiolysis and photolysis of organic iodides or bromides in the presence of radioactive iodine or bromine a radiation-induced isotopic exchange occurs:

$$R{-}X + {}^1/_2\ {}^*X_2 \longrightarrow R{-}{}^*X + {}^1/_2\ X_2 \qquad (3)$$

The *G* value for this exchange is usually greater than for the radiolysis products. Thus radiation-induced isotopic exchange can be used for labeling organic iodides and bromides. The method is of particular interest for aromatic halides that cannot be labeled in accordance with equation (1) or (2).

A study has been made of the radiation-induced isotopic exchange of iodobenzene *(1)*, *o*-iodobenzoic acid *(2)*, and *o*-iodohippuric acid with $^{131}I_2$ in the presence of oxygen by means of a $^{60}Co$ source (dose rate: $0.71\times10^6$ rad/hr) at about 30 °C [benzene/1,4-dioxane was used as solvent for *(2)* and *(3)*]. Radiolytic formation of iodine from *(1)*, *(2)*, and *(3)* was also measured.

*System iodobenzene/*$^{131}I_2$: With a radiation dose of $5\times10^{20}$ eV/g at $c_{I_2} = 0.02$ mole/l, the value of $G_{I_2}$ was 0.90. For the isotopic exchange the following values were found: $G_{IE}$ = 8.2 for $c_{I_2} = 0.17$ mole/l; $G_{IE} = 6.7$ for $c_{I_2} = 0.038$ mole/l; and $G_{IE} = 5.1$ for $c_{I_2} = 0.0056$ mole/l. Thermal isotopic exchange was not observed even when the solutions were kept standing for a longer time.

Iodobenzene is easily labeled at $c_{I_2} = 0.0056$ mole/l with a dose of $2.4\times10^6$ rad, under which conditions the exchange amounts to 86 %. The irradiated iodobenzene contains a total of only about 0.1 mole-% of organic radiolysis products and these can be easily separated.

*System o-iodobenzoic acid/*$^{131}I_2$: $G_{I_2} = 0.85$ for a solution of *(2)* ($c_{(2)} = 0.1$ mole/l) in a benzene/dioxane mixture (1:3). For a 1:1 benzene/dioxane mixture (as solvent) with $c_{(2)} = 0.66$ mole/l and $c_{I_2} = 10^{-3}$ mole/l, $G_{IE} = 1.5$ (exchange amounts to 90 % with a dose of $3\times10^6$ rad). The proportion of radiolysis products is larger for *(2)* than for *(1)*.

*System o-iodohippuric acid/*$^{131}I_2$: The exchange behavior of *(3)* and the radiolytic formation of iodine from *(3)* are similar to those for *(2)*.

## Study of the Radical Anion $SO_4^-$ by Pulse Radiolysis [2]

*E. Heckel*, Berlin (Germany)

OH radicals formed on radiolysis of water react with $HSO_4^-$ ions with formation of the radical anion $\cdot SO_4^-$. These particles have maximal extinction ($\varepsilon = 1.05\times10^3$ l mole$^{-1}$ cm$^{-1}$) at 4500 Å. The rate constant for the reaction of OH with $HSO_4^-$ amounts to $8\times10^5$ l mole$^{-1}$ sec$^{-1}$. In the presence of reducing substances the extinction at 4500 Å is reduced owing to scavenging of OH radicals; the reaction of OH with $HSO_4^-$ can thus be used for determination of the rate constants of reactions of the OH radical. The following rate constants have been found:

| Reaction | $k$ (l mole$^{-1}$ sec$^{-1}$) |
|---|---|
| $Fe^{2+} + \cdot OH$ | $5.0\times10^9$ |
| $Fe^{2+} + \cdot SO_4^-$ | $9.9\times10^8$ |
| $CH_3OH + \cdot SO_4^-$ | $2\times10^7$ |
| $C_2H_5OH + \cdot SO_4^-$ | $3\times10^7$ |

## Investigations, by Pulse Radiolysis, of the Reactivity of Catalase towards Hydrated Electrons and Free OH Radicals

*W. Karmann*, Berlin (Germany)

Catalase reacts in aqueous solution with the hydrated electron and with the OH radical with rate constants of $3.7\times10^9$ and $8.3\times10^{10}$ l mole$^{-1}$ sec$^{-1}$, respectively[3]. The reaction of OH with catalase is diffusion-controlled, although some of the amino acids of catalase do not, when in the isolated state, react with an OH radical at each encounter. A diffusion coefficient of $2.3\times10^{-5}$ cm$^2$ sec$^{-1}$ can be calculated for the OH radical from these measurements. The results are of interest in relation to the decomposition of catalase on irradiation in aqueous solution and in relation to the influence of catalase on the sensivity of biological systems to radiation. It is further suggested that reactions of small radicals with monomers, which although fast are not exclusively diffusion-controlled, may become diffusion-controlled if the reaction partner is a macromolecule consisting of the same monomer units.

## Depolymerization of Cellulose by $^{60}Co$-γ-Radiation

*H.-G. Klippel*, Hamburg (Germany)

In 1954 *Charlesby* reported that dry cellulose was degraded to a powdery material when irradiated with about $10^8$ rad in a reactor or with a γ-source. From the change in viscosity

[1] *H. Elias* in: Proceedings of the International Symposium on the Preparation and Biomedical Application of Labeled Molecules, Euratom 2000e, p. 467 (1964).

[2] *E. Heckel, A. Henglein*, and *G. Beck*, Ber. Bunsenges. physik. Chem. *70*, 149 (1966).

[3] *A. Henglein, W. Karmann, W. Roebke*, and *G. Beck*, Makromolekulare Chem. *92*, 105 (1966).

of Cu(II)-ethylenediamine solutions it was deduced that $10^6$ rad caused liberation of 0.16 % of the glucose units [4].

Increase in the swelling capacity of the cellulose parallels an increase in the rate of hydrolysis and can be explained as activation of the bonding (uptake of energy by the bonding electrons). Increasing the dose deepens the yellow color of the irradiated material, and this may be made the basis of a method for determining doses of the order of $10^{6.25}$ to $10^8$ rad (with an accuracy of ± 2 %) [5].

Medicinal cotton wool (prepared as described by *v. Bruns*), was irradiated in a circular isodose arrangement by a Co unit with a dosage of *ca.* 150 Ci, *i.e.* $1.5\times10^6$ rad/hr (distance from the $^{60}$Co cylinder 1 cm; diameter 1 cm). The irradiated cellulose was stored for five months in the dark under nitrogen; the degree of polymerization was then determined by *Jayme-Bergmann*'s method with EWNN, *i.e.* in an aqueous solution of hexasodium tritartratoferrate at defined $OH^-$ concentration, as solvent [6]. Use of this solvent in two stages of increasing EWNN concentration permits relatively rapid dissolution of the cellulose for the determination of viscosity. The viscosity was measured in a constant-temperature Ubbelohde viscometer.

Before irradiation the pre-treated, bleached cellulose had a degree of polymerization of *ca.* 20000. γ-Irradiation with a dose of $5\times10^6$ rad resulted in fission of the cellobiose chain into three fragments; increasing the dose to $10\times10^6$ rad reduced the degree of polymerization to about half its initial value; and further increase to $30\times10^6$ rad caused the cleavage of five hexose units per $10\times10^6$ rad. At higher doses not only does the chance of recombination increase but, in the presence of water, so does the rate of reaction with atmospheric oxygen and nitrogen oxides.

## Radiation Chemical Reduction of Aromatic Nitro Compounds

*E. Koerner von Gustorf*, Natick, Massachusetts (U.S.A.)

Direct reduction of aromatic nitro compounds to nitroso compounds can be achieved radiation chemically with the aid of $Fe(CO)_5$ in benzene solution according to the overall equation (1):

$$2\ Ar{-}NO_2 + 2\ Fe(CO)_5 \xrightarrow[\text{benzene}]{^{60}CO-\gamma} [Ar{-}NOFe(CO)_3]_2 + 2\ CO + 2\ CO_2 \quad (1)$$

The nitroso group is shielded from further reduction by formation of an iron tricarbonyl complex.

The mechanism of this reaction can be written as in (2)–(6):

$$C_6H_6 \rightsquigarrow C_6H_6^* \quad (2)$$

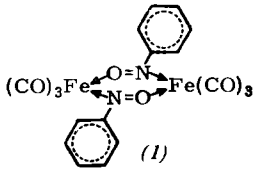
$$Fe(CO)_5 + C_6H_6^* \rightarrow C_6H_6 + Fe(CO)_5^* \quad (3)$$

$$Fe(CO)_5^* + Ar{-}NO_2 \rightarrow Ar{-}NO_2Fe(CO)_4 + CO \quad (4)$$

$$Ar{-}NO_2Fe(CO)_4 + C_6H_6^* \rightarrow Ar{-}NOFe(CO)_3 + CO_2 + C_6H_6 \quad (5)$$

$$2\ Ar{-}NOFe(CO)_3 \rightarrow [Ar{-}NOFe(CO)_3]_2 \quad (6)$$

Nitrobenzene gives only dimeric nitrosobenzene-tricarbonyliron of structure *(1)* [7], but *para*-substituted nitrobenzene derivatives give monomeric or dimeric complexes. Electron-repelling substituents favor formation of monomeric complexes, electron-attracting substituents favor that of dimeric complexes, as indicated by the Hammett σ-values. The relative electron density on the iron can be estimated from the position of the C≡O bands in the infrared spectra and is related to the σ-constants of the substituents [8].




*(1)*

Multiply substituted nitro compounds, *e.g.* 2-chloro-6-nitrotoluene, can also be reduced in accord with equation (1); with 2,2′-dinitrobiphenyl selective reduction of one nitro group can be achieved.

The *G* values for formation of $X{-}C_6H_4{-}NOFe(CO)_3$ lie in the range 0.1 to 2.0, depending on the substituent (X = *p*-$OCH_3$, *p*-$CH_3$, *p*-Cl, *p*-$COOCH_3$, *o*-$CH_3$, *o*-Cl, *m*-$CH_3$, *m*-Cl).

Tricarbonyliron complexes of aromatic nitroso compounds react, for instance, with aromatic amines, yielding azo compounds [7], and can replace the free nitroso compounds in preparative chemistry.

## Pulse Radiolysis of Dimethyl Sulfide in Aqueous Solution

*G. Meissner*, Berlin (Germany)

The hydrated electron hardly reacts at all with dimethyl sulfide, in accordance with mass-spectroscopic results. The OH radical reacts with dimethyl sulfide by removal of either an H atom or an electron. The absorption spectra of the products $CH_3SCH_3^+$ ($\lambda_{max}$ = 470 mμ) and $CH_2SCH_3$ ($\lambda_{max}$ = 290 mμ) have been measured. Both particles disappear from solution in a reaction of the second order. The rate of the reaction between $CH_3SCH_3^+$ and $CH_3SCH_3^+$ is increased by addition of an inert salt *e.g.* $NaClO_4$. A second sulfide molecule is required for formation of $CH_3SCH_3^+$; a complex of $CH_3S(OH)CH_3$ with $CH_3SCH_3$ occurs as intermediate.

## Degradation and Cross-Linking of Polydimethylsiloxane in Solution under the Influence of $^{60}$Co-γ-Radiation

*W. Schnabel*, Berlin (Germany)

Polymers that form a three-dimensional network when in the pure state are mainly degraded on irradiation in solution provided that the polymer concentration is less than the critical concentration [9]. With respect to previous measurements of the weight-average molecular weight it was not possible to relate the specific degradation density $p_o$ to the specific cross-link density $q_o$ [*] or to determine the dependence of $p_o/q_o$ on the polymer concentration.

The following facts have been established for the polydimethylsiloxane/toluene system by the use of weight- and number-average molecular weight data: $p_o/q_o$ (= 0.02 for the homogeneous polymer) increases with addition of toluene, equals 2 at the critical concentration, and tends to infinity at a mole fraction of polymer base units $x_p \leqslant 0.03$. The *G* value for cross-linking bonds decreases with decreasing polymer concentration and is zero in very dilute solutions, but the *G* value for main chain scissions increases from *ca.* 0.1 (homogeneous polymer) to *ca.* 0.8 ($x_p$ = 0.03). These results confirm *Henglein*'s theory in principle: according to this theory $p_o$ should be independent of the polymer concentration and $q_o$ should become continuously smaller with increasing dilution. The relatively small

[4] *A. Charlesby*, Nuclear Sci. Abstr. *8*, 3288 (1954).

[5] *R. C. L. Bosworth, J. Ernst*, and *J. L. Garnett*, Int. J. appl. Radiat. Isotopes *11*, No. 9, p. 152 (1961).

[6] *G. Jayme* and *H. Bergmann*, Papier *11*, 280 (1957).

[7] *E. Koerner von Gustorf* and *M.-J. Jun*, Z. Naturforsch. *20b*, 521 (1965).

[8] *E. Koerner von Gustorf, M. C. Henry, R. Sacher*, and *C. DiPietro*, unpublished work.

[9] *V. Ikada* and *W. Schnabel*, Makromolnculare Chem. *86*, 20 (1965).

[*] $p_o$ and $q_o$ are the fractions of monomer units degraded and crosslinked, respectively, by a dose of 1 Mrad.

increase in $p_o$ with increasing dilution is probably due to transfer of energy from the solvent to the polymer.

### γ-Radiolysis of 5-Bromouracil in Oxygen-Containing Aqueous Solutions

*O. Volkert, W. Bors, E. Gilbert,* and *D. Schulte-Frohlinde,* Karlsruhe (Germany)

5-Bromouracil can be incorporated into the DNA of bacteriophages in place of thymine. Phages containing 5-bromouracil are more sensitive to radiation than are normal phages, consequently a study of the radiochemistry of 5-bromouracil seemed important for clarification of this phenomenon.

Hydrogen, hydrogen bromide, hydrogen peroxide, isodialuric acid (main product), alloxan, isobarbituric acid, diisobarbituric acid, urea, and an unstable hydroperoxide are formed on irradiation of 5-bromouracil in oxygen containing aqueous solution. In order to elucidate the mechanism of the decomposition of 5-bromouracil the $G$ values for these products were determined and related to the dose and the concentration of 5-bromouracil. In dilute solutions ($<10^{-4}$ mole/l) only the OH radical reacts with 5-bromouracil. At increasing concentrations the reducing radicals formed by radiolysis of water begin to attack the 5-bromouracil. At concentrations greater than $2\times10^{-3}$ mole/l the $G_0$ value (initial value) for disappearance of 5-bromouracil equals the sum of the $G$ values of all the radicals resulting from the radiolysis of $H_2O$. Quantitative analysis of the kinetics showed that it is not only the concurrent reactions of the solvated electron with 5-bromouracil and with oxygen that are responsible for the increase in the $G_0$ value, but that at higher concentrations the $O_2^-$ radical also reacts with 5-bromouracil.

The first step in the reaction of the solvated electron with 5-bromouracil leads to separation of bromide ions, but the OH radical adds to the C=C double bond. Addition at the 6-position, with subsequent addition of $O_2$, leads to a peroxy radical, which by reaction with a $HO_2$ radical yields 4-hydroxy-5-uracilyl hydroperoxide. The hydroperoxide decomposes in solution by a second-order reaction, with loss of $O_2$ and formation of isodialuric acid. Addition of the OH radical at position 5 leads to an intermediate that cannot be isolated and at once reacts further, by ring opening, to yield a second intermediate, which is sensitive to hydrolysis; urea and mesoxalic acid were identified as secondary products.

### Radiation Chemical Formation and Optical Absorption Spectra of Organic Sulfur Radicals in Organic Glasses at —196 °C

*J. Wendenburg,* Berlin (Germany)

Organic disulfides, sulfides, mercaptans, and hydrogen sulfide have been exposed in tetrahydro-2-methylfuran or nydrocarbon glasses to γ-iradiation at −196 °C. The absorption spectra and extinction coefficients of the following radicals of uni-coordinate sulfur have been determined: $CH_3S$, n-$C_4H_9S$, t-$C_4H_9S$, $CH_2{=}CH{-}CH_2S$, $C_6H_5S$, $C_6H_5CH_2S$, and $SH(\lambda_{max} \approx 4200$ Å, $\varepsilon \approx 1.05 \times 10^4$ l mole$^{-1}$ cm$^{-1}$).

The disulfides form radicals by dissociative capture of electrons formed by ionization of the vitreous solvent. Mercaptans yield sulfur-containing radicals only as the glass warms up, the reaction being H abstraction by the radicals that result from radiolysis of the solvent. HS is formed when irradiated glasses containing $H_2S$ are warmed. Benzyl mercaptan and dibenzyl disulfide (the latter to a smaller extent) yield benzyl radicals by electron capture. Several new absorption bands were observed and have been ascribed to negative ions: $C_6H_5SH^-$ (8100 Å) from phenyl mercaptan, $C_6H_5SC_6H_5^-$ (broad absorption in the visible region) from diphenyl sulfide, $C_6H_5CHS^-$ and $C_6H_5CH^-SH$ from dibenzyl sulfide (*ca.* 3900 Å). Carbon tetrachloride, if present, inhibits all the reactions of free electrons in the glass, but the reactions that free radicals undergo on warming are not suppressed.

Glassy mixtures of methylcyclohexane and isopentane, containing olefins, give strong absorption bands between 7000 and 9000 Å, which are derived from positive ions. Olefin cations and protonated olefins absorb at longer wavelength the fewer H atoms are attached to the doubly bonded C atoms. Absorption by positive ions has also been observed for diphenyl disulfide (8500 Å) and diallyl disulfide (6840 Å). Small additions of readily protonated substances such as isopropyl alcohol and tetrahydromethylfuran weaken the absorption bands of positive ions.

### Radiation Chemical Synthesis of Dichloro-2-chloroalkylphosphines

*K. Wunder,* Berlin (Germany)

γ-Irradiation of mixtures of olefins and phosphorus trichloride affords the corresponding dichloro-2-chloroalkylphosphines by a chain reaction. The $G$ values reach *ca.* 2000 during irradiation at *ca.* 100 °C. Several new compounds 2-Cl−R−$PCl_2$ have been isolated in gram quantities (*e.g.* R = cyclopentyl, b. p. 238 °C; R = cyclohexyl, b. p. 256-260 °C; R = cycloheptyl, b. p. 286–288 °C).

At temperatures above 150 °C another chain reaction occurs, which leads to dichloro(alkyl)phosphines and β-chloroalkenes. Several olefins that have rather large groups attached at the double bond undergo the second reaction more often than the first, even at room temperature.

### γ-Irradiation of 3-Phenyl-1,4-cyclohexadiene in Benzene

*B. Zimmerli,* Lausanne (Switzerland)

3-Phenyl-1,4-cyclohexadiene (P), which is formed on radiolysis of benzene, is rapidly destroyed again. Solutions of P in benzene (B) show on irradiation a decrease in the concentration of P that can be expressed as a pseudo-first order reaction, in which $c_p = c_{p_0} \cdot e^{-kD}$ where $k$ is a constant and $D$ the radiation dose.

At 25 °C 17 % (24 % at 85 °C) of the P consumed in the radiolysis appears as biphenyl (Q). The following simplified scheme satisfactorily accounts for these results:

$$\text{(1)}\quad B \xrightarrow{k_1} B^*$$

$$\left.\begin{array}{ll} \text{(2)} & B^* + P \xrightarrow{k_2} \\ \text{(3)} & B^* + Q \xrightarrow{k_3} \\ \text{(4)} & B^* + B \xrightarrow{k_4} \end{array}\right\} \text{Products, deactivation}$$

If a stationary amount of excited benzene (B*) is assumed, this scheme leads to a linear relation between $1/k$ and the initial concentration $c_{p_0}$. $G$ values [$k_1 c_B = G(B^*)$] and the ratios $k_4/k_2$ and $k_3/k_2$ can be calculated from the intercept on the axis and the slope.

| Temp. [°C] | Q [μmole/g] | G(B*) [μmole/g·Mrad] | $k_4/k_2$ | $k_3/k_2$ |
|---|---|---|---|---|
| 25 | — | 2.2 ± 0.2 | (5.6 ± 1) × $10^{-3}$ | — |
| 85 | — | 1.8 ± 0.2 | (1.6 ± 0.3) × $10^{-2}$ | — |
| 25 | 340 | 1.9 ± 0.2 | — | 1 ± 0.2 |

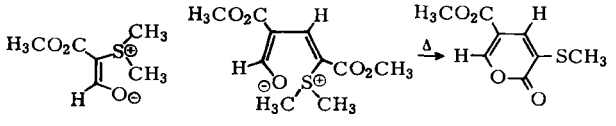
Within the range 25 to 85 °C the $G$ value for excited benzene seems to be independent of temperature. The two values of $k_4/k_2$ permit a difference in activation energies of 4 ± 2 kcal/mole to be estimated; *i.e.* the activation energy of reaction (4) is about 4 kcal/mole greater than that of reaction (2). The ratio $k_3/k_2$ indicates that Q and P react equally readily with B*. The present measurements do not permit any conclusion about the nature of B*. [VB 1000 IE]

German version: Angew. Chem. *78*, 778 (1966)

## Heterocycles from Acetylene Derivatives

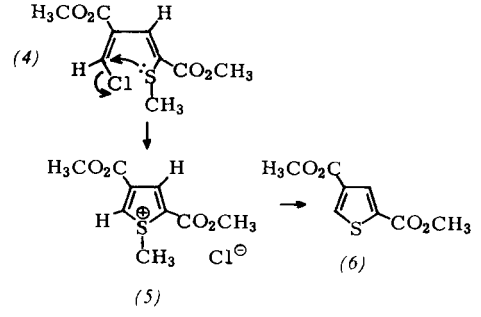
*E. Winterfeldt*, Berlin (Germany)

The betaine-like compounds *(1)* and *(2)* can be prepared from methyl propiolate and dimethyl sulfoxide. When high concentrations of the ester are used, only compound *(2)* can be isolated, but at high dilution the 1:1 adduct *(1)* is obtained at 125°C.



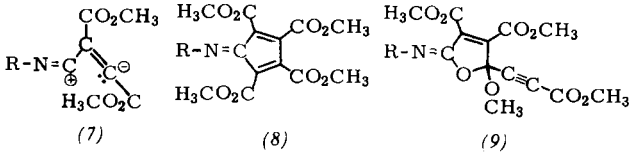
*(1)* *(2)* *(3)*

Both substances are crystalline and quite stable. When compound *(2)* is heated at 150°C in a vacuum the main product is the 2-pyrone *(3)*, and dimethyl 2,4-furandicarboxylate is formed only to a small extent. Thionyl chloride converts compound *(2)* quantitatively into dimethyl 2,4-thiophenedicarboxylate *(6)* at room temperature, by way of the stages *(4)* and *(5)*.



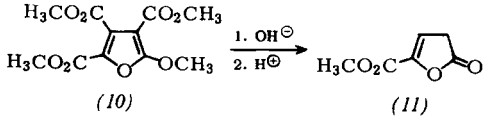
*(4)* *(5)* *(6)*

Reaction of dimethyl acetylenedicarboxylate with isocyanides usually leads to a large number of products, but if a large excess of isocyanide is used at −10°C the main products – probably formed from a primary product *(7)* – are the 1:2 adducts *(8)* and *(9)*; their structures are proved by infrared, ultraviolet, and NMR spectroscopy, by elemental analyses, and by molecular-weight determinations.

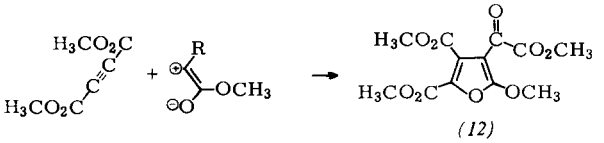


*(7)* *(8)* *(9)*

Heating dimethyl acetylenedicarboxylate in a sealed tube at 150–180°C in the presence of copper as catalyst and oxygen leads to a 50% yield of the furan derivative *(10)*, whose structure is supported by ultraviolet, infrared, and NMR data as well as by its mass spectrum and conversion into the enol lactone *(11)*. Alongside *(10)* carbon monoxide is evolved, and the reaction occurs only in the presence of oxygen.



*(10)* *(11)*



*(12)*

R = −CO−$CO_2CH_3$; −C̈−$CO_2CH_3$ + O

These results do not agree with a reaction mechanism recently proposed[1]. Instead, formation of an α-oxo-ester *(12)* by cycloaddition and oxidation is discussed. Trapping experiments with tolan and with sulfur support this hypothesis. The order of the two steps, uptake of oxygen and condensation, remains an open question.

[Lecture at Marburg (Germany), April 22nd, 1966]

[VB 999 IE]
German version: Angew. Chem. *78*, 757 (1966)

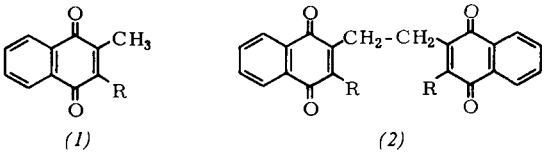
[1] *C. F. Huebner et al.*, Tetrahedron Letters *1966*, 1185.

## Recent Advances in the Chemistry of Quinones

*R. H. Thomson*, Aberdeen (Scotland)

2-Hydroxy-1,4-naphthoquinones can be prepared by autoxidation of α- and β-tetralones in t-butyl alcohol/potassium t-butoxide. The reaction probably proceeds *via* a 1,2-diketone which aromatizes to a 1,2-dihydroxynaphthalene whose semiquinone anion combines with a further mole of oxygen at position 4. Under the same conditions 1,2-dihydroxynaphthalenes rapidly absorb 1 mole of oxygen, giving 2-hydroxy-1,4-naphthoquinones. Autoxidation of 5,7,8-trimethoxy- and 5,6,7,8-tetramethoxy-1-tetralone, followed by demethylation, gives 2,5,7,8-tetrahydroxy- and 2,5,6,7,8-pentahydroxy-1,4-naphthoquinone. These products are identical, respectively, with mompain, a metabolite of *Helicobasidium mompa* Tanaka and spinochrome D, a pigment found in the spines of several species of sea urchin.

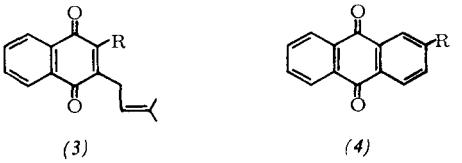
In the Dam-Karrer test for vitamin K and other allylnaphthoquinones (treatment with ethanol/sodium ethoxide) a blue mesomeric anion is formed by removal of a proton from the methylene group adjacent to the quinone ring. The colour is transient, changing to red-brown as a consequence of cleavage of the side chain to form phthiocol(2-hydroxy-3-methyl-1,4-naphthoquinone). 2-Benzyl-1,4-naphthoquinone behaves similarly, giving first a blue and then a red solution with the formation of lawsone (2-hydroxy-1,4-naphthoquinone) and benzaldehyde. The reaction is considered to be a special case of ketone autoxidation, the quinone behaving as a vinylogous benzyl ketone. If a methyl group is also present in the quinone ring [*(1)*, R = $CH_2C_6H_5$] cleavage of the benzyl group is accompanied by dimerization, and in



*(1)* *(2)*

general 2-methyl-1,4-naphthoquinones of type *(1)*, R = $C_2H_5$, iso-$C_3H_7$, $CH_2CH{=}CMe_2$, $CH_2C_6H_5$, $CH(C_6H_5)_2$, *p*-$CH_3C_6H_4$ Cl, Br dimerize at the methyl group (preferential formation of a primary carbanion) to give the corresponding diquinones *(2)* together with the quinhydrone of *(1)*.

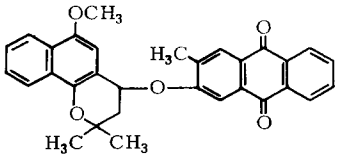
Re-examination of lapacho wood (*Tabebuia ipé*, Bignoniaceae), a well-known source of lapachol *(3)*, R = OH has shown it to contain *inter alia* the naphthoquinones *(3)*, R = H, $CH_3$, OH, $OCH_3$ and anthraquinones *(4)*, R = $CH_3$, $CH_2OH$, $CH_2OAc$, CHO, $CO_2H$), several of which also



*(3)* *(4)*

occur in teak wood (*Tectona grandis*, Verbenaceae). The unusual coexistence of these two groups of quinones suggests a biogenetic relationship which is supported by a simple

*in vitro* conversion of deoxylapachol *(3)*, R = H into tectoquinone *(4)*, R = $CH_3$, by treatment with boron trifluoride in acetic acid. Another compound present in lapacho wood in small amount belongs to both groups and probably has structure *(5)*.



*(5)*

[Lecture at Tübingen (Germany), May 6th, 1966]

[VB 1 IE]

German version: Angew. Chem. *78*, 783 (1966)

## Biosynthesis of Methionine by Bacteria

*L. Jaenicke*, Cologne (Germany)

The biosynthesis of methionine involves reaction between tetrahydrofolic acid and vitamin $B_{12}$. The central step is condensation of homocysteine with a methyl group bound to folate. This methyl group comes from the one-carbon reservoir of the cell and is transferred by way of 10-formyl- and 5,10-methylene-tetrahydrofolic acid to give 5-methyltetrahydrofolic acid.

Methionine synthetase from *S. faecalis* was enriched 800 times and appeared homogeneous by the usual criteria (particle weight 135000). It contains 1 molecule of a corrin derivative that, however, does not posses the full growth activity of complete vitamin $B_{12}$. In its properties it rather resembles a cobyric acid derivative.

The combining reaction requires a reductant (*in vivo* an FAD-containing reductase, which was also purified to homogeneity), but it requires neither ATP nor metal ions. A further activating factor is *S*-adenosylmethionine (SAM). Whereas with catalytic amounts of the enzyme 5-methyltetrahydrofolate (5-$CH_3$-folate) seems to donate its methyl group undiluted to homocysteine, with substrate amounts of the reactants the methyl group of SAM appears undiluted in the cobalt cofactor and hence in the newly formed methionine. 5-$CH_3$-folate dilutes its specific activity 1 : 1.

The results exclude a reaction course in which the cobalamine derivative is converted by ATP into the coenzyme, whose deoxyadenosyl residue is replaced by methyl which is then transferred. Instead, in model experiments with cobinamide and 5-methyltetrahydrofolic acid spectral changes were found indicating formation of a complex in which the folic acid derivative takes the position occupied by the dimethylbenzimidazole portion in the complete cofactor. In this way the tertiary methyl group is labilized sufficiently for transfer.

[Lecture at Darmstadt (Germany), on June 14th, 1966]

[VB 2 IE]

German version: Angew. Chem. *78*, 758 (1966)

## The Kerr Effect at High Pressures and its Relation to the Structure of Molecules and Liquids

*E. Kuss*, Hannover (Germany)

According to the Langevin-Born theory[1] electrical birefringence depends on the fact that a dipole moment is induced in a molecule by an electric field and that, because of the anisotropy of the polarizability, this moment does not lie in the direction of the field. Molecules without a permanent dipole moment thus also become oriented in the field and in such a way that the major axis of the polarizability ellipsoid lies in the direction of the electric field.

This orientation effect is, however, very small and with the fields used in practice its macroscopic result is equivalent to one in every ten thousand molecules being aligned with the field, the rest remaining randomly oriented. This partial orientation of the molecules causes a difference in the ninth decimal place of the refractive index for light polarized parallel to, or perpendicular to, the direction of the field.

When measured on gases or dilute solutions, the electrical double refraction can be used, on the basis of the Langevin-Born theory, to draw conclusions about molecular structure, as has been shown for 1,2-dichloroethylene[2]. The Kerr effect measured for liquids or compressed gases is, however, usually smaller than that expected theoretically, owing to restriction to rotation as well as change in local field strength. The differences from the expected values[3] permit conclusions about quantities characteristic of liquid structure, such as the anisotropy of the local field and the restriction potential.

Few measurements of birefringence at high pressure[4] have previously been made because the very small Kerr effect is overlaid by a considerably greater background birefringence of the high-pressure cell windows, which varies with time and distance across the window. Therefore a new apparatus has been developed for pressures up to 2000 atm, based on the application of an alternating instead of a direct voltage to the Kerr cell; the Kerr effect is thus modulated. The transmitted light is received on a photomultiplier where it generates an alternating signal, which after amplification passes to a ring demodulator. The demodulator receives a reference signal exactly equivalent in frequency and phase to the signal to be measured. It is generated by means of a supplementary optical path through another Kerr cell containing phenyl isothiocyanate, a photodiode, an amplifier, and a peak limiter, and because of the rapid response of the Kerr effect and the frequency doubling it matches the sought effect in frequency and phase. It has been shown by deliberate introduction of spurious birefringence that this method eliminates the latter completely. The Kerr constants are determined either from a galvanometer deflection or by using the galvanometer as a null instrument with a second, "crossed" Kerr cell that compensates the path difference to be measured[5].

With this technique the pressure-dependence of birefringence has been investigated for $CCl_4$, n-heptane, and benzene. The first two substances show a pressure-dependence smaller than expected from the Langevin-Born theory, but benzene shows an abnormally large pressure effect. Up to incipient solidification (600 atm at 25 °C) the double refraction increases by 84%; the pressure dependence is 7.3 times as great as expected theoretically.

This large influence of pressure cannot be explained by the theories of *Peterlin* and *Stuart* and of *Klages* and *Buckingham*[6] without additional assumptions. Presumably at high densities a deformation of the π-electron cloud occurs which is more noticeable by the Kerr effect than by any other method. According to these results the component of the polarizability perpendicular to the plane of the molecule decreases by 19.5% under the influence of pressure, and those in the plane increase by 4.4%.

[Lecture at Hannover (Germany), on May 26th, 1966] [VB4 IE]

German version: Angew. Chem. *78*, 782 (1966)

[1] *P. Langevin*, Ann. Chim. Physique *5*, 70 (1905); *M. Born*, Ann. Physik (4) *55*, 177 (1918); Optik. 2nd Edit., Springer, Berlin 1965, p. 365,

[2] *H. A. Stuart:* Die Struktur des freien Moleküls. Springer, Berlin 1952, p. 228.

[3] *H. A. Stuart:* Hand- und Jahrbuch der chemischen Physik. 10. Section III, 1939, p. 71.

[4] *E. Kuss* and *H. A. Stuart*, Phys. Zs. *42*, 95–105 (1941).

[5] *E. Kuss* and *H. Heydemann*, Z. physik. Chem. N.F. *43*, 97–112 (1964).

[6] *A. Peterlin* and *H. A. Stuart*, Z. Physik *113*, 663 (1939); *G. Klages*, Z. Naturforsch. *7a*, 669 (1952); *9a*, 602 (1954); *A. D. Buckingham* and *J. A. Pople*, Proc. physic. Soc. *A 68*, 905, 910 (1955).

## Solubility in, and Reaction with, Alkali Chloride/$AlCl_3$ Melts, of Metal Oxides and Oxide Halides

*H. Kühnl*, Hannover (Germany)

Molten $NaAlCl_4$ at 200 °C dissolves up to 7 atoms-% of oxygen (as oxide). Thus addition of arsenic-(III) oxide leads to replacement of chloride ions by oxide ions, and arsenic trichloride distils off quantitatively:

$$As_2O_3 + 6\,Cl^- \rightarrow 3\,O^{2-} + 2\,AsCl_3$$

In all alkali chloride/$AlCl_3$ melts, $AlCl_3$ acts as a strong acceptor for oxide ions, so that $CO_2$ is liberated from carbonates, and $NO_2$ and $O_2$ are liberated from nitrates.

Oxides of Fe(II), Co(II), and Ni(II) dissolve at 400 to 500 °C and, on cooling, the anhydrous chlorides crystallize; $CoCl_2$ and $NiCl_2$ are isolated from the melts by filtration and have been identified by analysis and Debye-Scherrer diagrams. $Sb_2O_3$ reacts with the melts, yielding $SbCl_3$, and $V_2O_5$ gives $VOCl_3$. $K_2Cr_2O_7$ reacts differently, according to the temperature and composition of the melt; with a $LiCl/AlCl_3$ melt at 120 °C a solution is formed from which $CrO_2Cl_2$ distils; in $NaAlCl_4$ at 160–180 °C principally $CrCl_3$, which is insoluble in the melts, is formed, with evolution of $Cl_2$; above 350 °C chromium(III) oxide is also formed; the oxide is obtained as main product if the dichromate is added to an $NH_4Cl/AlCl_3$ melt; both in the alkali-metal and the ammonium halide melts the proportion of $Cr_2O_3$ in the product is the greater the coarser is the potassium dichromate added; passing in $CrO_2Cl_2$ always leads to formation of chromium(III) chloride.

On reaction of $MoO_3$ or $Na_2MoO_4$ with melts containing more than one mole of $AlCl_3$ per mole of alkali-metal chloride, aluminium-molybdenum(VI) oxide chlorides are formed from 140 °C; these materials, which are volatile and very sensitive to moisture, can be obtained in four zones on vacuum sublimation in a temperature gradient. However, reaction with $NaAlCl_4$ at 400 °C gives a sublimate of $MoO_2Cl_2$. After addition of $Na_2WO_4$ or $WO_3$ to $LiAlCl_4$ containing an excess of $AlCl_3$ at 120 °C, $WOCl_4$ was isolated; in $NaAlCl_4$ at 400 °C pure $WO_2Cl_2$ is formed.

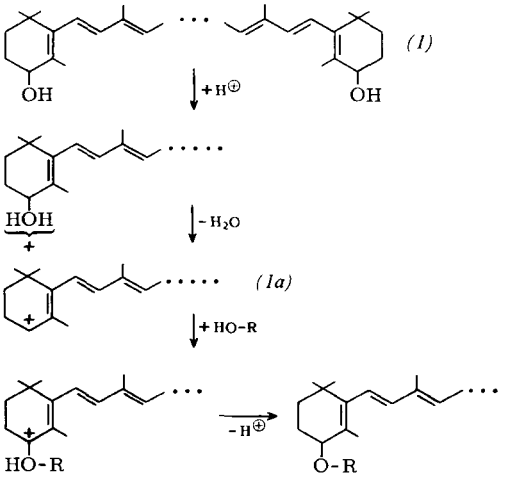
[Lecture at Hannover on May 26th, 1966] [VB 5 IE]
German version: Angew. Chem. 78, 782 (1966)

## Recent Results in Carotenoid Chemistry

*E. C. Grob*, Bern (Switzerland)

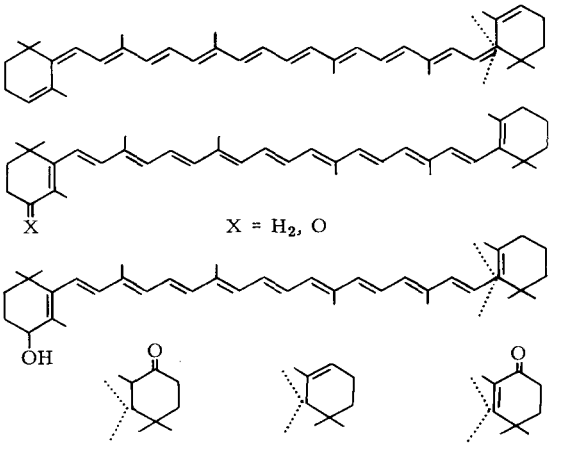
Certain carotenoids are extremely sensitive to acids. *Karrer* [1] has pointed out changes undergone by xanthophylls containing allylic hydroxyl groups when they are treated in chloroform solution with dilute mineral acids. For instance, hydroxyl groups are removed from eschholtziaxanthin by acid catalysis, a carotene hydrocarbon with two additional double bonds resulting.

We find non-allylic as well as allylic hydroxyl groups are eliminated under these conditions. However, if alcohols, ether, benzene, or light petroleum is used in place of chloroform as solvent, selective elimination of allylic hydroxyl groups can be achieved. Zeaxanthin, which does not contain an allylic hydroxyl group, is unchanged in alcoholic solution by 0.01 M HCl. Only the one allylic hydroxyl group is removed from lutein, the second group remaining unaffected. Both the allylic hydroxyl groups are removed from isozeaxanthin by treatment with acid. The chief product from lutein was shown to be a monoethoxy-monoalcohol. Isozeaxanthin gives the monoethoxy-monoalcohol as well as the diether, these ethers being apparently formed in accordance with Scheme 1 (formation of the monoether by the steps shown is repeated at the other end of the molecule, this leading to the diether).



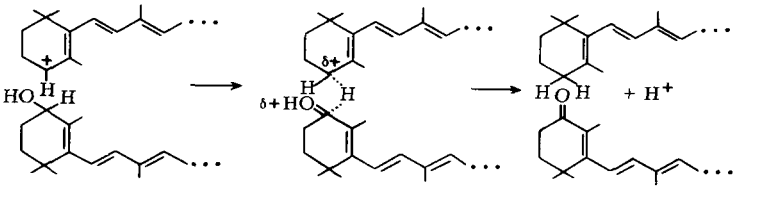

Scheme 1.

In the reaction of isozeaxanthin *(1)* in alcoholic solution a small amount of a monoalkoxy-monoketone is formed as well as the mono- and di-ether. If this reaction is effected in an inert solvent, *e.g.* benzene, seven products can be identified (see Scheme 2), including carotenoid ketones and hydrocarbons.



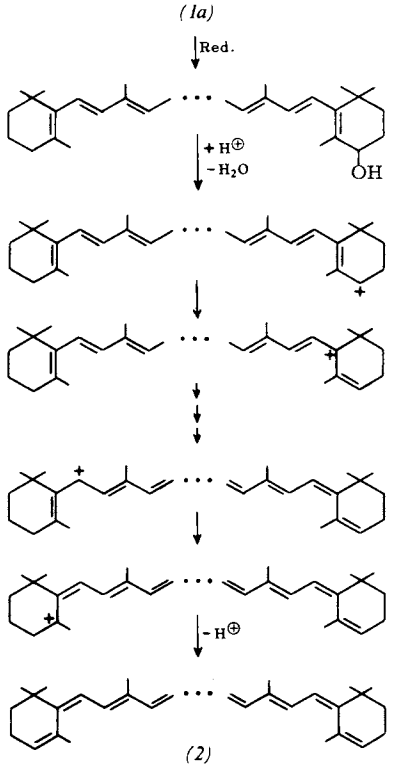

Scheme 2.

Their formation from isozeaxanthin must therefore be ascribed to redox reactions. According to *Steward* and *Bartlett* [2] carbonium ions can act as oxidizing agents towards *e.g.* alcohols, in that, after transfer of a H atom to the carbonium ion and loss of a proton, the alcohol is converted into the corresponding carbonyl compound: the carbonium ion thus affords a hydrocarbon. Transferring this reaction logically to isozeaxanthin leads to Scheme 3 for the formation of carotenoid ketones and β-carotene.




Scheme 3.

Formation of dehydroretro-β-carotene *(2)* proceeds by a somewhat different route. Since an additional double bond is formed in this case, the carbonium ion cannot have been stabilized by taking up a H atom; the new double bond must have arisen by loss of a further proton. Scheme 4 provides a representation of the course of this reaction.




Scheme 4.

Carotenoids are thus susceptible, in principle, to redox reactions. Whether they really are involved in redox reactions in the living cell cannot at present be decided.

[Lecture at Cologne (Germany) on May 20th, 1966] [VB 7 IE]

German version: Angew. Chem. *78*, 784 (1966)

[1] *P. Karrer*, Helv. chim. Acta *34*, 445 (1951).

[2] *R. Steward:* Oxidation Mechanisms. W. A. Benjamin, New York 1964; *P. D. Bartlett et al.*, J. Amer. chem. Soc. *78*, 1441 (1956).

## Spectroscopic Studies of Transition-Metal Fluorides

*D. Oelkrug*, Tübingen

In ionic complexes of Cr(II), Mn(III), and Cu(II) with coordination number 6 the ligands are in octahedral arrangement that is strongly distorted tetragonally (Jahn-Teller effect). Thus, in place of the one ligand-field transition ($E_g \rightarrow T_{2g}$) customary for octahedral symmetry, three transitions can occur ($B_{1g} \rightarrow A_{1g}$, $B_{1g} \rightarrow B_{2g}$, and $B_{1g} \rightarrow E_g$ for an octahedron extended in the $z$-direction), and these can be recognized in the reflectance spectra of most of the compounds as three absorption maxima. The assignment is ensured in particular through the Mn(III) fluorides, where because of the larger $Dq$ values two bands are shifted to higher energies whilst the position of the third is barely affected.

When the metal-ligand distances are known [*e.g.*, for Cu(II) fluorides] the term positions can be calculated by means of the electrostatic model[1], though the results may agree only approximately with the experimental values because of the approximations necessary. Comparison is best made for the fluorides, since they have the most marked ionic character. First the $B_{1g} \rightarrow B_{2g}$ band is used, with the asumption of 3d-radial functions similar to those for hydrogen to yield the effective nuclear charge number $Z_{eff}$ 6.35 for Cu(II), and then the positions of the other two maxima are determined. Except for $K_2CuF_4$, which is the only example yet proposed of a compressed octahedron[2], this method gives sensible term energies. The spectrscopic findings for $K_2CuF_4$, like those for other Cu(II) fluorides, can be better explained on the basis of an elongated octahedron.

Experimental and calculated position of bands ($cm^{-1}$) and experimental ligand-field parameters ($cm^{-1}$).

| Fluoride | $B_{1g} \rightarrow A_{1g}$ | $B_{1g} \rightarrow B_{2g}$ | $B_{1g} \rightarrow E_g$ | $Dq$ | $Ds$ | $Dt$ |
|---|---|---|---|---|---|---|
| $CrF_2$ | | 10950 | 14300 | 1095 | | |
| $KCrF_3$ | 9050 | 11100 | 14000 | 1110 | 1710 | 440 |
| $Na_2CrF_4$ | 9600 [a] | 11850 | 15200 | 1185 | 1850 | 440 |
| $K_3MnF_6$ | 9000 | 17400 [a] | 19600 | 1740 | 1600 | 520 |
| $Na_2MnF_5$ | 12500 | 18000 | 21000 | 1800 | 2210 | 730 |
| $CuF_2$ | 7500 [a] | 8800 | 11350 | 880 | 1435 | 350 |
| | 7580 [b] | | 12040 [b] | | | |
| $KCuF_3$ | 7200 [a] | 8900 | 11550 | 890 | 1410 | 310 |
| | 7425 [b] | | 12060 [b] | | | |
| $RbCuF_3$ | | 9000 | 11900 | 900 | | |
| $Na_2CuF_4$ | 8200? [a] | 9550 | 12200 | 955 | 1550 | 400 |
| | 9700 [b] | | 13700 [b] | | | |
| | $A_{1g} \rightarrow B_{1g}$ | $A_{1g} \rightarrow E_g$ | $A_{1g} \rightarrow B_{2g}$ | $Dq$ | $Ds$ | $Dt$ |
| $K_2CuF_4$ | 7800 [a] | 9200 | 11900 | 410 | −1500 | −360 |
| | 3390 [b] | 8050 [b] | 9460 [b] | | | |

[a] Shoulders.

[b] Calculated positions of bands.

This method also gives the correct order of the ligand-field transitions. The $B_{1g} \rightarrow B_{2g}$ band is found to be the most intensive, and the $B_{1g} \rightarrow A_{1g}$ band the weakest.

[Lecture at Tübingen (Germany), July 15th, 1966]

[VB 8/IE]

German version: Angew. Chem. *78*, 782 (1966)

[1] *H. A. Bethe*, Aun. Physik. [5] *3*, 133 (1929): *W. G. Penney* and *R. Schlapp*, Phys. Rev. *41*, 194 (1932); *42*, 666 (1932).

[2] *K. Knox*, J. chem. Physics *30*, 991 (1959), by X-ray analysis.

# SELECTED ABSTRACTS

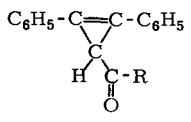
**Xenon dichloride,** $XeCl_2$, has been prepared by *H. Meinert* by high-frequency excitation (25 MHz, 150–350 mA) of a mixture of xenon, fluorine, and silicon tetrachloride or carbon tetrachloride [1:1:1 (v/v)] at a xenon pressure of *ca.* 10 Torr. The crystals can be purified by resublimation under reduced pressure. They decompose at 80 °C or in a high vacuum. The dichloride is presumably formed by way of $XeF_2$, which with $SiCl_4$ or $CCl_4$ or their radicals exchange fluorine for chlorine. / Z. Chem. *6*, 71 (1966) / −Ma

[Rd 498 IE]

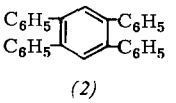
**Hydrocarbon solutions of Grignard reagents** can be prepared by using equivalent amounts of triethylamine, according to *E. C. Ashby* and *R. Reed*. For instance, dropping a benzene solution of an alkyl halide on to Mg turnings in benzene/triethylamine (reaction started by gentle warming) gives clear and usually colorless solutions. The temperature is kept at 40–50 °C. These Grignard reagents, which are readily soluble in benzene, contain Mg, halogen, and N in the atomic ratios 1:1:1. / J. org. Chemistry *31*, 971 (1966) / −De.

[Rd 510 IE]

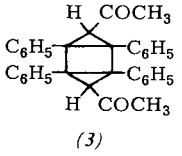
**Interesting photochemical rearrangements of 3-acylcyclopropene derivatives** are reported by *N. Obata* and *I. Moritani*. Ultraviolet irradiation of the compound *(1a)* in tetrahydrofuran at 65 °C affords 1,2,4,5-tetraphenylbenzene *(2)* in 25 % yield. Under the same conditions the analogue *(1b)* gives the new tricyclohexane derivative *(3)* as well as compound *(2)* and biacetyl, yields of the first two being 6.7 % and 20.6 %, respectively. On further irradiation, product *(3)* is converted into *(2)* in 43.4 % yield. Thus the cyclopropene *(1b)* dimerizes preferentially to the tricyclohexane *(3)*, which



*(1a)* R: $C_6H_5$
*(1b)* R: $CH_3$



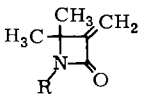
*(2)*



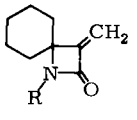
*(3)*

rearranges to the benzene derivative with α-fission and formation of a diradical. / Tetrahedron Letters *1966*, 1503 / —Ma. [Rd 491 IE]

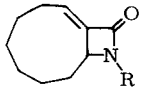
**β-Lactams with exocyclic methylene groups** are obtained by the reaction of allenes with chlorosulfonyl isocyanates, according to *J. F. Kelly* and *E. J. Moriconi*. 3-Methyl-1,2-butadiene, cyclohexylideneallene, and 1,2-cyclononadiene afford the *N*-chlorosulfonyl-2-azetidone derivatives *(1a)*, *(2a)*, and *(3a)*, respectively. Their reduction by thiophenol/pyridine in acetone leads to the β-lactams *(1b)*, *(2b)*, and *(3b)*. The allenes appear to be sufficiently polarized in the



*(1)*
*(a)*R: $SO_2Cl$



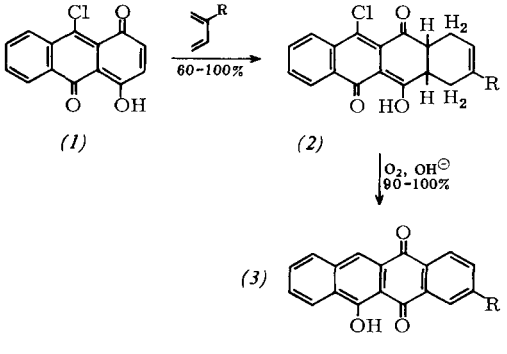
*(2)*
*(b)*R: H



*(3)*

ground state for reaction with the isocyanate to occur. / Amer. Chem. Soc. 151st Meeting *1966*, Abstr. K 76 / —Ma. [Rd 492 IE]

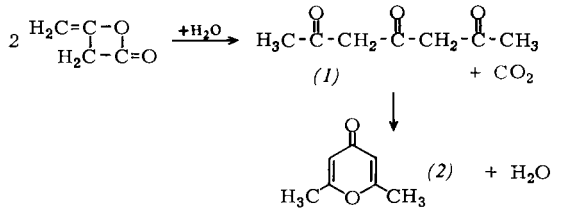
**A new three-stage synthesis of substituted naphthacenequinones** has been devised by *R. Winkler*. 1,4-Dihydroxyanthraquinone derivatives are converted by $SOCl_2$ into derivatives of the dienophilic 9-chloro-4-hydroxy-1,10-anthraquinone *(1)*, which adds 1,3-dienes, *e.g.* butadiene, isoprene, chloroprene, 2,3-dihalobutadienes, 2,3-dialkylbutadienes, 1-acetoxybutadiene, and 1-dimethylaminobutadiene, under relatively mild conditions, affording linear Diels-Alder monoadducts such




*(1)* *(2)* *(3)*

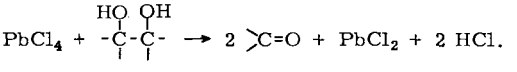
as *(2)*. These are dehydrogenated in alkaline solution by air to hydroxynaphthacenequinones *(3)*. Yields are usually high, and the products very pure. / Chimia *20*, 122 (1966) / —Ma. [Rd 496 IE]

**A new reaction of diketenes with water** has been described by *E. Marcus, J. K. Chan*, and *C. B. Strow*. Reaction in presence of a tertiary amine as catalyst affords 2,4,6-heptanetrione *(1)*, 2,6-dimethyl-4*H*-pyran-4-one *(2)*, and $CO_2$ as main products. Use of 1 mole of water per 2 moles of diketene is required if good yields of compounds *(1)* and *(2)* are to be obtained. The proportion *(1)*:*(2)* varies between 3:1 and 2:3 according to the reaction conditions. Under optimal conditions, with 1,4-diazabicyclo[2.2.2]octane as catalyst,



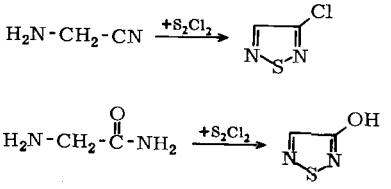

the total yield amounts to 78 %. / Amer. Chem. Soc. 151st Meeting *1966*, Abstr. K 80 / —Ma. [Rd 493 IE]

**The reaction of lead (IV) chloride with vicinal diols** has been studied by *I. May, D. Schreiber*, and *G. G. Schlesinger*. $PbCl_4$, prepared by decomposition of pyridinium hexachloroplumbate, was dissolved in $CCl_4$ and added to a suspension of the diols in $CCl_4$:



The reagent is more selective than lead tetraacetate. Ethylene glycol and *meso*-1,2-diphenylethyleneglycol undergo the expected C—C fission to formaldehyde and benzaldehyde, respectively, and 2,3-diphenyl-2,3-butanediol is chlorinated and cleaved to ω-chloroacetophenone. The butanediol, as well as pinacol and tetraphenylethyleneglycol, give 1:1 adducts of various stabilities with $PbCl_4$. *Cis*- and *trans*-cyclohexanediol and 2,3-butanediol do not react. / Amer. Chem. Soc. 151st Meeting *1966*, Abstr. K46./Ma. [Rd 494 IE]

**A new general synthesis of 1,2,5-thiadiazoles** is described by *L. M. Weinstock, P. Davis, B. Handelsman*, and *R. Tull*. Compounds containing an acyclic N—C—C—N group, such as α,β-diamines, α-amino-amides, α-amino-amidines, α-amino-nitriles, cyanoformamide, α,β-dioximes, and dicyanogen, react with $S_2Cl_2$ or $SCl_2$ in dimethylformamide at room temperature with formation of the 1,2,5-thiadiazole derivatives.

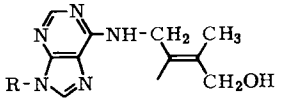



Yields amount to 50—90 %. 1,2,5-Thiadiazole itself can be obtained from ethylenediamine and $S_2Cl_2$. / Tetrahedron Letters *1966*, 1263 / —Ma. [Rd 495 IE]

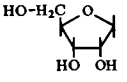
**2-Diazo-1,1,1-trifluoropropane** *(1)* has been prepared by *R. A. Shepard* and *P. L. Sciaraffa* by several routes, *inter alia*, by oxidation of 1,1,1-trifluoroacetone hydrazone, which is obtained from 1,1,1-trifluoroacetone, hydrazinium dichloride, and sodium acetate. The product *(1)* is intermediate in its reactions between the unstable 2-diazopropane and the stable 2-diazoperfluoropropane. Its solutions are very stable at room temperature but react with acids. The compound is a volatile, orange-red liquid which must be kept at 0 °C since it explodes at room temperature. / J. org. Chemistry *31*, 964 (1966) / —Kr. [Rd 506 IE]

**A sparingly soluble compound of NaCl and racemic 2,3-bis-(*p*-aminophenyl)butane** [1,2-dimethylethylenedi(aniline)] is precipitated from an aqueous solution of the components, according to *N. P. Marullo* and *R. A. Lloyd.* The precipitate, which is considered to be a coordination compound of sodium with a donor nitrogen ligand, melts at 200 °C. It contains three molecules of the diamine per molecule of NaCl. X-Ray analysis and the infrared spectrum are compatible with the assumption that the sodium is surrounded octahedrally by amino groups. The *meso*-isomer of diamine does not give a precipitate with NaCl. The salts NaBr, NaI, $NaNO_3$, and $NaN_3$, but not $Na_2CO_3$, $Na_2SO_4$, $Na_2S$, or $CH_3COONa$, react like NaCl. Some halides of other alkali and alkaline-earth metals are similarly precipitated. / J. Amer. chem. Soc. *88*, 1076 (1966) / –Kr. [Rd 505 IE]

**A synthesis of zeatin** (a factor from maize, similar to kinetin, that activates cell division) has been described by *G. Shaw, B. M. Smallwood,* and *D. V. Wilson.* *trans*-4-Amino-2-methyl-2-buten-1-ol sulfate is treated with 6-(methylthio)- or 6-chloro-purine or with 6-chloro-9-β-D-ribofuranosylpurine in presence of triethylamine in warm butanol, whereby pure zeatin *(1)* or, in the last case, zeatin riboside *(2)* crystallizes out in excellent yield after 1 hr.



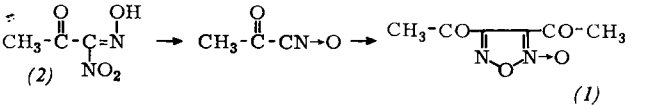
*(1)*, R = H

*(2)*, R = 

The zeatin [6-(4-hydroxy-3-methyl-*trans*-2-butenylamino)-purine], which forms needles (from water), m.p. 207–208 °C, is identical in melting point, mixed melting point, paper and thin-layer chromatography, $^1H$–NMR, mass, and UV spectra, and biological activity with the natural material which is thus unambiguously proved to be the *trans*-form. / J. chem. Soc. (London) (C) *1966*, 921 / –De. [Rd 508 IE]

**Synthesis of tetramethylammonium tetranitratoborate,** $[(CH_3)_4N][B(NO_3)_4]$, was effected by *C. R. Guibert* and *M. D. Marshall.* They mixed tetramethylammonium tetrachloroborate with liquid dinitrogen tetroxide ($N_2O_4$: $BCl_4^- > 8:1$) at –78 °C and allowed the temperature to rise to 0 °C in 2 hr. After removal, at room temperature, of the excess of $N_2O_4$ and the NOCl produced there remained a white residue from which the tetranitratoborate could be extracted with $NH_3$. The structure was proved by, *inter alia*, infrared and $^{11}B$–NMR spectroscopy. The product is stable at room temperature and is neither dissolved nor hydrolysed by cold water, but dissolves in methanol, acetonitrile, or dimethylformamide. Almost complete dissociation into two ions was shown to occur in acetone. / J. Amer. chem. Soc. *88*, 190 (1966) / –Kr. [Rd 482 IE]

**Furazan 2-oxides (furoxans)** have been synthesized by *L. I. Peterson* by reaction of aliphatic or aromatic methyl ketones with dinitrogen tetroxide. Acetone and anhydrous $N_2O_4$ at 0 to 5 °C give an unstable compound that decomposes explosively on attempted distillation and, when heated at 50 °C. slowly decomposes (NO evolution) affording diacetylfuroxan *(1)* as a yellow liquid, b.p. 100 °C/1 Torr (yield 93 %). The reaction presumably proceeds by way of the labile



*(2)* *(1)*

intermediate *(2)* which is transformed into *(1)* by thermal fission and dimerization. Acetophenone and pinacolin can be similarly converted into furoxan derivatives. / Tetrahedron Letters *1966*, 1727 / Ma. [Rd 497 IE]

**Metal/halogen exchange between aryl-metal and aryl-halogen compounds** has been studied by *H. J. S. Winkler* and *H. Winkler.* The ligands in the system

$$ArBr + Ar'Li \rightleftarrows ArLi + Ar'Br \quad (Ar, Ar': \text{aryl})$$

in ether are exchanged at a measurable rate at room temperature. For analysis the mixture is treated with trimethylsilyl chloride, the aryl-lithium yielding the aryltrimethylsilane rapidly and quantitatively. The exchange can be followed by quantitative gas-chromotagraphic analysis. The equilibrium constants, but not the rates of establishment of equilibrium, are largely independent of the medium, added salts, and temperature. Exchange is 100- to 1000-fold faster in tetrahydrofuran than in ether. "Salt-free phenyl-lithium" [from $(C_6H_5)_2Hg + Li$] reacts faster than the "salt-containing" reagent (from $C_6H_5Br + Li$). At equilibrium lithium prefers aryl ligands containing electron-attracting groups. The measured equilibrium constants and known substituent effects σ afforded the reaction constant $\rho = 5.5$. Reaction between phenyl-lithium and substituted bromobenzenes is accelerated by electron-attracting substituents in the bromide ($\rho = 4.0$). Although detailed interpretation of the process is made difficult by aggregation of the aryl-lithium compounds, it can be concluded that the aryl bromides behave as bromonium salts and that the equilibrium constants can serve as a measure of the stability of substituted phenyl anions. / J. Amer. chem. Soc. *88*, 964, 969 (1966) / –Eb. [Rd 500 IE]

# BOOK REVIEWS

**Biochemie der Nebennierenrinden-Hormone** (Biochemistry of the Adrenal Hormones). Monograph in the Series "Biochemie und Klinik". By *H. J. Hübener* and *H. W. Staib.* Georg Thieme Verlag, Stuttgart 1965. 1st Edit., 253 pp., 35 figs., 37 tables, cardboard, 58.– DM (about $ 15.–).

After a description of the chemistry of the steroids, the biosynthesis of steroid hormones is reviewed. The chapter on the control mechanism of adrenal hormone secretions is of particular interest to endocrinologists since it describes, not merely the physiology and therapeutic use of adrenocorticotropic hormone (ACTH), but also the pharmacological influence of the hypophysis-hypothalamus system, the metopiron test, and the biochemical basis of functional disorders of the suprarenal gland. The control of aldosterone secretion, the Conn syndrome, and secondary aldosteronism are reviewed in a separate chapter. The metabolism of the adrenal hormones is reported from the point of view of the enzymology of individual metabolic steps, so that this chapter is of special value to the steroid biochemist. The section on the physiological function of adrenal hormones as enzyme inductors is confined mainly to reproduction of the findings and theories of *H.-J. Hübener* The chemist interested in the development of new corticoids, and the pharmacologist will read the chapter on Synthetic Analogues of Steroid Hormones" with particular interest.

In accord with the aim of the book, therapy by means of adrenal hormones is merely indicated. The steroid analyst will

warmly welcome the detailed description of analytical methods for adrenal hormones.

There are a few printing errors, and some sentences sound unusual to the chemist, but these are only minor blemishes. The book is at once textbook, laboratory guide, and reference work, and with its 1275 literature citations is a rich source of references.

*E. Gerhards* [NB 466/319 IE]

**Stoffwechsel der Galaktose und ihrer Derivate.** (Metabolism of Galactose and its Derivatives). From the series "Biochemie und Klinik". By *W. Fischer* and *H. Weinland.* Edited by *G. Weitzel* and *N. Zöllner.* Georg Thieme Verlag, Stuttgart 1965. 1st Edit., xii + 256 pp., 51 figs., 82 tables, cardboard DM 59.– (about $14.50).

Anyone who does not already know it will be convinced by reading this book that galactose is one of the most widely distributed constituents of living systems. It is a component of the oligosaccharides that occur in high concentration in the capillary fluids of plants and are responsible for transport of the products of assimilation from the leaves to those parts of the plant that do not assimilate. It is a component of the cell walls and membranes of the most varied organisms. It contributes to the formation of cerebrosides and gangliosides, and as galactolipids constitutes a notable proportion of the lipid fraction of green leaves. Also it plays an almost unique role as a constituent of lactose in the milk of mammals. Its importance is evident also from the dynamics of formation and decomposition of galactose-containing compounds. On infusion into the circulation it is resorbed much faster than any other monosaccharide, and as a component of the lipid fraction of green algae it is the fraction that takes up radioactivity from $^{14}CO_2$ fastest and to the greatest extent. The great importance of galactose metabolism in man is shown by the catastrophic results that follow a defect in the enzyme system responsible for utilization of galactose in the suckling (galactosemia).

All these and many other aspects of the metabolism of galactose and galactose-containing compounds are carefully and comprehensively reviewed and discussed in the present book. There are more than 3000 references, partly extending to 1965. Thus this book will be most warmly welcomed by all who work in this field or might like to do so: it will save them much literature searching; and in particular it is a rich source for the less accessible, older literature that is often forgotten.

If the reviewer were asked how an ideal book on galactose would differ from the present one, the following points would arise. 1. It would not contain linear projections for all structural formulae of sugars, as these give no indication of reactivity 2. It would have a chapter on the detection and determination of galactose, galactose derivatives, and galactose-affecting enzymes. There is, it is true, a reference, in two lines of small type to an enzymic method of determining galactose, but paper- and gas-chromatographic analysis are not mentioned, nor is diagnosis of galactosemia or determination of galactose loading. 3. The ideal book would lay less emphasis on some statements from the literature, just because of its greater emphasis on analytical aspects. For instance, it depends on the method of determination whether or not free galactose is "completely absent" from blood on failing exogenic addition. The high content in *Forsythia* pollen mentioned in "Occurrence of Lactose in Plants" has been found to be erroneous [Chem. Ber. *93*, 1009 (1960)], fission of *O*-methylated galactosides by galactosidase depending on the nature of the aglycone. The tables showing acceleration of mutarotation by mutarotases are useless without statement of the experimental conditions and the quantities of enzymes. Some rules can be laid down for acceptor specificity in transfer reactions, and in the framework of induction of the lac-operon of *E. coli* there is a biological meaning to the transgalactosidation, lactose → allolactose – at least in the coli bacterium. In sum, however, this monograph is to be rated a valuable addition to the literature.

*K. Wallenfels* [NB 472/325 IE]

**Lignin Biochemistry.** By *W. J. Schubert.* Academic Press, New York-London 1965. ix + 131 pp., 17 figs., 26 tables, linen $8.–.

The size of this little monograph is already enough to show that it provides only a somewhat superficial discussion of its subject. The value of the book residues in the fact that it is primarily a review of the numerous contributions made to the biochemistry of lignin from the Laboratories of Organic Chemistry and Enzymology of the Fordham University in New York which endeavors to show how these results fit into the overall picture of the current knowledge of lignification and its associated phenomena. This approach is necessarily accompanied by limitation of the extent to which the work of other groups is evaluated, if at all, and consequently irregularities in the overall perspective may result. The user of the book who is not a thorough expert in this field must bear this in mind, otherwise he may obtain only a somewhat incomplete and slightly distorted picture of the present status of knowledge on the processes of lignification. For instance, there is no mention of the numerous studies of lignification that have been carried out with plant tissue cultures, whereas the metabolism of methyl *p*-methoxycinnamate in a single microorganism is discussed at length, even though this has no direct connection with lignification.

The text is divided into four main sections: a short introduction to the chemistry of lignin (37 pp.), a description of the biogenesis of aromatic compounds in microorganisms (12 pp.) because of its significance for the corresponding processes in higher plants (described on 20 pp.), and a discourse on the microbiological degradation of lignin. The treatment is concise and readily understandable throughout. A subject index with about 450 entries and an author index containing about 270 names combine with the attractively presented formulae to make a most useable volume.

*J. M. Harkin* [NB 482 IE]

**Conformation Theory.** By *M. Hanack.* Transl. from the German manuscript by *H. C. Neumann.* Vol. 3. Organic Chemistry, a Series of Monographs[1]. Edited by *A. T. Blomquist.* Academic Press, New York-London 1965. 1st Edit., ix + 382 pp., numerous figs. and tables, bound $14.50.

Evidently there is a need for textbooks and monographs giving a comprehensive survey of the development of organic stereochemistry, for after a long period of quiet there now appear numerous books concerned with this subject at various levels. One of the most important recent advances in stereochemistry is the widespread and logical use of the concept of conformation, with the theoretical prediction and the experimental determination of the properties of the different conformations of a molecule that are termed conformational analysis.

"Conformational Analysis", the comprehensive monograph by *E. L. Eliel, N. L. Allinger, S. J. Angyal,* and *G. A. Morrison,* and the present book, "Conformation Theory"[2] by *Hanack* have been published within a short interval.

In a field that is in rapid development it is no simple task to keep a due proportion between the importance and the quantity of the material discussed, and it is interesting to compare these two new books on conformations in this respect. *Hanack's* book is less comprehensive and goes less deep than that of *Eliel et al.* and will be preferred mainly by those or-

[1] Cf. Angew. Chem. *73*, 304 (1961).

[2] This title seems unfortunate, for there is no question of a theory here.

ganic chemists who, without much previous knowledge, wish to learn from the beginning about conformational analysis.

Two of the eight chapters are devoted to a short general introduction to stereochemistry, four treat in detail the conformations of alicyclic and one each the conformations of heterocyclic and aliphatic compounds.

The numerous references (some even up to 1964) will help those who wish to form their own opinion about this field, which is of the utmost importance in many areas of organic chemistry.

*V. Prelog* [NB 489a IE]

**Fundamentals of Carbanion Chemistry.** By *D. J. Cram.* Organic Chemistry – A Series of Monographs. Edited by *A. T. Blomquist.* Vol. 4. Academic Press, New York-London 1965. 1st edit., viii + 289 pp., numerous figs. and tables, bound, $ 9.50.

In spite of the apparent antipodal relation between carbanions and carbonium ions, carbanion chemistry is much less well defined and is much younger than carbonium ion chemistry as a field of work in its own right within organic chemistry. To carbanion chemistry belong molecules whose negative charge lies mainly or wholly on carbon. It includes therefore above all the chemistry of organic derivatives of the alkali metals, and extension of the acid-base concept to other carbon acids than the classical "active methylene compounds". Since there is no comprehensive treatment of this heterogeneous, rapidly developing field, one is eager to turn to *Cram*'s book.

The critical survey of the thermodynamic and kinetic acidity of carbon acids given in the first section is so good that it alone would justify purchase of this book. A discussion of the structure and stability of carbanions is followed by three chapters on the stereochemistry of carbanions and electrophilic substitution reactions, which make up half of the book. Their center of interest is the author's own fundamental work in this field. The conclusion is a racily written, brief summary of molecular rearrangements that proceed by way of carbanions.

Perusal of this monograph is strongly recommended to all who are interested in reaction mechanism. The author's repute is guarantee for a competent and clear treatment of the material. However, the book has some regrettable gaps. Important papers on the stereochemistry of simple carbanions are omitted and there is no mention of, for instance, the class of high acidic hydrocarbons or of radical ions. Work on organic compounds of the alkali metals, which is of such supreme importance to carbanion chemistry, is mentioned only in passing, showing the almost complete failure to evaluate, in particular, the German literature, and without that a standard textbook of carbanion chemistry would be unthinkable. This does not diminish the value of *Cram*'s book; it is indeed questionable whether a comprehensive text on the whole topic can yet (or still) be written. The reader lays down the book with the wish that an equally good one on other aspects of carbanion chemistry were available.

*G. Köbrich* [NB 489b IE]

**Symmetry in Chemistry.** By *H. H. Jaffé* and *M. Orchin.* John Wilev & Sons, Inc., New York-London-Sydney 1965. 1st edit., x + 191 pp., several figs. and tables, bound, £2.2.–, paperback £1.10.– (about $ 6.– and $ 4.20).

A few years ago there was a dearth of textbooks on group theory that presented this field in a way suitable for chemists or molecular physicists, but today there is a large choice of such books. *Jaffé* and *Orchin*'s monograph is distinguished by the simplicity of the presentation

After a lightly philosophical introduction on "Symmetry and Beauty" the authors introduce the terms symmetry operations, multiplication of symmetry operations, symmetry groups, and symmetry species clearly and convincingly with the aid of examples familiar to chemists. Although it is a good idea to try an essentially non-mathematical treatment it does not seem possible to follow this idea to the end. Reference to "reducible" and "irreducible representation" is avoided as long as possible; therefore arguments in which these terms are nevertheless needed are not very convincing.

A reader who is not interested in mathematics and in understanding symmetry thoroughly, but who rather wants to get an idea of how group theory can be used in practice, will probably appreciate this book more than others on the same topic.

*W. Kutzelnigg* [NB 491 IE]

**Quantum Mechanics in Chemistry.** By *M. W. Hanna.* W. A. Benjamin, Inc., New York-Amsterdam 1965. 1st Edit., 253 pp., numerous figs. and tables, paperback $ 4.35, bound $ 7.70.

This book is intended for undergraduates.

Mathematical methods and concepts that go beyond school mathematics but are essential for an understanding of modern theoretical chemistry are presented clearly and intelligibly in an introductory chapter. The fundamentals of quantum theory are introduced axiomatically. It is didactically wise to treat rotations and vibrations of molecules as the first applications of quantum mechanics, and only thereafter the electronic structure of atoms and the theory of the chemical bond. Therefore the book can be recommended also – and in fact particularly – as an introduction to molecular spectroscopy.

The author is concerned mainly with defining the fundamental concepts precisely and in an understandable way. The mathematical formulations are compact and conform to international usage. The reader is not embarassed with lengthy derivations. The well chosen problems allow him to find the easier proofs himself, whereas for more complicated ones he finds references to more detailed monographs. Each chapter has a summary.

One should not expect from a textbook intended for beginners a survey of quantum chemistry. In fact it offers the minimum of what a modern chemist should know about quantum mechanics. It is recommended particularly for those young students who do not mind some mathematics and are ready, not just to read a textbook, but to study it carefully.

The printing is agreeable and clearly arranged. The only error the reviewer found is the value of 1.37 Å instead of 1.06 Å for the equilibrium distance in $H_2^+$.

*W. Kutzelnigg* [NB 492 IE]

**Chemistry of the Iron Group Metallocenes: Ferrocene, Ruthenocene, Osmocene.** Part I. By *M. Rosenblum.* Interscience Publishers, New York-London-Sydney 1965. 1st Edit., xv + 241 pp., numerous figs., bound, £4.15.–.

The development of the chemistry of organometallic compounds during the last ten years justifies the metaphor "explosive". Consequently an attempt at a new edition of a book such as *E. Krause* and *A. von Grosse*'s "Die Chemie der metallorganischen Verbindungen", which contained all the metallorganic compounds known in 1937, would appear utopian. Interscience Publishers have now begun to cover the most important sections of organometallic chemistry by a series of monographs edited by *D. Seyferth.* The first of these is devoted to the metallocenes of the iron group, with particular emphasis on ferrocene as the prototype of dicyclopentadienylmetal compounds.

The first three chapters of present volume deal with the preparation, electronic structure, bonding, and physical properties of metallocenes. The bonding, which has in the past been the subject of controversial discussion, is purposely not treated in full detail; only the important results based on MO treatment are presented. Chapters 4, 5, and 6 deal with the acyl-, alkyl-, and aryl-metallocenes that were obtained by replacement of ring protons, their preparation illustrating

also the reactivity of the starting materials $M(C_5H_5)_2$ (M = Fe, Ru, or Os). The mechanisms of the replacement reactions are discussed in detail, whereby attention is directed to the problem of the "aromatic character of metallocenes". At the end of each of these chapters all the known derivatives and their most important properties are tabulated.

The author has contributed to the development of this field from its very beginnings. He has managed to extract what is most worthwhile from more than 1000 papers and he has given fair consideration to the contributions of the various schools. The literature is almost completely covered up to the middle of 1963, and many results are included that had not then been published. The outward appearance of the book is very pleasing but it is unfortunate that some misprints have escaped correction.

The reviewer hopes that the second Part will turn out as well as the present Part I, so that there will then be a standard work on the chemistry of the metallocenes of the iron group.

*H. Werner* [NB 486 IE]

**The Chemistry of the Vitamins.** By *S. F. Dyke*. J. Wiley & Sons Ltd., London-New York-Sydney 1965. 1st Edit., 363 pp., several figs., bound, £3.7.–.

This book is the sixth in the series "The Chemistry of Natural Products" edited by *K. W. Bentley*. It treats the well-known vitamins or vitamin groups, and in particular the elucidation of their structures and their synthesis. It describes also relations between structure and activity of the vitamins, and their biosynthesis and biological function, but not their isolation which is often so troublesome and in which the natural products chemist would probably be interested. The material is arranged in a useful and clear manner; understanding is facilitated by the numerous formulae and figures. At a first, superficial examination one is glad to have found a short introduction that may be useful for lectures and for student use. Closer scrutiny shows, however, that the book is not intended as an introduction or a textbook. It contains mainly references to original papers, including some from the previous century, and it is not clear to the reader on what basis they were chosen. Wherever the chemistry (determination of structure and synthesis) of the vitamins is complete, citation of an appropriate review would have sufficed. On the other hand there are very few references to papers later than 1960: the reader is given the impression that the chemistry of the vitamins came to a standstill in that year. No indication is given of the aims of present-day vitamin chemistry or of the properties and reactivity of vitamins in the molecular-biological sense. So one is left in the dark as to the audience for which the book is intended. Further, the subject matter overlaps extensively with that of "Vitamins and Coenzymes" by *A. F. Wagner* and *K. Folkers* which was published a year previously.

*K. Bernhauer* [NB 485 IE]

**Constantes Sélectionnées Pouvoir Rotatoire Naturel** (Selected Values of Optical Rotatory Power). By *J. Jacques, H. Kagan, G. Ourisson*, and *S. Allard*. Tables de Constantes et Données Numériques. No. 14. Ia. Stéroïdes. Pergamon Press, Oxford-Paris 1965. 1st Edit., 1031 pp., about $54.

In 1956 there appeared the first collection of specific rotations of about 8000 steroids included in the literature up to 1952. In the present volume the literature is covered up to 1960 inclusive, and data are given for more than 21000 steroids. This, incidentally, provides an impressive picture of the growth of the literature in this field.

The introduction, in French and English, describes in readily intelligible form the arrangement adopted and the nomenclature. The recommendations of the IUPAC Nomenclature Commission for Steroids have been followed strictly, with extensions, where necessary, in the same spirit. In the main part of the work the compounds are arranged according to molecular formula, and the systematic name (French), melting point, and molecular weight follow. For each substance the specific rotation, conditions of measurement (wavelength, temperature, concentration, and solvent) are then given, with references. The list of references is very clearly arranged according to year and journal at the end of the Tables. An author index and an alphabetic index of substances, including all the trivial names, close this comprehensive volume. Skilful arrangement of the tables and indexes make it a simple matter to find any required compound in spite of the new systematic and often unfamiliar names used.

The specific rotations are generally given as averages of the published data, together with their range of variation. In this respect the literature is considered critically and the less certain values are designated as such. Revised formulae are included up to 1963 inclusive, and occasionally the authors themselves suggest new structures on the basis of the specific rotations. This, of course, admits the danger of correct formulae being changed, *e.g.* because of an erroneous measurement or a misprint in the original paper. Restriction of space prevented curves or table of optical rotatory dispersion from being reproduced, but when such measurements exist the appropriate paper is cited. Such citations are often as "personal communications"; presumably, however, these data have meanwhile all been published.

A comprehensive set of tables such as this is of value only if truly complete and essentially free from error. As a test the reviewer undertook a large number (about 50) of random tests. As luck hat it, in the first case a page number was wrong, in the second a reference was missing and in the third an incorrect reference was given – but all the others were correct. One cannot but admire the authors' achievement in not merely providing a complete collection of the published [α] values for the steroid field but also, as a by-product as it were, an excellent review of the literature for most of the steroids recorded to date. Since the specific rotation is often a better criterion than the melting point it is cited by almost all authors. Instead of searching several Collective Indexes of Chemisches Zentralblatt or Chemical Abstracts for a particular compound one can use these tables to cover at least 95 % of the literature up to 1960. In this connection it is particularly valuable that the derivatives are listed immediately after the parent compound in the alphabetical index.

The "Pouvoir Rotatoire Natural" is thus of the greatest value to steroid chemists, not merely because of the specific rotations collected therein, but also especially as a source of references. This fact justifies the very high price; though this price will certainly prevent very wide distribution, each group of steroid chemists, at least, should possess a copy of this standard work; the saving in time as a source of references will soon have reimbursed the cost.

*G. Snatzke* [NB 484 IE]

**Condensation Polymers: By Interfacial and Solution Methods.** By *P. W. Morgan*. John Wiley & Sons, New York-London-Sydney 1965. 1st Edit., xviii + 561 pp., numerous figs., several tables, bound, £9.10.–.

*Paul W. Morgan*'s book is the tenth volume of a series on polymers edited by *H. F. Mark* and *E. H. Immergut*. Its aim is to present an up-to-date review of polymer chemistry. The author has limited his treatment to condensation polymerization and has collected his material under several main headings. First he treats polycondensation methods which below 100 °C generally lead to linear polymers and in which the components react at an interface. The preparation of polyamides, polyureas, polyurethanes, polysulfonamides, polyphosphonamides, and polyesters is described in detail.

The preparative procedures are accompanied by very clear descriptions of the unusual properties of the products obtained by interfacial-polymerization and these are compared, where appropriate, with polymers obtained in the classical way. Noteworthy is the large number of monomers that the author describes as suitable for low-temperature condensation.

*Morgan* makes little use of mathematics; evidently low-temperature polycondensation has so far been studied mainly in a qualitative way. Presumably future investigations will be concerned above all with mathematical treatment of these relatively simple polymerization systems.

The author's aim to acquaint the reader with both the methods and the products of polycondensation at low temperatures can be considered completely successful. Moreover, more than 1000 references help to introduce the beginner to the field and the specialist to orient himself more quickly – the more so as the literature is considered up to 1965.

This volume is a valuable enrichment of the literature for all polymer chemists.

*R. Zimmermann* [NB 483 IE]

**Einheitliche Schreibweise in naturwissenschaftlichen Werken** [Uniform Spelling in (German) Scientific Writing]. By *R. Herrmann*. Neumann Verlag, Radebeul 1965. 2nd Edit., 148 pp., linen, DM 14.– (about $3.50).

The first edition of this book appeared in 1957. Particularly its first part "Spelling, Nomenclature, and Technical Terms") was at that time strongly criticized [1]. The same criticisms apply to the second edition. As before, we are presented with "Ribonucleinsäurenucleotid"; as before, the formula of D-glyceraldehyde is ascribed to the L-compound and *vice versa*; as before, the entries are listed at random in the singular or the plural. The statement about the revised spelling "Oxid" is attached to the word "Oxycain" (probably the author himself could not say why) and ingeniously remarks that this spelling applies only in inorganic chemistry. The principle on which the choice of entries is based remains obscure, but meeting words such as "50-ml-Becherglas", "Citrone" [*sic*!], and "Collapsus" indicates that it must have been a very amusing principle. Incidentally, is it not remarkable that although one is told to write "Cytochrom", one must also write "Zytochromoxydase"?

[1] Cf. Angew. Chem. *72*, 146 (1960).

The list of criticisms could be extended. But since this would presumably not prevent the issue of a third edition with the same defects, a warning will suffice. It is not worthwhile buying this book, even though the publishers describe it as "essential".

*H. Grünewald* [NB 487 IE]

**Titrations in Non-Aqueous Solvents.** By *J. Kucharsky* and *L. Šafařik*. Elsevier Publishing Company, Amsterdam-London-New York 1965. xi + 286 pp., 29 figs., 33 tables, linen DM 39.– (about $ 9.50).

This volume is an expanded English edition of the Czech edition published in 1961. It is written by analysts for chemists working in analytical laboratories, with the emphasis strongly on acid-base titrations in non-aqueous media. Redox titrations and titrimetric determinations of equivalent weights of some classes of compound are treated, but only to a very modest extent. The authors devote about 40 pages to an introduction into the theory of acid-base equilibria and the influence of the solvent. To this theoretical preface is added a more practical part dealing with solvents, determination of end points, media for titration, acidimetric standards, techniques of titration, and titration of various classes of compound. Here, however, more recent theoretical aspects are missing: for instance the discussion of curves obtained on titration in acetic acid and of the effect of water on them does not mention the fundamental and generally recognized papers by *Kolthoff* and *Bruckenstein*.

A comprehensive chapter (more than 100 pages) on acid-base titrations of 21 classes of compound forms the nucleus of the book and is particularly valuable in that it contains procedures that have been tested in the authors' laboratories. The literature cited in this and other chapters is complete up to 1963.

This book will interest mainly the analytical chemist and will be of value to him in his daily work.

*W. Simon* [NB 471/324a IE]

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# Electron Pyrolysis, a New Method of Organic Microanalysis

BY PROF. H. SCHILDKNECHT
BASED ON STUDIES BY DR. F. ENZMANN, K. GESSNER, K. PENZIEN, F. RÖMER, AND DR. O. VOLKERT

ORGANISCH-CHEMISCHES INSTITUT, UNIVERSITÄT HEIDELBERG (GERMANY)

*Organic compounds incubated with tritiated water of specific activity 5 Ci/ml are specifically fragmented. The β-active fragments can be detected in very small quantities by chromatographic separation. Chemical identification of these fragments provides information about the original compounds, as has been shown by experiments with amino acids, esters, lactones, amides, quinones, terpenes, nitrogen-sulfur heterocycles, and natural products.*

## 1. Introduction

"The object and the chief aim of all chemistry is skilfully to break down substances into their components, to discover their properties, and to combine them in various ways". With these words, *Scheele* placed analysis in the forefront of all the chemist's activities.

The earliest method used to decompose organic substances was simply to heat them, *i.e.* to *pyrolyse* them. Several methods are now known to supply the energy leading to cleavage of chemical bonds. Thus we observed that β-resorcylic acid is decarboxylated not only when heated at 150 °C, but also at room temperature in tritiated water. We called this process *Elektronenbrenzen* ("electron pyrolysis") [1]; it was not known at that time that often not only the β-radiation, but also the water itself or its radiolysis products, such as hydrated electrons or OH-radicals [2], can be of use in the fragmentation. However, we were aware of the fact that the unavoidable labeling with tritium greatly facilitates detection of fragments formed only in traces, and is often the only means of detection.

Succinic acid also is decarboxylated on electron pyrolysis, forming tritium-labeled propionic acid [3]. Decarboxylation of mandelic acid yielded benzaldehyde as a result of the oxidation of the initially formed benzyl alcohol by the oxidizing components of the tritiated water. The formation of n-hexanal from n-hexanol and of cyclohexanone from cyclohexanol in tritiated water confirmed this assumption. All carbonyl compounds could be detected as active 2,4-dinitrophenylhydrazones. At the beginning of our investigations we could thus already define electron pyrolysis as the breakdown of organic molecules into smaller, readily detectable complementary fragments involving reduction, oxidation, and labeling.

It was still necessary to determine whether it is possible to establish fragmentation rules by means of which a structure could be suggested on the basis of the fragments obtained. This question can now be partly answered in the affirmative, though many investigations will still be necessary to make electron pyrolysis a generally useful method for the elucidation of the structures of organic compounds.

## 2. Experimental Procedure

Samples varying in size from a few μg to several mg are sealed in glass tubes some 5 cm long and having an internal diameter of 3 mm, together with 2.5 to 50 mg of tritiated water of specific activity 5 Ci/ml. The solution or suspension is left at or above room temperature for several days to a few weeks, until the contents of the tube become discolored. The products are separated chromatographically.

In thin-layer chromatography, the fractions are recorded by means of a thin-layer scanner, and in gas chromatography by a flow detector. This gives activity curves which resemble spectra, the bands of which can often be assigned to chemi-

[1] *H. Schildknecht*, Kerntechnik *6*, 249 (1964). We suggest the application of the German term *Elektronenbrenzen* in English as well, rather than "electron pyrolysis" or "fragmentation by electron impact".

[2] Basic Mechanisms in the Radiation Chemistry of Aqueous Media, Radiat. Res. Suppl. *4*, 1–217 (1964).

[3] *H. Schildknecht* and *O. Volkert*, Z. analyt. Chem. *216*, 97 (1966).

cally identifiable products. We have, therefore, included the thin-layer chromatographic distribution of the fragments in each figure showing "electron pyrolysis spectra". This shows which fragments were detected chemically and which were detected only on the basis of their radioactivity or of their fluorescence. The tritiated fragments were also identified in every case by comparative thin-layer chromatography on Kieselgel G plates, using at least three different solvent systems. The active spots were eluted from the plate and chromatographed once more, and in most cases the ultraviolet and infrared absorption spectra of the eluted compound were determined.

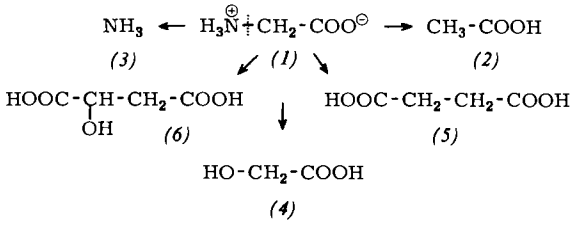
Electron pyrolysis with tritium gas is carried out as follows:

As a precaution the tritium is bound to uranium powder. Uranium hydride is decomposed at 450 °C and $10^{-3}$ mm Hg to hydrogen and uranium powder. The tritium gas (3 Ci, 97.7 %) is adsorbed on the latter at room temperature; it is regenerated as needed at 450 °C. The tritium is pumped into a reaction vessel (5 ml) containing the substance to be analysed. The powdered sample is continuously stirred in the dark with a glass-coated magnetic wire.

## 3. Electron Pyrolysis of Known Compounds

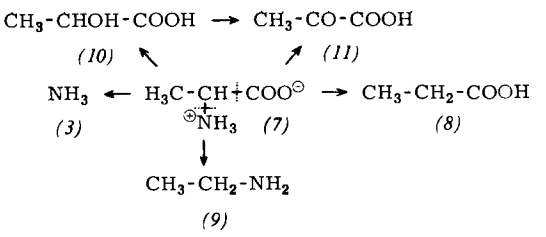
### 3.1. Electron Pyrolysis of Amino Acids [4]

In the electron pyrolysis of glycine *(1)* we obtained only two products, formed by simple cleavage of bonds with no secondary reactions. In the paper radiochromatogram we found the ammonium salt of acetic acid, which was used as an eluent, and in another chromatogram acetic acid *(2)*. Here and in subsequent electron pyrolysis schemes, the bonds which are broken are indicated by dotted lines. No indication is given that part of the hydrogen in all compounds is replaced




by tritium. This labeling is a direct result of the saturation of the $\cdot CH_2-CO_2H$ radical with tritium atoms. OH (OT) radicals also can react with $\cdot CH_2-CO_2H$, as is shown by the formation of glycolic acid *(4)* and malic acid *(6)*. In agreement with literature reports [5] on the radiolysis of organic compounds in water with $\gamma$-rays, the formation of succinic acid *(5)* can be explained only on the basis of intermediate free-radical fragments.

In view of these results on glycine, we were not surprised to find lactic acid *(10)* and pyruvic acid *(11)* on chromatographic analysis of the solution obtained on electron pyrolysis of alanine *(7)*. According to *Garrison* [5], OH radicals are also involved in the radiolytic formation




of pyruvic acid; however, *(11)* may also be formed directly from *(10)*. As can be seen from the thin-layer radio-chromatogram (Fig. 1), the main product apart

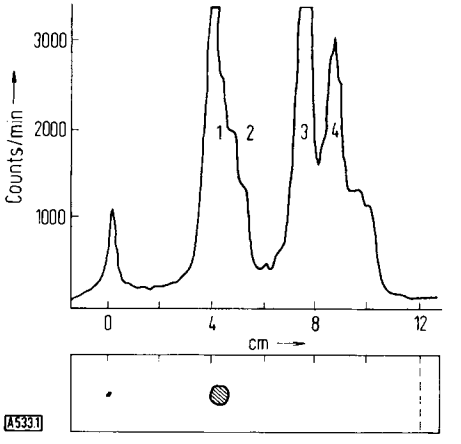



Fig. 1. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 5 µg of alanine *(7)*. Solvent system: ethanol/$NH_3$/$H_2O$ (80:4:16 v/v).

1, alanine *(7)*; 2, lactic acid *(10)*; 3, propionic acid *(8)* + pyruvic acid *(11)*; 4, alanine ethyl ester.

from *(11)* was propionic acid *(8)*. The cleavage of the C–N bond is understandable in view of the fact that in amino acids in solution, the distance between the protonated N atom and the C atom is 1.50 Å, as compared with the normal value of 1.32 Å [6]. Thus the C–N bond is weakened in the zwitterion. If the compound is not in the form of the zwitterion, as in the gas

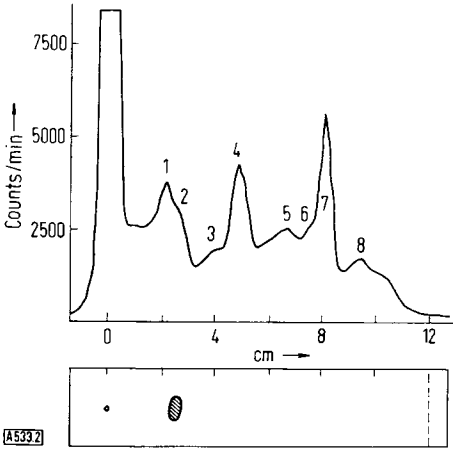



Fig. 2. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 5 µg of aspartic acid *(12)*. Solvent system: ethanol/$NH_3$ (7:3 v/v).

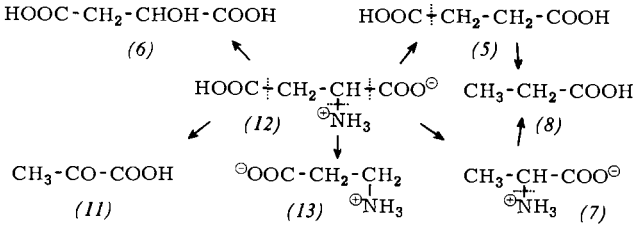
1, malic acid *(6)*; 2, aspartic acid *(12)*; 3, succinic acid *(5)*; 4, β-aminopropionic acid *(13)*; 5, alanine *(7)*; 6, propionic acid *(8)*; 7, pyruvic acid *(11)*; 8, diethyl aspartate.

[4] *K. Geßner*, Diploma Thesis, Universität Heidelberg, 1966.
[5] *W. M. Garrison*, Radiat. Res. Supp. *4*, 158, (1964).
[6] *R. B. Corey* and *J. Donohue*, J. Amer. chem. Soc. *72*, 2899 (1950).

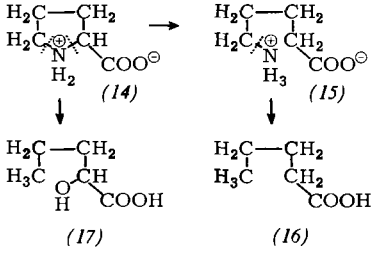
phase in the mass spectrometer, cleavage occurs preferentially in the next-weaker C–CO bond [7]. However, decarboxylation with formation of ethylamine *(9)* can also be observed to a minor extent in solution.

Decarboxylation is particularly pronounced in the electron pyrolysis of aspartic acid *(12)*. As can be seen from the corresponding thin-layer radio-chromatogram (Fig. 2), alanine *(7)*, β-aminopropionic acid *(13)*, and propionic acid *(8)* could be unambiguously detected even when *(12)* was simply allowed to stand at room temperature with tritiated water. This result emphasizes clearly the specific action of the tritiated water.

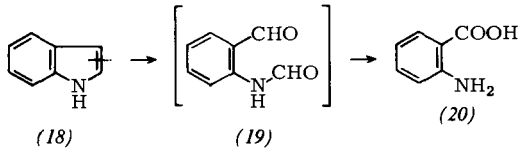
The products again contained succinic acid *(5)*, formed by reductive deamination, and propionic acid *(8)*, formed from the succinic acid, while malic acid *(6)* and pyruvic acid *(11)* were formed by oxidation; *(8)* may have been formed also from *(7)*.




In the electron pyrolysis of proline *(14)*, the ring was opened in a particularly simple manner, and *(14)* was degraded to valeric acid *(16)*. Activity measurements showed that the yields were lower than in the pyrolysis




of alanine *(7)*. The compounds containing 5-membered rings (as is also shown in mass spectrometry [8]) are probably more stable than open-chain compounds, or else chain degradation may be preceded by hydrolytic ring cleavage. Thus tryptophan *(21)* is degraded slightly to indole *(18)* when simply heated with water. The electron pyrolysis of *(21)* also leads to the formation of *(18)*, which, when itself pyrolized, gives anthranilic acid *(20)*, probably *via (19)*.




This fragmentation is quite unimportant in the electron pyrolysis of tryptophan *(21)*, since according to the thin-layer radiochromatogram (Fig. 3), relatively many primary cleavage products are formed.

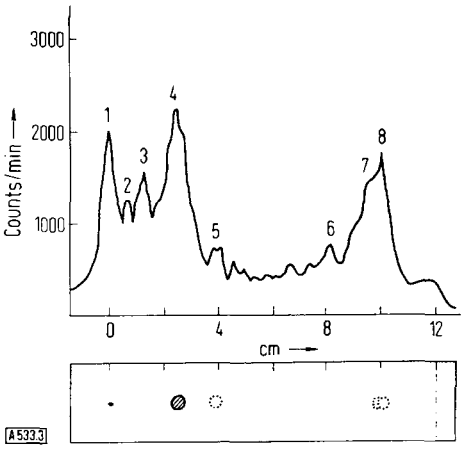
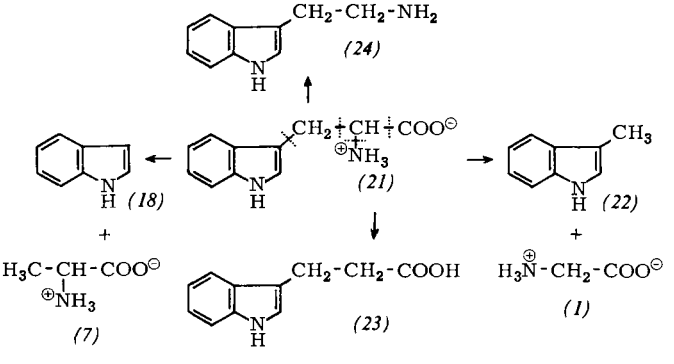



Fig. 3. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 10 μg of tryptophan *(21)*. Solvent system: butanol/$NH_3$ (7:3 v/v).

1, starting peak; 2, glycine *(1)*; 3, alanine *(7)*; 4, tryptophan *(21)*; 5, 3-indolyl-β-propionic acid *(23)*; 6, tryptamine *(24)*; 7, indole *(18)*; 8, skatole *(22)*.

Radiolysis of *(21)* with X-rays [9] also yields several cleavage products resulting from decarboxylation and changes in the carbon skeleton. No deamination is found, as on mass spectrometry [8]; the strongest mass peak occurs at $m/e = 130$, suggesting that fragmentation tends to stop at the skatole *(22)* stage. The same result is found in electron pyrolysis, where the greatest activity, apart from the band for the starting material *(21)*, was obtained for the skatole fraction. The complementary fragment, glycine *(1)*, was also found. The structure of the starting material can, however, be deduced from the fragments *(18)* and *(7)*, as well as from the above fragments.




As in the case of tryptophan *(21)*, we obtained indole *(18)* and skatole *(22)* as well as acetic acid in the electron pyrolysis of the growth hormone 3-indoleacetic acid.

### 3.2. Electron Pyrolysis of Esters, Lactones, and Amides [10]

The principal product in the electron pyrolysis of benzyl benzoate was benzoic acid which, like the former, was strongly labeled, but which could not be detected

[7] *G. Junk* and *H. Svec*, J. Amer. chem. Soc. *85*, 839 (1963).
[8] *K. Biemann*: Mass Spectrometry. McGraw-Hill, New York 1962, pp. 260–296.
[9] *G. Peter* and *B. Rajewsky*, Z. Naturforsch. *18b*, 110 (1963).
[10] *H. Schildknecht* and *F. Enzmann*, Z. analyt. Chem., in press.

chemically on the thin layer either with Bromocresol Purple or with Bromophenol Blue. *p*-Hydroxybenzoic acid was formed in addition, though this was naturally absent when tritium gas was used instead of tritiated water; benzaldehyde, on the other hand, was formed in both cases. Owing to the high radioactivities of the fragments, it was possible to characterize as little as 0.1 μg of benzyl benzoate.

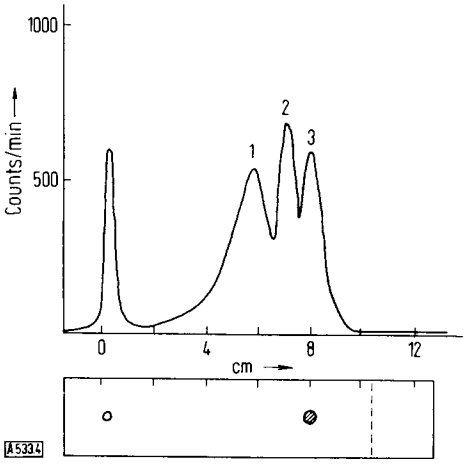



Fig. 4. Thin-layer radio-chromatogram of the electron pyrolysis products of 4 μg of benzyl benzoate in tritium gas. Solvent system: benzene/dioxane/glacial acetic acid (90:25:4 v/v).

1, benzoic acid; 2, benzaldehyde; 3, benzyl benzoate.

In the formulation of the radiolytic reaction, it is conceivable that the O-benzyl bond is broken, in agreement with considerations by *McLachlan*[11,12] and with *Emery*'s mass-spectrometric results[13], but this does not explain the high activity of the benzoic acid. It could be due to labeling in the phenyl nucleus, which could in turn point to the presence of a resonance-stabilized benzoyl radical. The radical combines with hydrogen to form benzaldehyde, which is partly oxidized to benzoic acid by the oxygen in the tritium gas.

The electron pyrolysis of phenyl salicylate in tritiated water or tritium gas yields salicylic acid, and phenol has also been detected. The acid is evidently not formed by hydrolysis, but by nucleophilic displacement at the C=O carbon atom by thermal electrons.

Attempted electron pyrolysis of dibenzyl succinate under the above conditions was unsuccessful at first. The radio-chromatogram shown in Figure 5 was obtained only after the addition of uranium dioxide powder to the reaction mixture. The ester was then degraded, *via* succinic acid, to propionic acid or benzyl propionate. The benzyl group again gave benzaldehyde, which could be detected as the 2,4-dinitrophenylhydrazone.

The large number of fragments formed in the electron pyrolysis of tributyrin *(25)* with tritiated water can be seen from Figure 6. A surprising feature is that the butyric acid residue is degraded primarily to the acetic acid residue, as is shown in the following scheme.

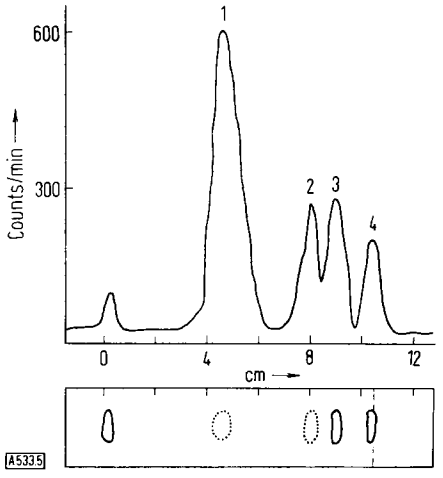
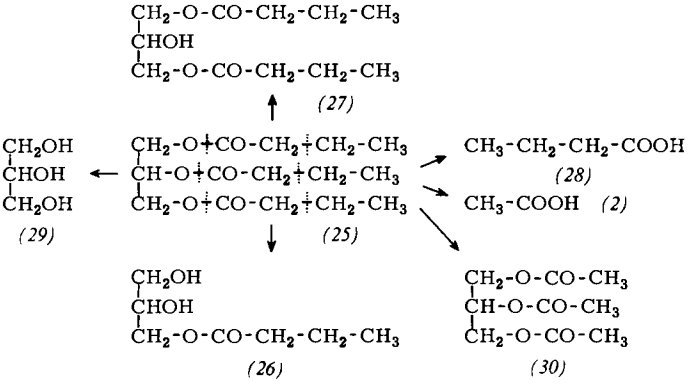



Fig. 5. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 5 μg of dibenzyl succinate in tritiated water with added $UO_2$. Solvent system: ethanol/ammonia/water (100:16:12 v/v).

1, succinic acid; 2, propionic acid; 3, dibenzyl succinate; 4, benzyl propionate.



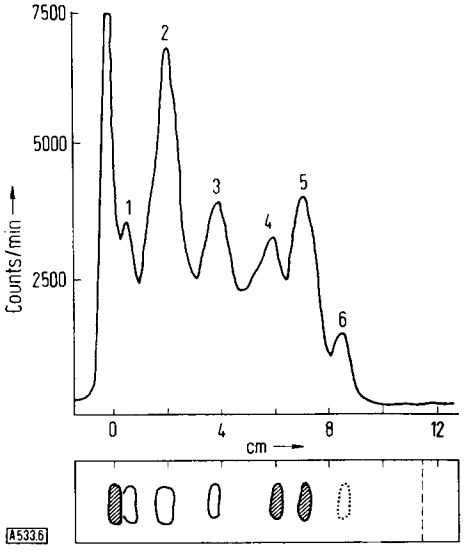




Fig. 6. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 10 μg of tributyrin *(25)*. Solvent system: benzene/dioxane (90:25 v/v).

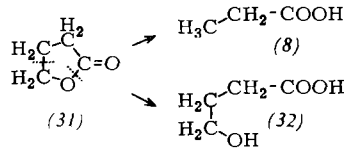
1, monobutyrin *(26)*; 2, butyric acid *(28)*; 3, acetic acid *(2)*; 4, dibutyrin *(27)*; 5, triacetin *(30)*; 6, tributyrin *(25)*.

Though we were unable to distinguish chromatographically between 1,3- and 1,2-dibutyrin, it may be assumed from the secondary products that the electron pyrolysis of *(25)* yields 1,3-dibutyrin *(27)*. Glycerol *(29)* also could be separated from the other components in a second chromatogram. The

[11] *A. M. McLachlan*, J. Amer. chem. Soc. *82*, 3309 (1960).
[12] *A. M. McLachlan*, J. org. Chemistry *29*, 1598 (1964).
[13] *E. M. Emery*, Analytic. Chem. *32*, 1495 (1960).

radio-chromatogram in this case contains practically no activity maximum, since the labile tritium is almost completely exchanged during the development of the chromatogram. However, glycerol can be made visible with $KMnO_4$/$H_2SO_4$.

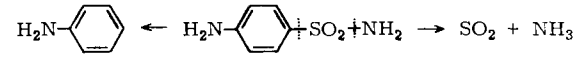
γ-Butyrolactone *(31)* is only partially hydrolysed by water to hydroxybutyric acid *(32)*, and only on prolonged heating. With tritiated water, however, *(32)* is formed even at room temperature and in higher yields.



*(31)* *(8)* *(32)*

In addition to *(32)*, propionic acid *(8)* is formed. A $C_3$ fragment is formed also in the mass spectrometry of γ-butyrolactone, and is recorded as the $C_3H_4O^{\oplus}$ ion [14].

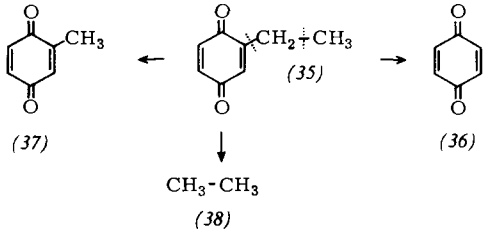
In order to avoid hydrolysis, sulfanilamide *(33)* was incubated for 10 days with 3 Ci of tritium gas. The fragmentation led to aniline *(34)*, ammonia, and probably sulfur dioxide.



*(34)* *(33)*

### 3.3. Electron Pyrolysis of Quinones [15]

The behavior of quinones on electron pyrolysis was of interest to us, because the defensive substances of arthropods [16] and also of plants [17], which we were studying, quite often are *p*-benzoquinones. Particularly when only a few μg of such a compound are available for analysis, the nature and position of side chains in alkylated *p*-benzoquinones can be found only with great effort. We therefore applied the new fragmentation procedure to quinones of this type. Already in the first example studied, ethyl-*p*-benzoquinone *(35)*, we observed that the ethyl group is split off in stages; benzoquinone and toluquinone were found by thin-layer chromatography, and tritium-labeled ethane by radio-gas chromatography.



*(37)* *(35)* *(36)* *(38)*

In addition to the tritium-labeled quinones *(35)*, *(36)*, and *(37)*, labeled hydroquinones are also formed in every case. This agrees with *Vermeil*'s findings [18], according to which hydroquinone is formed as a principal product on γ-irradiation of *p*-benzoquinone in water. The formation of hydroxyquinones, which react further to humic acids, can be avoided if benzene, toluene, or ethanol is added to the tritiated water as a solubilizing agent. Moreover, when an organic solvent is present, the temperature can be raised from 40 to 80 °C without danger of formation of large quantities of polymers during the electron pyrolysis.

After electron pyrolysis of n-propyl-*p*-benzoquinone, thin-layer chromatography revealed the presence of toluquinone *(37)* in addition to the expected hydroquinones. Benzoquinone was detected only as hydroquinone. After electron pyrolysis of thymoquinone *(39)*, only half of the active pyrolysis product could be stained on the thin layer by spray reagents (Fig. 7). The

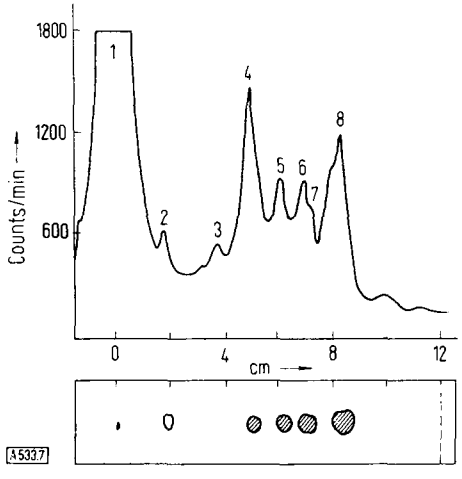
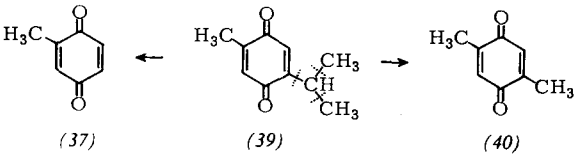



Fig. 7. Thin-layer radio-chromatogram of the solution obtained by electron pyrolysis of 40 μg of 2-isopropyl-5-methyl-*p*-benzoquinone *(39)*. Solvent system: petroleum ether (60—70 °C)/ethyl acetate (6:4 v/v). 1, humic acids; 2, dithymoquinone; 3, toluhydroquinone; 4, 2,5-dimethylhydroquinone; 5, thymohydroquinone; 6, toluquinone *(37)*; 7, 2,5-dimethyl-*p*-benzoquinone *(40)*; 8, thymoquinone *(39)*.

presence of toluquinone *(37)* and 2,5-dimethylquinone *(40)* showed that the isopropyl side chain had been split off and fragmented. 2-Ethyl-5-methyl-*p*-benzoquinone must have been formed as intermediate, the ethyl group then being further degraded, as described above. The methyl group, on the other hand, appears to be more stable, as was shown by the electron pyrolysis of toluquinone *(37)* itself. Thus degradation occurs mainly at the longer and possibly branched side chains. In the electron pyrolysis of phenyl-*p*-benzoquinone, even the phenyl group is readily split off, with formation of benzoquinone.



*(37)* *(39)* *(40)*

[14] *L. Friedman* and *F. A. Long*, J. Amer. chem. Soc. *75*, 2832 (1953).

[15] *F. Römer*, Diploma Thesis, Universität Heidelberg, 1966.

[16] *H. Schildknecht*, Angew. Chem. *75*, 762 (1963); Angew. Chem. internat. Edit. *3*, 73 (1964).

[17] Nachr. Chem. Techn. *12*, 177 (1964).

[18] *C. Vermeil*, *G. Roquet*, and *L. Salomon*, J. Chim. physique *60*, [5], 659 (1963).

In the study of the defense substances of arthropods we had encountered methoxy-*p*-benzoquinones [19], which we also examined by electron pyrolysis. We found that the methoxy group is readily eliminated. This is particularly significant in the elucidation of the structures of complex methoxyquinones, which can be converted by electron pyrolysis into simpler, and hence in most cases known, alkylated *p*-benzoquinones. Not only methoxy-*p*-benzoquinone *(42)*, but also 2,6-dimethoxy-*p*-benzoquinone *(41)* gave labeled benzoquinone *(36)*, again together with the corresponding hydroquinones, when treated with tritium (cf. Fig. 8).

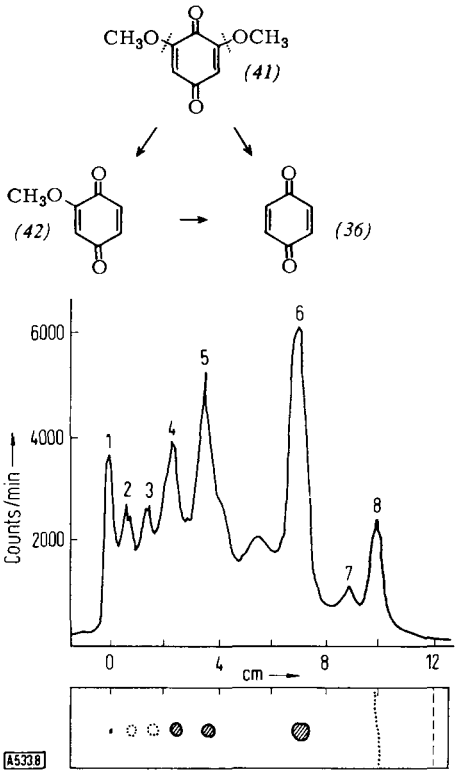
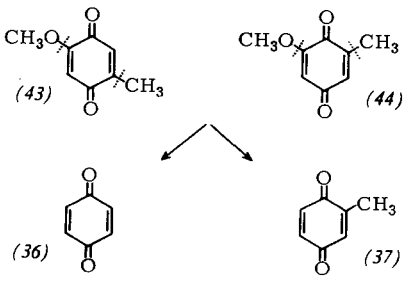



Fig. 8. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 50 µg of 2,6-dimethoxy-*p*-benzoquinone *(43)*. Solvent system: chloroform/petroleum ether (60—70 °C)/ethanol (60:37:4 v/v).

1, polymer; 2, hydroquinone; 3, methoxyhydroquinone; 4, 2,6-dimethoxyhydroquinone; 5, 2,6-dimethoxy-*p*-benzoquinone *(41)*; 6, methoxy-*p*-benzoquinone *(42)*; 7, *p*-benzoquinone *(36)*; 8, second solvent front.

In the electron pyrolysis of the isomers 2-methoxy-5-methyl-*p*-benzoquinone *(43)* and 2-methoxy-6-methyl-*p*-benzoquinone *(44)*, only toluquinone *(37)* is found in addition to benzoquinone. Thus the methoxy group is removed more readily than the methyl group.




[19] *H. Schildknecht* and *K. H. Weis*, Z. Naturforsch. *166*, 810 (1961).

### 3.4. Electron Pyrolysis of Menthol and Thymol[20]

We used menthol *(45)* purified by zone melting. The starting band in Figure 9 is due to adsorbed tritiated water and hydroxylated menthol. Band 2 was assigned to *cis*-3-methylcyclohexanol *(49)*, which we prepared by reduction of 3-methylcyclohexanone with $LiAlH_4$. The *trans*-isomer *(50)* was also formed in the electron

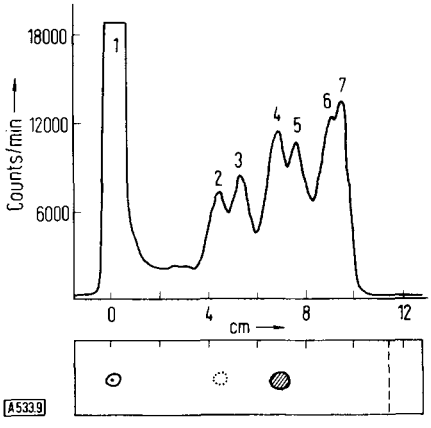
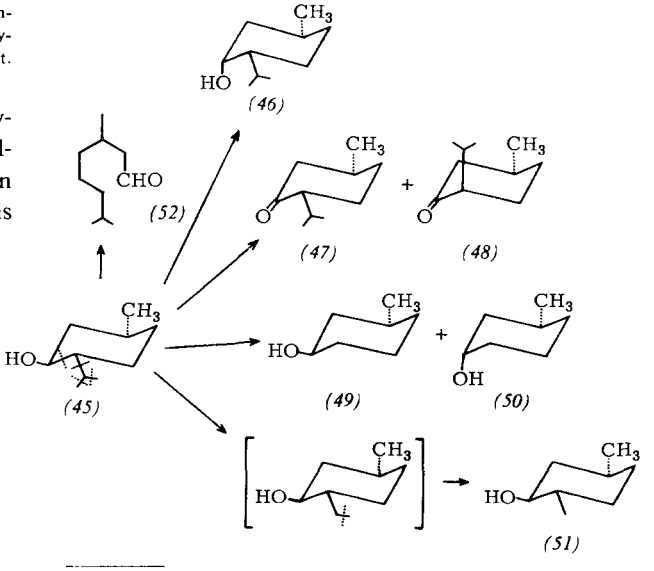



Fig. 9. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 15 µg of menthol *(45)*. Solvent system: chloroform/petroleum ether (60—70 °C)/ethanol (60:37:3 v/v).

1, hydroxylated menthol; 2, *cis*-3-methylcyclohexanol *(49)*; 3, *trans*-2-*cis*-5-dimethylcyclohexanol *(51)*; 4, menthol *(45)*; 5, neomenthol *(46)*; 6, menthone *(47)*; 7, 3,7-dimethyloctanal *(52)*.

pyrolysis, but with weaker labeling. Band 3 corresponds to *trans*-2-*cis*-5-dimethylcyclohexanol *(51)*. The formation of this isomer during the electron pyrolysis is in agreement with *Hückel*'s findings [21], according to which *(51)* is the predominant species in equilibrium mixtures with its isomers. It corresponds to menthol in its configuration. Owing to the equality of the $R_f$ values of menthol and isomenthol, band 4, and of neomenthol and neoisomenthol, band 5, it was not possible to assign these bands to a particular isomer. A second chromatogram (solvent system: methylene chloride) showed the



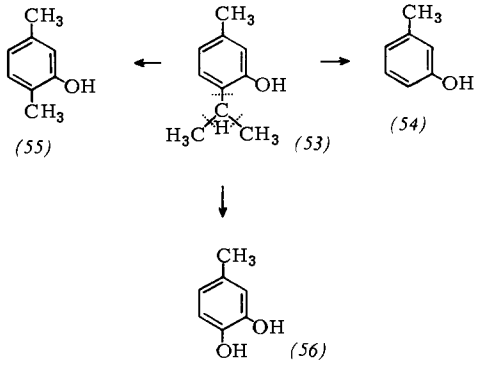

[20] *H. Schildknecht* and *K. Penzien*, Z. analyt. Chem. *219*, 102 (1966).

[21] *W. Hückel, H. Feltkamp*, and *S. Geiger*, Liebigs Ann. Chem. *637*, 1 (1950).

presence of isomenthone *(48)*, menthone *(47)*, and 3,7-dimethyloctanal *(52)* among the products of the electron pyrolysis of menthol.

As in the fragmentation of thymoquinone *(39)*, the isopropyl group of menthol *(45)*, too, is split off. This cleavage is probably favored by the high stability of the isopropyl radical presumably formed. The fact that no removal of the methyl group attached to the ring in menthol was observed supports this interpretation. It is still remarkable that 2,5-dimethylcyclohexanol *(51)* is found, but no 2-ethyl-5-methylcyclohexanol, since it is unlikely that the cleavage of two C–C bonds takes place simultaneously. Thus *Hentz*[22] found, *inter alia*, benzene, ethylbenzene, and toluene in the $^{60}$Co-γ-radiolysis of isopropylbenzene. The 3,7-dimethyloctanal *(52)* obtained from menthol in tritiated water is probably formed because the bond between the C atom carrying the hydroxyl group and that carrying the isopropyl group is the weakest of the C–C bonds in the ring. The dissociation energy of a C–CO bond is smaller than that of a C–C bond. As far as the mechanism is concerned, the dealkylation is best explained by the attack of a solvated electron. However, the oxidation, reduction, and ring cleavage reactions may be initiated by the other radiolysis products of water, particularly by the OH radicals.

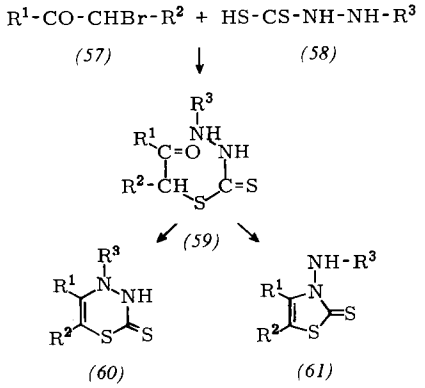
The results of the electron pyrolysis of thymol *(53)* agreed closely with the fragmentation observed in the case of menthol. Of particular interest to the natural



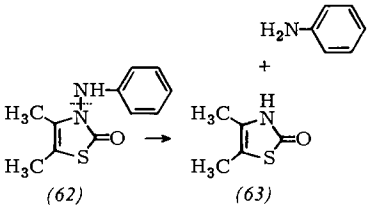

products chemist may be the fact that the isopropyl group again is successively and preferentially split off.

## 4. Elucidation of the Structures of Thiazoles and Thiadiazines by Electron Pyrolysis [23]

The derivatives *(59)* obtained from α-halogenoketones *(57)* and *N*-substituted hydrazides of dithiocarbonic acid *(58)* can undergo ring closure to form either a 3,4-dihydro-2*H*-1,3,4-thiadiazine-2-thione *(60)* or a 1,3-thiazole-2-thione *(61)*.




For $R^3$ = H, the presence of the 5-membered ring in *(61)* can be readily demonstrated by deamination, if detection of the amino group by the formation of a Schiff base is not sufficient in itself. However, this proof is no longer possible when $R^3$ is an organic group. For $R^3$ = CO–$C_6H_5$, *Sato*[24] formulated a 6-membered ring, since compounds of this type are soluble in alkali and this property can be explained by thiol formation. However, *Ege*[25] found that solubility in alkali is not a criterion for the 6-membered cyclic structure. The 5-membered cyclic structure could not be proved either chemically or spectroscopically (NMR, ultraviolet, infrared) in the case of 3-anilino-4,5-dimethyl-2*H*-1,3-thiazol-2-one *(62)*.




The electron pyrolysis of *(62)* should lead to the formation of aniline. In fact, the two complementary fragments aniline and 4,5-dimethyl-2*H*-1,3-thiazol-2-one *(63)* could be detected both chemically and with the thin-layer scanner in the thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 20 μg of *(62)* (cf. Fig. 10).

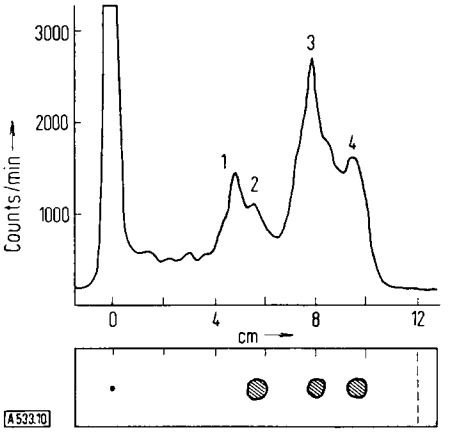



Fig. 10. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 20 μg of *(62)*. Solvent system: $CHCl_3/CH_3OH$ (95:5 v/v).

1, uncertain; 2, 4,5-dimethyl-2*H*-1,3-thiazol-2-one *(63)*; 3, aniline; 4, 3-anilino-4,5-dimethyl-2*H*-1,3-thiazol-2-one *(62)*.

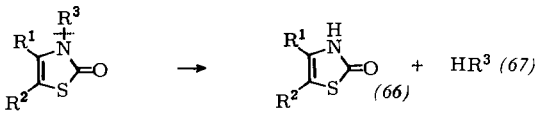
Electron pyrolysis of the compounds *(64)* and *(65)* also confirmed the 5-membered cyclic structure established by *Ege*, since *(66)* and *(67)* were detected in the thin-layer chromatogram. Similarly, the electron pyrolysis of 3-benzoylamido-4-phenyl-2*H*-1,3-thiazol-2-thione *(68)*

[22] *R. R. Hentz*, J. physic. Chem. *66*, 1622 (1962).

[23] *G. Ege, K. Geßner*, and *H. Schildknecht*, unpublished.

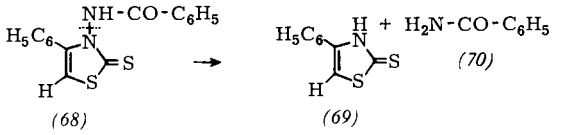
[24] *T. Sato* and *M. Ohta*, J. pharmac. Soc. Japan (Yakugakuzasshi) *75*, 1535 (1955); Chem. Abstr. *50*, 10727 (1956).

[25] *G. Ege*, unpublished.



*(64)*, $R^1$: $C_6H_5$; $R^2$: H; $R^3$: HN-CO-$C_6H_5$
*(65)*, $R^1 = R^2$: $CH_3$; $R^3$: HN-CO-$C_6H_5$

with methanol as a solubilizing agent led to the formation of benzamide *(70)* and 4-phenyl-2*H*-1,3-thiazol-2-thione *(69)*.



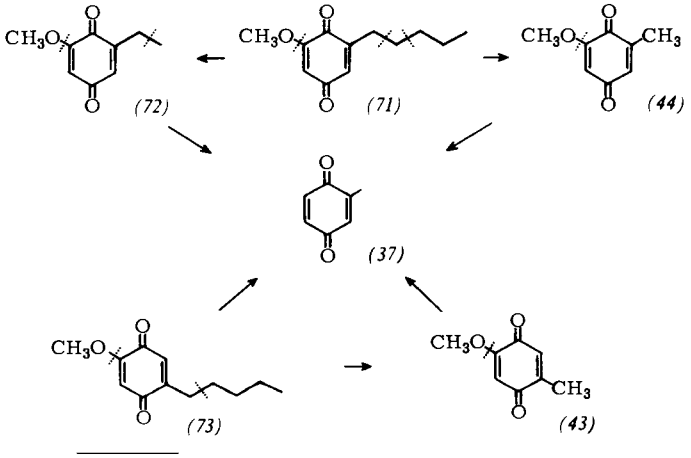
*(68)* *(69)* *(70)*

In the electron pyrolysis of thiazoles and thiadiazines, the mode of fragmentation remarkably often led to conclusive structure proofs, conclusive in that the thiadiazines do not rearrange to the corresponding 5-membered compounds, but are degraded into as yet unidentified fragments. It is likely that during the electron pyrolysis the hydrolytic action of water is superposed on the specific fragmenting action of the hydrated electron.

## 5. Elucidation of the Structures of Natural Products by Electron Pyrolysis

The results obtained with model substances encouraged us to use electron pyrolysis in order to confirm structures proposed for unknown natural products.

For example, we had found by a comprehensive spectroscopic analysis that the poison of the primrose, which *Karrer* had named primin, is a methoxy-n-pentyl-*p*-benzoquinone [26]. Several synthetic quinones had to be used as reference substances in order to show that primin is 2-methoxy-6-n-pentyl-*p*-benzoquinone*(71)* [27]. We later found that the two possible isomers can be easily distinguished by electron pyrolysis, since the known compounds 2-methoxy-5- and 2-methoxy-6-methyl-*p*-benzoquinones, *(43)* and *(44)*, are formed as fragments. This is shown in the following scheme:



*(72)* *(71)* *(44)* *(37)* *(73)* *(43)*

[26] *H. Schildknecht, I. Bayer*, and *H. Schmidt*, Z. Naturforsch. in press.

[27] *H. Schildknecht* and *H. Schmidt*, Z. Naturforsch., in press.

In agreement with the observations made in the electron pyrolysis of other substituted *p*-benzoquinones, the alkyl side chain fortunately is broken down only to such an extent that the positions of the substituents on the quinone nucleus of primin are fixed by the remaining methyl group and by the methoxy group still present. The alkyl group is satisfactorily characterized by the detection, by radio-gas chromatography, of n-butane among the volatile components.

It was mentioned at the beginning that, hopefully, structures can be proposed by properly arranging the electron-pyrolysis fragments like the pieces of a jig-saw puzzle. This hope may yet be realized. Certainly, the identification of the fragments of the arthropod alkaloid glomerine [28] has required much more time than did the rational combination to give the proposed structure [29]. Glomerine, a 1,2-dimethylquinazol-4-one *(74)*, was fragmented by electron pyrolysis to anthranilic acid *(20)*, *N*-methylanthranilic acid *(76)*, *N*-methylanthranilamide *(75)*, and acetic acid (cf. Fig. 11).

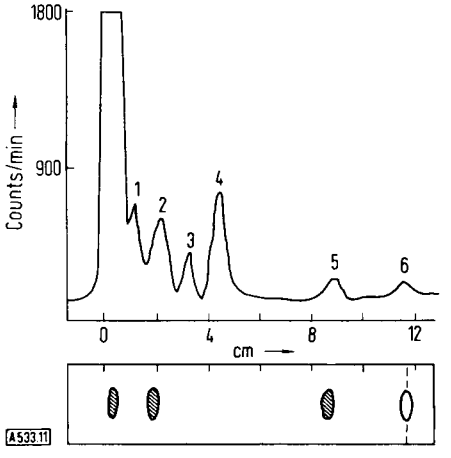



Fig. 11. Thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of 5 µg of glomerine *(74)*. Solvent system: petroleum ether (60—70 °C)/ether/pyridine (1:1:1 v/v).

1, unidentified; 2, anthranilic acid *(20)*; 3, unidentified; 4, acetic acid *(2)*; 5, *N*-methylanthranilamide *(75)*; 6, *N*-methylanthranilic acid *(76)*; start, glomerine *(74)*.

The synthesis of glomerine was a reversal of the fragmentation, since anthranilic acid was converted *via (76)* into *(75)*, which in turn was converted into *(74)* by means of acetic acid. The biosynthesis of glomerine probably also starts from anthranilic acid.

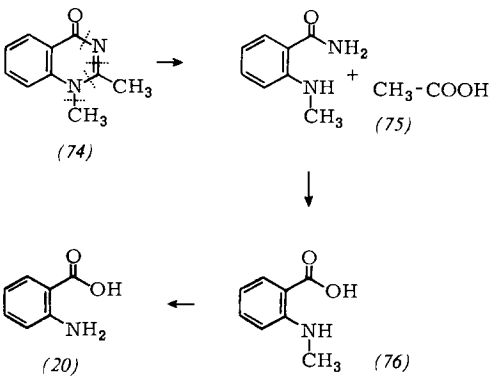
The composite proanthocyanidins [30] are condensation or dehydrogenation products of two flavonoids, a monomolecular proanthocyanidin, and a catechol. The two halves of the molecule may be linked either by an ether oxygen, by a C–C linkage, or by a ketal linkage. In order to clarify the structure, therefore, *Weinges* and *Ebert* [31] examined model substances corresponding to the composite proanthocyanidins with a C–C linkage, and attempted to achieve an informative cleavage by

[28] *H. Schildknecht, K. H. Weis, W. F. Wenneis*, and *U. Maschwitz*, Z. Naturforsch. *21b*, 121 (1966).

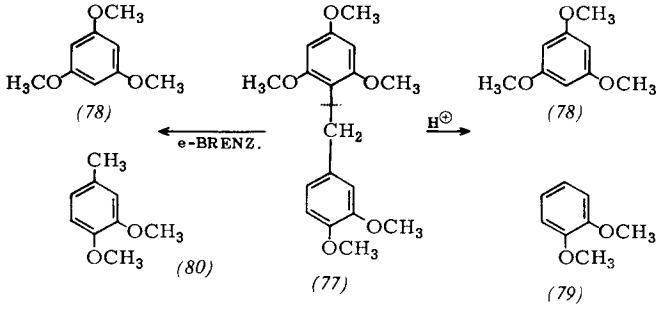
[29] *H. Schildknecht* and *W. F. Wenneis*, *Z. Naturforsch. 21b*, 552 (1966).

[30] *K. Freudenberg* and *K. Weinges*, Tetrahedron Letters *1961*, 267.

[31] *W. Ebert*, Diploma Thesis, Universität Heidelberg, 1965.



chemical methods. In the presence of acids, however, 2,4,6,3′,4′-pentamethoxydiphenylmethane *(77)* was broken down to phloroglucinol trimethyl ether *(78)* and veratrole *(79)*, with loss of the central methylene group. Consequently, the substitution position in the veratrole residue could not be established in this way. In the thin-layer radio-chromatogram of the solution obtained on electron pyrolysis of *(77)*, on the other hand, one fraction could be satisfactorily assigned to homoveratrole *(80)*.



## 6. Prospects

In all chemical methods of structural elucidation it should be known *which* bonds in the unknown molecule are attacked by the reagent. In reactions with tritiated water, the attack usually takes place on the weakest bonds, and C–N, C–C, C–O, and C–H bonds can be broken oxidatively and reductively. Of great advantage in this case is that part or all of the alkyl side chain is removed from the basic structure, *e.g.* a quinone nucleus, so that information is obtained not only about the nature of the side chain, but also about the substitution site.

The selectivity observed in the fragmentation by electron pyrolysis is surprising, since the β-decay energy of tritium is higher by a factor of $10^3$ than the dissociation energies of the above-mentioned bonds. It must therefore be concluded that the interaction leading to fragmentation occurs between the molecule and an energy-transfer agent, the energy of which is comparable to the bond energy. Whether the energy is transferred *via* H atoms, OH radicals, electrons, radiation, or even excited water molecules is of no importance to the above argument. Nevertheless, efforts will be made to find a mechanistic interpretation of electron pyrolysis, simply to permit the prediction of the course of fragmentation. The growing understanding of the radiolysis of organic compounds in aqueous solution with X- and γ-rays is particularly valuable in this connection.

We believe that solvated electrons may be assumed to be particularly important in the fragmentations observed by us. Consequently, the fragmentation in the mass spectrometer often can be used for comparison. However, whereas only one half of the complementary fragments is recorded in mass spectrometry, both parts can be expected to be detected in electron pyrolysis. Further, the fragments formed in electron pyrolysis are "frozen" by saturation with H (or T) atoms or OH (OT) radicals and by reaction with the tritiated water, whereas the primary radicals formed in the mass spectrometer are stabilized intramolecularly, with further fragmentation. This often leads to a spectrum with a large number of peaks. Moreover, it is not always possible to distinguish between isomeric ions by mass spectrometry, whereas after electron pyrolysis the isomeric fragments can be separated by chromatography and identified.

Concerning the future of radio-gas chromatography, we hope that it will not only become possible to detect all fragments as a result of the development of more sensitive radiation detectors, but also that these will often be sufficiently well characterized by their retention times alone. The long incubation periods ranging from a few days to some weeks will then no longer be necessary if tritiated water having a specific activity of 25 Ci/ml instead of 5 Ci/ml is used. This requires particularly careful work, which can be guaranteed better in gas chromatography than in thin-layer chromatography.

*These experiments, sometimes not entirely without danger, and the unconventional and, to an organic chemist, somewhat unfamiliar techniques required great diligence and idealism on the part of my doctorate candidates, for which I express my sincere thanks. The investigations would not have been possible without the generous support of the Ministerium für wissenschaftliche Forschung, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie. We are grateful to Prof. W. Hückel and to the Dragoco-Werke for the donation of chemicals.*

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# Silicon-Nitrogen Heterocycles

BY DR. W. FINK

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*Great progress has recently been made in the chemistry of the silicon-nitrogen bond* [1–5]. *Whereas attention was formerly concentrated on open-chain silazanes and silylamines, growing interest is now being shown in the cyclic SiN compounds. A major factor which has contributed to the rapid development in this field is the need for better polymers and liquids for use above 350 °C* [6]. *The present article deals with monomeric cyclic compounds containing at least one silicon-nitrogen bond in the ring, as well as the polycyclic compounds derived from these.*

## 1. Heterocycles with SiN Bonds in the Ring

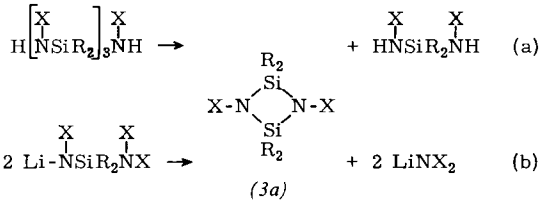
### 1.1. Cyclodisilazanes [7, 8]

For a long time the existence of 4-membered silazane rings with alternating Si-N bonds was doubtful. *Pflugmacher* and *Dahmen* [9] isolated a cyclic perchlorinated silazane *(2)*, formed *via* the condensation of tris(trichlorosilyl)amine *(1)*, from the products of the glow discharge of $SiCl_4/N_2$ mixtures. By analogy with the results obtained by *Schumb* and *Towle* [10], these authors postulated a cyclotetrasilazane structure (n = 4) for their product. They ruled out 4-membered silazane rings because of the high ring strain expected.

$$n\ N(SiCl_3)_3 \rightarrow (Cl_2SiNSiCl_3)_n + n\ SiCl_4$$
*(1)* *(2)*

However, the compound appears to have the structure of a cyclodisilazane [11].

In 1961, 1,3-bis(trimethylsilyl)-2,2,4,4-tetramethylcyclodisilazane *(3a)* was obtained in accordance with equations (a) [12] and (b) [12] by thermolysis of long-chain metalated silazanes [13] [see *(27)*] and of *N*-trimethylsilylated and permethylated cyclotri- and cyclotetrasilazanes [14, 15]. The elucidation of the structure of this

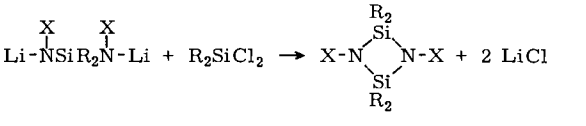


*(3a)*

$R = CH_3$, $X = (CH_3)_3Si$

compound [16] established the existence of 4-membered silazane rings, and a number of methods have recently been developed for the preparation of such rings [*].

The cyclodisilazane ring can be formed in good yields by the reaction of doubly metalated octamethyltrisilazane *(4a)* with organodi- and -trichlorosilanes or with silicon tetrachloride [12, 14]. The products are 1,3-bistrimethylsilyl compounds.



*(4a)* R = $CH_3$, X = $(CH_3)_3Si$ *(3a)* R = $CH_3$, X = $(CH_3)_3Si$
*(4b)* R = X = $CH_3$ *(3b)* R = X = $CH_3$

*Lienhard* and *Rochow* [17, 18] applied this method to doubly metalated bis(methylamino)dimethylsilane *(4b)* (R = X = Me), and isolated cyclodisilazanes *(3)* with methyl substituents on the nitrogens. Other *N*-alkylated and *N*-arylated

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[1] *C. Eaborn*: Organosilicon Compounds. Butterworths, London 1960, p. 339.

[2] *R. Fessenden* and *J. S. Fessenden*, Chem. Reviews *61*, 361 (1961).

[3] *K. A. Andrianov, I. Haiduc*, and *L. M. Khananashvili*, Uspekhi Khim. *32*, 563 (1963); Chem. Abstr. *59*, 8782 (1963).

[4] *U. Wannagat*, Advances inorg. Chem. Radiochem. *6*, 265 (1964).

[5] *I. Haiduc*: Westep do Chemii Nieorganicznych Zwiazkow Pierscieniowych. WPN, Warsaw 1964, Chap. 10 (in Polish).

[6] Cf. *E. G. Rochow*, Chim. et Ind. *85*, 897 (1961).

[7] The nomenclature is based on rules proposed for silicon-nitrogen compounds [*E. J. Crane*, Chem. Engng. News *30*, 4517 (1952)]. The usual nomenclature in Russian literature is described by *I. Haiduc* and *K. A. Andrianov*, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1963*, 1537.

[8] The following abbreviations are used: Me = methyl, Et = ethyl, Pr = propyl, Bu = butyl, Vi = vinyl, All = allyl, Ph = phenyl, Ans = anisyl, Dod = dodecyl, Xe = 4-biphenylyl, Ano = $NH_2$–$C_6H_4$, Be = benzyl, Toy = tolyl, Ch = cyclohexyl.

[9] *A. Pflugmacher* and *H. Dahmen*, Z. anorg. allg. Chem. *290*, 184 (1957).

[10] *W. C. Schumb* and *L. H. Towle*, J. Amer. chem. Soc. *75*, 6085 (1953).

[11] *H. Ernst*, Dissertation, Technische Hochschule Aachen, 1958.

[12] *W. Fink*, Chem. Ber. *96*, 1071 (1963).

[13] *W. Fink*, Helv. chim. Acta *46*, 720 (1963).

[14] *W. Fink*, Angew. Chem. *73*, 736 (1961).

[15] *W. Fink*, Helv. chim. Acta *45*, 1081 (1962).

[16] *P. J. Wheatley*, J. chem. Soc. (London) *1962*, 1721.

[*] Our investigations have shown that the cyclodisilazane $[(Me_3SiO)_2Si)NH]_2$ (m.p. 103 °C, b.p. 180–183 °C/4 mm) prepared by *K. A. Andrianov* and *N. V. Delazari* (Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1961*, 2169) is probably the trimer (found m.p. 108 °C); monoclinic, space group $P2_1/c$; a = 11.22, b = 43.29, c = 19.31 Å; β = 106 ° 15′ [82].

[17] *K. Lienhard* and *E. G. Rochow*, Angew. Chem. *75*, 638 (1963); Angew. Chem. internat. Edit. *2*, 325 (1963).

[18] *K. Lienhard* and *E. G. Rochow*, Z. anorg. allg. Chem. *331*, 316 (1964).

rings *(3)* have been prepared in a similar manner from the dilithium compounds of the corresponding silylamines *(4)* [19,20]. The direct reaction of the dilithium compounds of primary (preferably aromatic) amines with diorganosilicon dichlorides can be used for the synthesis of *(3)* [19].

$$2\,XN{-}Li_2 + 2\,R_2SiCl_2 \rightarrow (3) + 4\,LiCl$$

The pyrolysis of diaminodiorganosilanes *(5)* at 200–450 °C is particularly useful for the preparation of *N*-alkylated and *N*-arylated compounds *(3)* [19].

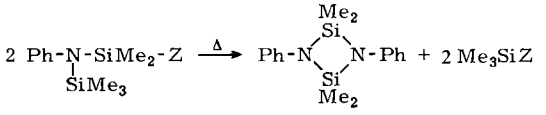
$$\underset{(5)}{2X{-}NHSiR_2HN{-}X} \xrightarrow{\Delta} (3) + 2\,XNH_2 \qquad (c)$$

This method, in which (particularly by use of compounds *(5)* with X = aryl) yields of 90% and more are not unusual, is restricted to compounds *(5)* which decompose below their boiling points. A variant of reaction (c) which makes use of transamination [21] is useful when the removal of the (high-boiling) amine is difficult [19,22].

$$\underset{(5)}{2\,X{-}NHSiR_2HN{-}X} \xrightarrow[-2\,XNH_2]{+2\,X'NH_2} 2\,X'{-}NHSiR_2HN{-}X \xrightarrow[-2\,XNH_2]{\Delta} (3)$$

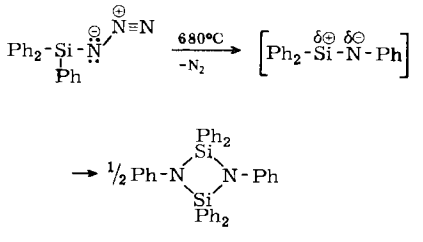
The reaction occurs only when the boiling point of $X'NH_2$ is higher than that of $XNH_2$. Some examples of substituted cyclodisilazanes are given in Table 1.

The formation of *N*-phenylated rings *(3c)* [Z=Cl, $C_6H_5{-}N{-}Si(CH_3)_3$] is also based on pyrolysis [19].



*(3c)*

*Reichle* [23] reported the formation of hexaphenylcyclodisilazane *(3d)* in the decomposition of triphenylsilyl azide at 680 °C.



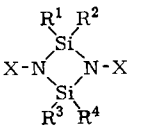
*(3d)*

A reaction of particularly wide scope is the silylation of primary aliphatic and aromatic amines and of triorgano silanamines with disilanes to form *(3)*, between 0 and 100 °C in the presence of alkali metals or their hydrides as catalysts [equation (d)] [24]. This reaction, which is generally spontaneous and very fast, can be carried out in polar (tetrahydrofuran, 1,2-dimethoxyethane, diethyl ether) or non-polar (benzene, hexane) solvents, or even without a solvent, and proceeds almost quantitatively.

$$2\,XNH_2 + 2\,H_2SiR^1R^2 \xrightarrow{-2\,H_2} \underset{H\ H}{2\,XN{-}SiR^1R^2} \xrightarrow{-2\,H_2} (3) \quad (d)$$

*(6)*

Table 1. *N*-Substituted cyclodisilazanes *(3)*.



| X | $R^1$ | $R^2$ | $R^3$ | $R^4$ | B.p. (°C/mm) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|---|---|
| $Me_3Si$ [a] | Me | Me | Me | Me | 85/7 | 39 | [12, 14] |
| $Cl_3Si$ | Cl | Cl | Cl | Cl | | 84 | [9, 11] |
| $Me_3Si$ [b] | Me | Me | EtO | EtO | 75/1.5 | | [12] |
| $Me_3Si$ [c] | Me | Me | Cl | Cl | 118/21 | 28 | [12] |
| $Me_3Si$ [d] | Me | Et | Me | Et | 74/0.9 | | [12] |
| $Me_3Si$ | Et | Et | Et | Et | 80–82/0.9 | | [12] |
| n-$Bu_3Si$ | Ph | Ph | Ph | Ph | 240–242/0.04 | 111 | [24] |
| $Me_3Si$ | Me | Me | Ph | Ph | 120/0.03 | 52 | [24] |
| $ClMe_2Si$ | Me | Me | Me | Me | 64/0.08 | 59 | [25] |
| Me [e] | Me | Me | Me | Me | 52/51 | 17 | [17, 18] |
| Me [f] | Me | Me | Me | Ph | 69–71/3 | | [17, 18] |
| Me [g] | Me | Me | Ph | Ph | 144/4 | | [17, 18] |
| Me | Et | Et | Et | Et | 115–120/0.01 | 95 | [20] |
| Me | Ph | Ph | Ph | Ph | | 262 | [22] |
| Et [h] | Me | Me | Me | Me | 98/82 | | [19] |
| Et | Ph | Ph | Ph | Ph | | 196 | [19] |
| Et [i] | Vi | Et | Vi | Et | 54/0.05 | | [24] |
| Et [j] | All | All | All | All | 90/0.02 | | [24] |
| Et [k] | Vi | Vi | Vi | Vi | 100/12 | | [20] |
| All | Me | Me | Me | Me | 74/11 | | [24] |
| All | Ph | Ph | Ph | Ph | | 167 | [24] |
| n-Bu [l] | Me | Me | Me | Me | 89/6 | | [24] |
| t-Bu [m] | Me | Me | Me | Me | 100/12 | 35 | [24] |
| Ch | Me | Me | Me | Me | 123/0.01 | 105 | [19] |
| n-Dod | Ph | Ph | Ph | Ph | 300/0.05 | | [24] |
| Ph | Me | Me | Me | Me | subl. 210/720 | 252.5 | [19] |
| Ph | Ph | Ph | Ph | Ph | | 355.5 | [19] |
| Ph | Ph | Ph | Me | Me | | 181 | [19] |
| Ph | Me | Me | Me | Cl | | 243–245 | [19] |
| Ph | Me | Me | Cl | Cl | | 210–215 | [19] |
| α-Naphthyl | Me | Me | Me | Me | | 253 | [19] |
| β-Naphthyl | Me | Me | Me | Me | | 237 | [19] |
| β-Naphthyl | Ph | Ph | Ph | Ph | | 319.5 | [19] |
| Ph | $-(CH_2)_4-$ | | $-(CH_2)_4-$ | | | 227 | [22] |
| Ph | H* | Me | H | Me | 193/0.05 | 91 | [29] |
| Ph | [n] | | | | | 322 | [22] |
| 3-F–$C_6H_4$ | Ph | Ph | Ph | Ph | | 312 | [19] |
| 4-F–$C_6H_4$ | Ph | Ph | Ph | Ph | | 323 | [19] |
| 2,5-$F_2$–$C_6H_3$ | Ph | Ph | Ph | Ph | | 326 | [22] |
| 2,4-$F_2$–$C_6H_3$ | Ph | Ph | Ph | Ph | | 338 | [22] |
| 3-$CF_3$–$C_6H_4$ | Ph | Ph | Ph | Ph | | 183–185 | [19] |
| 3,5-$(CF_3)_2$–$C_6H_3$ | Ph | Ph | Ph | Ph | | 364 | [22] |
| 3-Cl–$C_6H_4$ | Ph | Ph | Ph | Ph | | 262 | [19] |
| 3-Br–$C_6H_4$ | Ph | Ph | Ph | Ph | | 272 | [22] |
| 3-Ans | Me | Me | Me | Me | | 171 | [22] |
| 2,4,6-$(CH_3)_3$–$C_6H_2$ | Me | Me | Me | Me | | 250 | [22] |
| 2-Xe | Me | Me | Me | Me | | 188 | [22] |
| 4-Xe | Me | Me | Me | Me | | 273–276 | [22] |
| 4-Ano | Ph | Ph | Ph | Ph | | 241 | [22] |
| $Me_3Si{-}CH_2$ | Me | Me | Me | Me | | 63–64 | [22] |
| 3-$C_6H_5O$–$C_6H_4$ | Ph | Ph | Ph | Ph | 470/728 | 169–172 | [22] |
| 4-$C_6H_5O$–$C_6H_4$ | [o] | | | | 425–435/721 | | [22] |
| 2,6-$(C_6H_5O)_2$-$C_6H_3$ | Me | Me | Me | Me | 315–319/728 | | [22] |
| 3′-$C_6H_5O$-3-$C_6H_4O$–$C_6H_4$ | Me | Me | Me | Me | | 212 | [22] |

[a] $n_D^{45} = 1.4237$, $d_4^{20} = 0.998$ [12]; [b] $n_D^{20} = 1.4312$ [12]; [c] $n_D^{45} = 1.4360$ [12]; [d] $n_D^{20} = 1.4502$ [12]; [e] $n_D^{20} = 1.4210$ [17, 18], $d_4^{22} = 0.8403$ [19]; [f] $n_D^{20} = 1.4932$ [17, 18]; [g] $n_D^{20} = 1.5460$ [17, 18], $d_4^{24} = 1.0234$ [17, 18]; [h] $n_D^{20} = 1.4250$ [19]; [i] $n_D^{20} = 1.4638$ [24]; [j] $n_D^{20} = 1.4877$ [24]; [k] $n_D^{20} = 1.4745$ [20]; [l] $n_D^{20} = 1.4367$ [24]; [m] $n_D^{20} = 1.4450$ [24]; [n] = $R^1 = R^2 = R^3 = R^4$ = 4-$C_6H_5O$–$C_6H_4$, [o] $R^1 = R^2 = R^3 = R^4$ = 3-$C_6H_5O$–$C_6H_4$.

[19] *W. Fink*, Helv. chim. Acta *47*, 498 (1964).

[20] French Pat. 1359379 and Addition Pat. 85867 (1963, 1965), Monsanto, inventor: *W. Fink*.

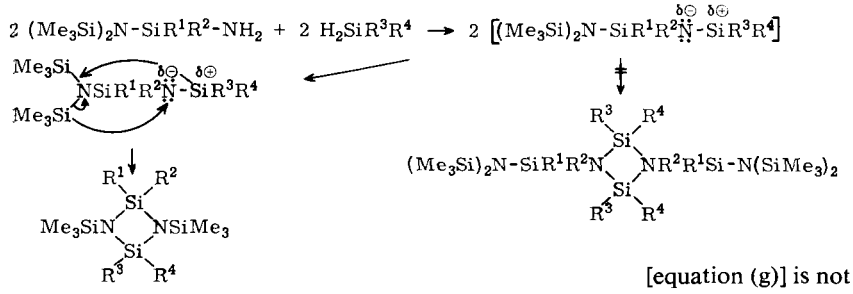
[21] Cf. [2], p. 369.

[22] Belg. Pat. 645148 (1964), Monsanto, inventor: *W. Fink*.

[23] *W. T. Reichle*, Inorg. Chem. *3*, 402 (1964).

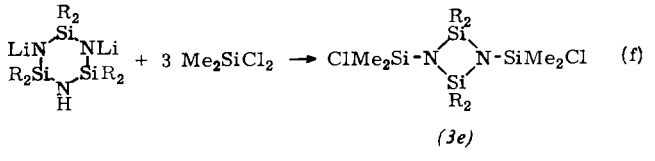
[24] Belg. Pat. 665774 (1965), Monsanto, inventor: *W. Fink*.

The intermediate *(6)* can be used directly in the reaction [24]. Compounds *(3)* with dissimilar substituents on the two ring silicon atoms and compounds with X = trimethylsilyl can be obtained by reaction (e), in which the intermediate is stabilized, not by dimerization, but by migration of the $(CH_3)_3$ Si group [24].



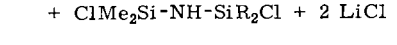
(e)

Cyclodisilazanes *(3e)* with chlorodimethylsilyl groups on the nitrogen atoms are used to synthesize linear polymers with cyclodisilazane units in the chain. Compound *(3e)* is synthesized by the reaction of at least doubly metalated cyclotri- or -tetrasilazanes with diorganosilicon dichlorides [25], *e.g.*:

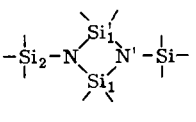


(f)

*(3e)*



The structure of 1,3-bis(trimethylsilyl)-2,2,4,4-tetramethylcyclodisilazane *(3a)* was determined by X-ray analysis [16]. It crystallizes monoclinically in the space group $P2_1/n$ (a = 6.75 ± 0.02, b = 13.18 ± 0.04, c = 11.22 ± 0.03 Å; β = 104° 23′ ± 0.5′, V = 968.7 Å$^3$, d = 0.998).

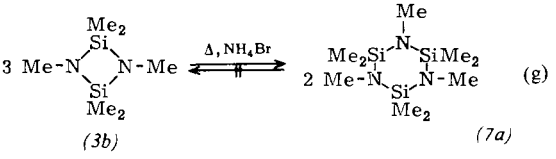


Bond angles and bond lengths in *(3a)*:

| | | | |
|---|---|---|---|
| Si(1)NSi(1′) | 91.7°; | Si(1)N | 1.725 Å |
| N′Si(1)N | 88.3°; | Si(1′)N | 1.724 Å |
| Si(1)NSi(2) | 135.4°; | Si(2)N | 1.707 Å |
| Si(1′)NSi(2) | 132.8°. | | |

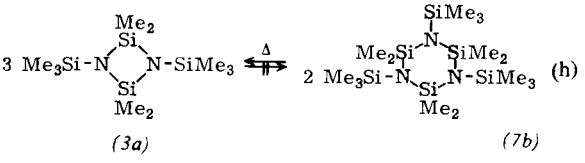
The Si-N bonds in the ring are shorter than those in hexamethylcyclotrisilazane (1.78 ± 0.03 Å) [26,27], but somewhat longer than the exocyclic Si-N bonds. The ring skeleton is highly strained in comparison with that of hexamethylcyclotrisilazane (117 ± 4°) or octamethylcyclotetrasilazane (123 ± 4°) [26,27]. Compound *(3a)* has a planar Si-N framework, as is also indicated by proton magnetic resonance measurements [28], which show unusually strong π-bonding in the exocyclic Si-N bonds.

The deformation of the nitrogen bond angle in cyclodisilazanes to approximately the angle between pure p orbitals can be seen in the weakening of the ring Si-N bond from *(3b)* to *(3a)* [18,28]. The reactivity of this bond should increase in the same direction, but the reverse is true. Whereas hexamethylcyclodisilazane *(3b)* is readily solvolysed [18], *(3a)* is stable towards water and alkali [29]. The stability of the cyclodisilazanes towards acids increases (for R = $CH_3$) in the order X = alkyl < trimethylsilyl < aryl. The hydrolysis is further hindered by large groups on the silicon. The quantitative catalytic ring expansion of *(3b)* (and other *N*-methylated cyclodisilazanes) [17,18] to form a 6-membered ring *(7)* [equation (g)] is not possible in *(3a)* or in *N*-phenylated compounds.



(g)

*(3b)* *(7a)*

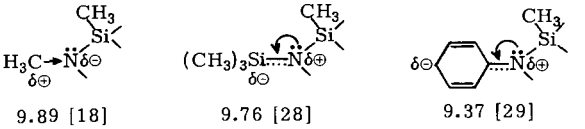


(h)

*(3a)* *(7b)*

Compound *(3a)* does not react with ammonium bromide; *N*-phenylated cyclodisilazanes react only above 400 °C, and then only very slowly, with formation of nonuniform products, which do not include the trimer [29]. 1,3,5-Tris(trimethyl)silylated cyclotrisilazanes such as *(7b)*, on the other hand, tend to undergo ring contraction at 400 to 425 °C in accordance with equation (h); this reaction cannot be brought about even at 450 °C with 1,3,5-trimethylated cyclotrisilazanes such as *(7a)*.

The difference in stability between the various types of cyclodisilazanes can be explained on the basis of different electron density distributions (Scheme 1). The electrons of the silazane nitrogen are partly delocalized. Owing to the marked deformation of the Si-N-Si bond angle in the small rings, the electron density on the nitrogen is higher than in the acyclic silazanes. A substituent on the nitrogen may cause either a further increase or a decrease in the electron density as a result of inductive effects, as is shown by the τ values of the rings. Reactions involving the Si-N bond, *e.g.* hydrolysis, normally proceed by protonation of the nitrogen, the ease of which increases with increasing nucleophilic character The



9.89 [18] 9.76 [28] 9.37 [29]

Scheme 1. Comparison of the τ-$SiCH_3$ values (figures under the formulae) in the $^1$H—NMR spectra of Si-methylcyclodisilazanes.

direction of the I-effect of the exocyclic groups changes in the order + H, $CH_3$, $(CH_3)_3Si$, $C_6H_5$ −; the electron density on the nitrogen, and hence its basicity, decreases in the same order, and the stability of the cyclodisilazanes towards elec-

[25] Ger. Pat. 1187615 (1965), Monsanto, inventor: *W. Fink*.

[26] *M. Yokoi* and *K. Yamasaki*, J. Amer. chem. Soc. *75*, 4139 (1953).

[27] *M. Yokoi*, Bull. chem. Soc. Japan *30*, 100 (1957); Chem. Abstr. *51*, 13485 (1957).

[28] *H. Schmidbaur*, J. Amer. chem. Soc. *85*, 2336 (1963).

[29] *W. Fink*, unpublished.

trophilic attack increases. The $d_\pi$ $p_\pi$ character of the ring Si-N bond also decreases in this order, as is shown by the $\tau$ values for $SiCH_3$.

*N*-Phenylated and *N*-trimethylsilylated cyclodisilazanes are surprisingly thermostable. Even at 450 °C, they show no tendency towards appreciable breakdown of the Si-N skeleton [30].

| | | |
|---|---|---|
| $(SiMe_2-NSiMe_3)_2$ | $(SiMe_2-NPh)_2$ | $(SiPh_2-NPh)_2$ |
| *(3a)* 503 | *(3c)* 481 | *(3d)* 455 |
| $(SiMe_2-NSiMe_3)_3(SiMe_2-NH)$ | $(SiMe_2-NSiMe_3)_3$ | |
| *(8a)* 438 | *(7b)* 418 | |
| $(SiMe_2-NSiMe_3)_2(SiMe_2-NH)$ | $[(Me_3Si)_2N]_2SiMe_2$ | |
| *(7c)* 417 | ≈345 | |

Scheme 2. Comparison of the thermal stabilities of some cyclic and linear silazanes (the decomposition temperature [°C] at a decomposition rate of 1%/h is given under the formulae).

## 1.2. Cyclotrisilazanes and Cyclotetrasilazanes

### 1.2.1. Preparation by Ammonolysis

When the classic route to the silazanes, *i.e.* the ammonolysis of the silicon-halogen bond, is applied to difunctional halogenosilanes (preferably chlorosilanes), the main products are largely strainless 6- (n = 3) and 8-membered (n = 4) silazane rings *(7)* and *(8)*.

$$n\ R_2SiCl_2 + 3n\ NH_3 \rightarrow \underset{(7),(8)}{(R_2SiNH)_n} + 2n\ NH_4Cl \qquad (i)$$

Separation of the ammonium salt by means of aqueous alkali gives *(7)* and *(8)* almost quantitatively [31–35]. Some examples of cyclotri- and -tetrasilazanes are given in Table 2. Whether trimeric or tetrameric cyclosilazanes, mixtures of the two, polysilazanes, silanediamines, or diaminodisilazanes are formed depends on the substituents R and on the reaction conditions.

In reaction (i), diorganosilicon dichlorides $RR^1SiCl_2$ with $R = R^1 = H$ give only polysilazanes [36]; when R = H, $R^1 = CH_3$, cyclic silazanes are formed as well as polysilazanes [37], while the combination R = H, $R^1 > CH_3$ gives both cyclotri- and -tetrasilazanes [38, 39]. A tert-butyl group (with $R^1 > H$) [40] or two α-naphthyl [41], tert-butoxy [42,43], isopropoxy [44], or phenoxy groups [45] favor the formation of silanediamine [42,43] and diaminodisilazane [42,44]; this does not appear to be entirely due to steric factors, since a diaminodisilazane has been isolated with $R = CH_3$, $R^1 = CF_3-CHF-CF_2$ [47]. Except in the case of the very stable di-t-butyldiaminosilane [40], however, these intermediates can be forced to cyclize by the use of heat [44,45] or acidic catalysts (*e.g.* ammonium sulfate) [43,46].

Table 2. Cyclotri- *(7)*, (n=3) and cyclotetrasilazanes *(8)*, (n=4) $(RR^1Si-NH)_n$.

| R | $R^1$ | B.p. (°C/mm) | M.p. (°C) | $n_D^{20}$ | $d_4^{20}$ | Ref. |
|---|---|---|---|---|---|---|
| n = 3 | | | | | | |
| Me | Me | 188/756 | −10 | 1.4448 | 0.9196 | [37, 54–57, 65] |
| Et | Et | 150/10 | −41 | 1.4670 | 0.9287 | [55, 58, 52, 66] |
| n-Bu | n-Bu | 193/2 | | 1.4654 | 0.8912 | [40] |
| Ph | Ph | | 214 | | | [59] |
| MeO | MeO [a] | 185/10 | 186 | | 1.021 | [60, 51] |
| EtO | EtO | 220/10 | 89 | | | [60, 51] |
| i-PrO | i-PrO | 147/4 | | | | [44, 45] |
| n-BuO | n-BuO | 250/12 | | | | [61] |
| t-BuO | t-BuO | | 190 | | | [42, 43, 46] |
| ChO | ChO | | 65–70 | | | [51] |
| H | Et | 62/0.5 | | 1.4700 | 0.9596 | [38] |
| Me | Et | 115/3 | | 1.4564 | | [62] |
| Me | $BrCH_2CH_2$ | 80/1 (decomp.) | | 1.5462 | | [63] |
| Me | Ph | 240/5 | 113 | | | [53, 62, 64] |
| Me | MeO | 115/1.5 | 217 | | | [51] |
| Me | EtO | | 101 | | | [51] |
| Me | i-PrO | | 45 | | | [51] |
| Me | t-BuO | | 44 | | | [51] |
| Me | PhO | | 95 | | | [51] |
| Me | ChO | | 77 | | | [51] |
| Ph | MeO | | 157 | | | [51] |
| Me | $CF_3CFHCF_2$ | 115–130/1 | | 1.3762 | 1.4079 | [47] |
| MeO | Vi | | 159 | | | [51] |
| Me | Vi | 65/1 | | 1.4820 | 0.9662 | [34, 48] |
| Me | All | 95/1 | | 1.4872 | 0.9528 | [34] |
| n = 4 | | | | | | |
| Me | Me | 225/756 | 97 | | | [37, 54–57] |
| Et | Et | 192/10 | 16 | 1.4769 | 0.9521 | [37, 54, 55] |
| i-PrO | i-PrO | 191/2 | | | | [44, 45] |
| PhO | PhO | | 130 | | | [44] |
| Me | H | 54/1 | | 1.4780 | 1.0069 | [38] |
| Et | H | 102/0.5 | | 1.4810 | 0.9767 | [38] |
| Me | Vi | 103/1 | | 1.4980 | 0.9979 | [48] |

[a] $d_4^{15}$ given instead of $d_4^{20}$

Cyclotri- and cyclotetrasilazanes *(7)* and *(8)* with vinyl [34,48,51] or allyl [34,49] substituents on the silicon can also be synthesized by reaction (i) [34,48,50] or by co-ammonolysis (j) of vinyl- or allyldichlorosilanes (a technique developed for the preparation of cyclotri-

[30] *I. B. Johns*, personal communication.

[31] *D. Ya. Zhinkin, E. A. Semenova*, and *N. V. Markova*, Plasticheskie Massy *1962*, No. 8, p. 18; Chem. Abstr. *58*, 7863 (1963).

[32] USSR-Pat. 140430 (1961), inventors: *D. Ya. Zhinkin, E. A. Semenova*, and *N. V. Markova*; Chem. Abstr. *56*, 10190 (1962).

[33] *U. Wannagat, E. Bogusch*, and *P. Geymayer*, Mh. Chem. *95*, 801 (1964).

[34] *D. Ya. Zhinkin, N. V. Markova*, and *M. V. Sobolevskii*, Zh. obshch. Khim. *33*, 1293 (1963); Chem. Abstr. *59*, 11549 (1963).

[35] *K. Rühlmann*, Angew. Chem. *74*, 468 (1962); Angew. Chem. internat. Edit. *1*, 400 (1962); Liebigs Ann. Chem. *657*, 1 (1962); East Ger. Pat. 22194 (1961); Chem. Abstr. *58*, 4598 (1963).

[36] *A. Stock* and *K. Somiesky*, Chem. Ber. *54*, 740 (1921).

[37] *S. D. Brewer* and *C. P. Haber*, J. Amer. chem. Soc. *70*, 3888 (1948).

[38] *E. A. Semenova, D. Ya. Zhinkin*, and *K. A. Andrianov*, Izvest. Akad. Nauk. SSSR, Otd. Khim. Nauk. *1962*, 269; Chem. Abstr. *57*, 15140 (1962).

[39] Brit. Pat. 881178 (1959), Imperial Chemical Industries, inventor: *W. St. Lindsay*; Chem. Abstr. *56*, 7357 (1962).

[40] *L. H. Sommer* and *L. J. Tyler*, J. Amer. chem. Soc. *76*, 1030 (1954).

[41] *V. S. Chugunov*, Zh. obshch. Khim. *23*, 777 (1953); Chem. Abstr. *48*, 4461 (1954).

[42] *E. Larsson* and *B. Smith*, Svensk kem. Tidskr. *62*, 141 (1950); Chem. Abstr. *45*, 2858 (1950).

[43] *C. S. Miner jr., L. A. Bryan, R. P. Holysz*, and *G. W. Pedlow*, Ind. Engng. Chem. *39*, 1368 (1947).

[44] *R. Schwarz* and *F. Weigel*, Z. anorg. allg. Chem. *268*, 291 (1951).

[45] Ger. Pat. 901174 (1954), Siemens-Schuckert, inventor: *F. Weigel*, and *K. Knoll*.

[46] *P. D. George, L. H. Sommer*, and *F. C. Whitmore*, J. Amer. chem. Soc. *75*, 6308 (1953).

[47] *D. Ya. Zhinkin* and *G. N. Malnova*, Zh. obshch. Khim. *34*, 1477 (1964); Chem. Abstr. *61*, 5683 (1964).

[48] *K. A. Andrianov, I. Haiduc*, and *L. M. Khananashvili*, Dokl. Akad. Nauk SSSR *150*, 93 (1963); Chem. Abstr. *59*, 7551 (1963).

[49] *D. Ya. Zhinkin, N. V. Markova*, and *M. V. Sobolevskii*, Zh. obshch. Khim. *33*, 2638 (1963); Chem. Abstr. *60*, 540 (1964).

[50] *K. A. Andrianov, I. Haiduc, L. M. Khananashvili*, and *M. B. Lotarev*, Izvest. Akad. Nauk SSSR, Odt. Khim. Nauk *1963*, 948; Chem. Abstr. *59*, 7552 (1963).

silazanes with mixed substituents[48–50,52,53]). Di-t-butyl peroxide can be used for the polymerization of these compounds, particularly the vinyl derivatives.

$$n\ RR^1SiCl_2 + m\ R^3_2SiCl_2 \xrightarrow[-NH_4Cl]{+NH_3} (RR^1SiNH)_n(R^3_2SiNH)_m \quad (j)$$

*(7), (8)*

Some examples of compounds *(7)* and *(8)* (n + m = 3 or 4) are given in Table 3.

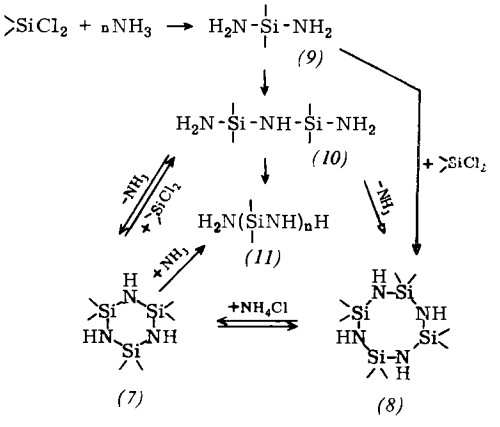
Table 3. Cyclotri- *(7)*, n + m = 3 and cyclotetrasilazanes *(8)*, n + m = 4 $(RR^1SiNH)_n(R^3_2SiNH)_m$.

| R | $R^1$ | $R^3$ | n | m | B.p. (°C/mm) | $n_D^{20}$ | $d_4^{20}$ | Ref. |
|---|---|---|---|---|---|---|---|---|
| Me | Me | Et | 2 | 1 | 58–59/1 | 1.4540 | 0.9291 | [52] |
| Et | Et | Me | 2 | 1 | 78–80/1 | 1.4630 | 0.9381 | [52] |
| Me | Ph | Me | 1 | 2 | 111/3 | | | [53] |
| Me | Ph | Me | 2 | 1 | 170–172/2 | | | [53] |
| Me | Vi | Me | 2 | 1 | 58–60/1 | 1.472 | 0.9605 | [48-50] |
| Me | Vi | Me | 1 | 2 | 50–53/1 | 1.469 | 0.9563 | [48-50] |
| Me | Vi | Et | 2 | 1 | 84–86/1 | 1.4742 | 0.9515 | [50] |
| Me | Vi | Et | 1 | 2 | 105–107/1 | 1.4706 | 0.9432 | [50] |
| Me | All | Me | 1 | 2 | 59–62/1 | 1.459 | 0.9249 | [49] |
| Me | All | Me | 2 | 1 | 78–80/1 | 1.475 | 0.9435 | [49] |
| Me | Vi | Me | 2 | 2 | [a] | | | [50] |

[a] M.p. 63–64 °C.

The formation of cyclosilazanes in accordance with equations (i) and (j) is complicated, and probably involves a series of simultaneous reactions and equilibria[67].

The intermediates *(9)* to *(11)* and their condensation to form *(7)* and *(8)* are known[43–46], as are condensations between halogenosilanes and silanamines[69]. A reaction of diorganodichlorosilane with *(9)* or *(10)* to form the trimer or tetramer is not impossible. The reverse reaction of $R_2SiCl_2$ with *(7)*, which leads to the equilibrium between cyclotrisilazane and longer-chain SiCl-terminated silazanes[70], equilibria between cyclotri- and cyclotetrasilazanes[71], and the ring-cleavage of *(7)* by the action of ammonia to form *(11)* are possible[68]. The direction of the reaction is very strongly influenced by the reaction conditions.




## 1.2.2. Preparation by Aminolysis

The aminolysis of $R_2SiCl_2$ with primary amines does not lead to *N*-alkylated or *N*-arylated cyclotri- and cyclotetrasilazanes. In these cases the reaction generally stops at the stage of the *N*-substituted diaminodiorganosilane *(5)*.

$$n\ R_2SiCl_2 + 4n\ R^1NH_2 \xrightarrow[-2n\ R^1NH_2\cdot HCl]{} n\ R^1NHSiR_2HNR^1 \quad (k)$$

*(5)*

$$\downarrow -n\ R^1NH_2$$

$$(R^1NSiR_2)_n \quad (l)$$

*(7), (8)*

The preparation of *(7)* and *(8)* by reactions (k) and (l) succeeds for reactions of $RR^1SiCl_2$ with R = H, $R^1$ = $CH_3$, $C_2H_5$[72], or $NHC_2H_5$[73] and methylamine or ethylamine. *Andrianov et al.*[76] obtained the compounds *(7)* and *(8)* also at low temperatures (−30 °C) under suitable conditions. Prolonged heating of *(5)* with an excess of diorganodichlorosilane is not very effective[74] and, as was shown with nonamethylcyclotrisilazane *(7a)*, leads only to the equilibrium between cyclic and linear silazanes[75] [cf. equation (q)]. The cyclization of *(5)* to give *(7)* as main product can sometimes be carried out at high temperatures and under pressure (with moderate

[51] *U. Wannagat* and *P. Geymayer*, unpublished.

[52] *D. Ya. Zhinkin*, *N. V. Markova*, and *M. V. Sobolevskii*, Zh. obshch. Khim. *32*, 2652 (1962); Chem. Abstr. *58*, 9114 (1963).

[53] *K. A. Andrianov* and *G. Ya. Rumba*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963*, 290; Chem. Abstr. *58*, 13980 (1963).

[54] Brit. Pat. 650822 (1951), British Thomson-Houston; Chem. Abstr. *46*, 2564 (1952).

[55] US-Pat. 2462635 (1949), inventor: *C. P. Haber*; Chem. Abstr. *43*, 5033 (1949).

[56] *E. Larsson* and *B. Smith*, Acta chem. scand. *3*, 486 (1949).

[57] *R. C. Osthoff* and *S. W. Kantor*, Inorg. Syntheses *5*, 61 (1957).

[58] *W. DeMan*, *J. van Steenis*, and *H. I. Waterman*, Recueil Trav. chim. Pays-Bas *67*, 864 (1948).

[59] *E. Larsson* and *L. Bjellerup*, J. Amer. chem. Soc. *75*, 995 (1953).

[60] *L. Rosnati*, Gazz. chim. ital. *78*, 516 (1948).

[61] *E. Larsson*, Acta chem. scand. *8*, 1084 (1954).

[62] *K. Hizawa* and *E. Nojimoto*, J. chem. Soc. Japan, ind. Chem. Sect. (Kogyo Kagaku Zasshi) *59*, 1445 (1956); Chem. Abstr. *53*, 4176 (1959).

[63] *W. Simmler*, *H. Walz*, and *H. Niederprüm*, Chem. Ber. *96*, 965 (1963).

[64] *Th. W. Ray* and *R. E. Burks jr.*, Annual Rep., Southern Research Institut, Birmingham, Alabama, Feb. 20th, 1961, p. 30.

[65] US-Pat. 2553314 (1951), inventor: *C. P. Haber*; Chem. Abstr. *45*, 6777 (1951).

[66] US-Pat. 2564674 (1951), inventor: *N. D. Cheronis*; Chem. Abstr. *45*, 10675 (1951).

[67] Cf. [2], p. 366.

[68] *G. Redl* and *E. G. Rochow*, Angew. Chem. *76*, 650 (1964); Angew. Chem. internat. Edit. *3*, 516 (1964).

[69] *K. A. Andrianov* and *A. M. Knononov*, Dokl. Akad. Nauk SSSR *156*, 858 (1964); Chem. Abstr. *61*, 7039 (1964).

[70] *K. Moedritzer* and *J. R. Van Wazer*, Abstracts, 144th Meeting, Amer. Chem. Soc. 1963, 6 K.

[71] *K. A. Andrianov* and *G. Ya. Rumba*, Dokl. Akad. Nauk SSSR *145*, 1049 (1962); Chem. Abstr. *58*, 2467 (1963).

[72] *E. A. Semenova*, *D. Ya. Zhinkin*, and *K. A. Andrianov*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1962*, 2036; Chem. Abstr. *58*, 9114 (1963).

[73] *Z. I. Sergeeva* and *Chiang-Lang Hsieh*, Zh. obshch. Khim. *32*, 1987 (1962); Chem. Abstr. *58*, 4594 (1963).

[74] See [64], p. 23.

[75] *J. R. Van Wazer* and *K. Moedritzer*, J. physic. Chem. *41*, 3122 (1964).

[76] *K. A. Andrianov*, *T. V. Vasil'eva*, and *A. A. Minaeva*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963*, 2227, Chem. Abstr. *60*, 9307 (1964).

yields)[77]. The ring closure is best forced by heating *(5)* in the presence of acidic catalysts such as ammonium salts[77–79] [equation (l)]. The yields depend strongly on steric factors; they decrease with increasing bulk of the substituents on the silicon and on the nitrogen. The influence of the nitrogen substituent dominates [*e.g.* in *(5)* with R = $CH_3$: $R^1$ = $CH_3$, 93%; $C_2H_5$, 66%, $CH_2=CH-CH_2$, 21%; $C_6H_5-CH_2$, 19%; $C_6H_5$, 0% of *(7)* or *(8)*[79]]. Examples of *N*-alkylated cyclotri- and cyclotetrasilazanes are given in Table 4.

Table 4. *N*-Alkyl-substituted cyclotri- *(7)* (n = 3) and cyclotetrasilazanes *(8)* (n = 4) $(R^1R^2Si-N-X)_n$.

| X | $R^1$ | $R^2$ | B.p. (°C/mm) | M.p. (°C) | $n_D^T$ | Ref. |
|---|---|---|---|---|---|---|
| n = 3 | | | | | | |
| Me | Me | Me | 91/12 | 36 | | [74,77,79,85] |
| Me [a] | Me | Et | 93/1 | | 1.4600[20] | [76, 77, 79] |
| Me | Me | All | 82–85/0.1 | | 1.4795[27] | [79] |
| Et | Et | Me | | 167–169 | | [79] |
| Me | Ph | Ph | | 219–221 | | [79] |
| Me | Me | Be | | 57–60 | | [79] |
| Me | Vi | Me | 110–113/4 | | 1.4783[27] | [79] |
| Me [b] | H | Me | 56/5 | | 1.4580[20] | [72] |
| Et [c] | H | Me | 74/1.5 | | 1.4680 | [72] |
| NHEt [d] | H | Et | 93–97/9–11 | | 1.4472 | [73] |
| Me | Me | NHMe | | 136–138 | | [78] |
| Me | Et | NHMe | | 189–192 | | [78] |
| Me | n-Pr | NHMe | | 69–70 | | [78] |
| n = 4 | | | | | | |
| Me [e] | H | Me | 88/2 | | 1.4810 | [72] |
| Et [f] | H | NHEt | 120–122/10–11 | | 1.4527 | [73] |

$d_4^{20}$ = [a] 0.9162 [76]; [b] 0.9297 [72]; [c] 0.9324 [72]; [d] 0.9229 [73]; [e] 0.9776 [72]; [f] 0.9231 [73].

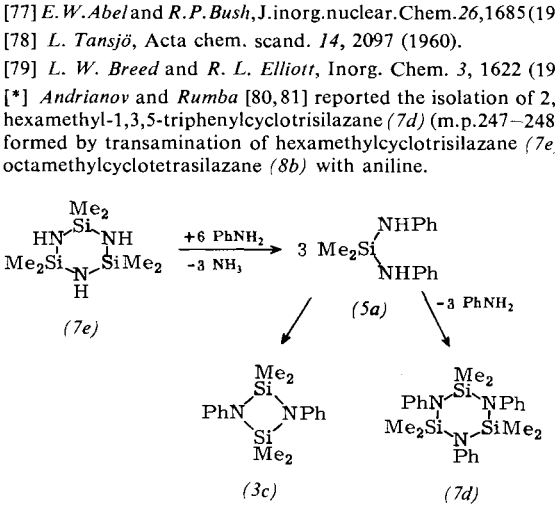
Whereas the thermolysis of *(5)* in the absence of catalyst leads to 4-membered silazane rings [cf. equation (c)], it yields 6- or 8-membered ring systems when carried out in the presence of a catalyst (except in the pyrolysis of *N*-arylated *(5)*, which leads to cyclodisilazanes in both cases[*] [79,29]). Thus it is possible to fix the direction of the reaction by the addition of a catalyst.

[77] *E. W. Abel* and *R. P. Bush*, J. inorg. nuclear. Chem. *26*, 1685 (1964).

[78] *L. Tansjö*, Acta chem. scand. *14*, 2097 (1960).

[79] *L. W. Breed* and *R. L. Elliott*, Inorg. Chem. *3*, 1622 (1964).

[*] *Andrianov* and *Rumba* [80,81] reported the isolation of 2,4,6-hexamethyl-1,3,5-triphenylcyclotrisilazane *(7d)* (m.p. 247–248 °C) formed by transamination of hexamethylcyclotrisilazane *(7e)* or octamethylcyclotetrasilazane *(8b)* with aniline.




These authors assume that *(7e)* is completely broken down to *(5a)*, which then condenses to *(7d)*. However, the infrared spectra and debyeograms of the products obtained in accordance with equation (c) [compound *(3c)*] and by transamination [compound *(7d)*], as well as the molecular weights found from X-ray data[82], are identical [*(7d)* and *(3c)*: space group 61 Pbca (orthorhombic), a = 11.65, b = 8.60, c = 16.88, d = 1.2 Å, M = 298].

Since *N*-alkylated cyclodisilazanes can be catalytically rearranged to cyclotrisilazanes [cf. equation (g)], it may be assumed that the catalytic condensation of *(5)* proceeds *via* the initial formation of cyclodisilazanes, which (apart from the *N*-phenyl compounds, which do not undergo rearrangement) then undergo ring expansion under the influence of the catalyst to form the trimer *(7)*.

### 1.2.3. Other Methods of Preparation

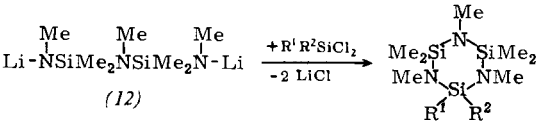
The cyclotri- and cyclotetrasilazane skeleton can also be built up by reaction of amino-Grignard compounds with dichlorosilanes[77],

$$3\ R^1N(MgBr)_2 + 3\ R_2SiCl_2 \rightarrow (R^1NSiR_2)_3 + 6\ MgClBr, \quad (m)$$

the condensation of methylsilylamine at 400 °C[84],

$$4\ MeN(SiH_3)_2 \rightarrow (MeNSiH_2)_4 + 4\ SiH_4$$

and the reaction of *N*-(triethoxysilyl)aniline with magnesium/tetraethoxysilane[83]. *Lienhard* and *Rochow*[85] synthesized *N*-methylated cyclotrisilazanes *via* dilithium bis(methylamino)pentamethyldisilazane *(12)*.




*(12)*

| $R^1$ | $R^2$ | B.p. (°C/mm Hg) | M.p. (°C) |
|---|---|---|---|
| Me | Me | 91/12 | 36 |
| Me | Ph | 125–127/3 | |
| Ph | Ph | 165–167/4 | 62–64 |
| Cl | Cl | 86–88/4 | 55–58 |
| Ph | Cl | 136–142/4 | 39 |

*N*-Triorganosilylated cyclotri- and cyclotetrasilazanes are obtained *via* the singly to quadruply metalated cyclosilazanes (which are thermally stable but sensitive to oxygen) and their reaction with triorganosilane[15, 86,87]; with cyclotrisilazanes, the reaction proceeds in accordance with equation (n).

Cyclotri- and cyclotetrasilazanes can be metalated with butyl-lithium[15,86], sodium/styrene[87], potassamide/liquid $NH_3$, sodamide/benzene[88], sodium bis(trimethyl-

[80] *K. A. Andrianov* and *G. Ya. Rumba*, Zh. obshch. Khim. *32*, 1993 (1962); Chem. Abstr. *58*, 4592 (1963).

[81] *K. A. Andrianov* and *G. Ya. Rumba*, Dokl. Akad. Nauk SSSR *145*, 1049 (1962); Chem. Abstr. *58*, 2467 (1963).

[82] *J. J. Daly*, personal communication.

[83] US-Pat. 3054818 (1962), Union Carbide Corp., inventors: *E. J. Pepe* and *B. Kanner*; Chem. Abstr. *58*, 8968 (1963).

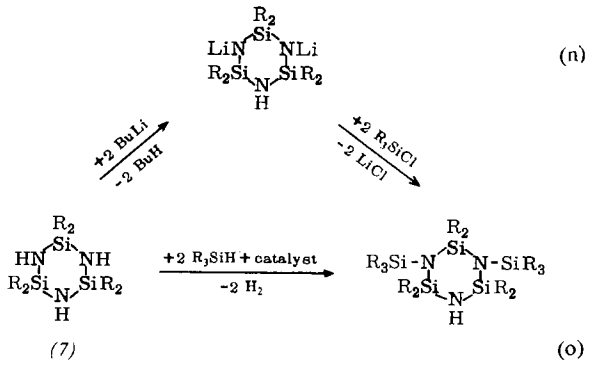
[84] *B. J. Aylett*, *G. M. Burnett*, *L. K. Peterson*, and *N. Ross*, Soc. chem. Ind. (London) Monograph *13*, 5 (1961).

[85] *K. Lienhard* and *E. G. Rochow*, Z. anorg. allg. Chem. *331*, 307 (1964).

[86] *W. Fink*, Angew. Chem. *73*, 467 (1961).

[87] *L. W. Breed* and *R. L. Elliott*, Inorg. Chem. *2*, 1069 (1963).

[88] *U. Wannagat* and *H. Niederprüm*, Chem. Ber. *94*, 1540 (1961).



(n)

(o)

*(7)*

silyl)amide [89], or, in the case of *(7)* where R = $C_6H_5$, directly with potassium [90].

Single and double silylations of *(7)* and *(8)* proceed readily and in good yields. Triple silylations proceed only with difficulty, and do not go to completion [*(7)*]. The yields are also reduced by lithium-catalysed fragmentations, which are probably favored by steric factors. The complete silylation of cyclotetrasilazanes yields only cyclodisilazanes *(3)* [15].

The introduction of triorganosilyl groups into *(7)* and *(8)* (which can also be accomplished in good yields with triorganosilanes and sodium, potassium, or their hydrides [29] [equation (o)]) leads, particularly with the trimethylsilylated compounds, to a marked depression of the melting point, and to a sudden increase in the stability of the ring towards hydrolysis and heat, particularly with doubly silylated compounds.

Mention should also be made of the isolation of octachloro-1,3,5,7-tetrakis(trichlorosilyl)cyclotetrasilazane from the products of the reaction of silicon tetrachloride with ammonia at 825 °C [10] and the preparation of cyclotrisilazane, $(H_3Si-N-SiH_2)_3$ [91], by the condensation of trisilylamine in the liquid phase in accordance with reaction (m) or by reaction of monochlorosilane with ammonia. Some examples of $(R_2Si-N-SiR_3)_{3 \text{ or } 4}$ are given in Table 5.

Table 5. *N*-Trialkylsilylated and *N*-trichlorosilylated cyclotri- and cyclotetrasilazanes $(R_2Si-N-SiR_3)_n$.

| Compound | B.p. ( °C/mm) | M.p. (°C) | $n_D^T$ | Ref. |
|---|---|---|---|---|
| $(Me_2SiNH)_2(Me_2SiNSiMe_3)$ | 112/10 | | $1.4596^{26}$ | [87] |
| $(Ph_2SiNH)_2(Ph_2SiNSiMe_3)$ | 293–300/1 | 156 [a] | | [15] |
| $(Me_2SiNH)(Me_2SiNSiMe_3)_2$ | 81/2 | −74 | $1.4420^{20}$ | [15] |
| $(Et_2SiNH)(Et_2SiNSiMe_3)_2$ | 333/720 | −65 | $1.4751^{20}$ | [86] |
| $(Me_2SiNH)(Me_2SiNSiEt_2Me)_2$ | 248/0.04 | 66 | $1.5621^{20}$ | [24] |
| $(Me_2SiNSiMe_3)_3$ | 143/0.09 | −43 | $1.4823^{20}$ | [86, 15] |
| $(Et_2SiNSiMe_3)_3$ | 359–362/720 | −35 | $1.4868^{20}$ | [86] |
| $(Cl_2SiNSiCl_3)_4$ | 103/2 | *ca.* 50 | | [10] |
| $(Me_2SiNH)_3(Me_2SiNSiMe_3)$ | 108/1.5 | −17 | $1.4613^{20}$ | [15] |
| $(Me_2SiNH)_2(Me_2SiNSiMe_3)_2$ | 122–124/3 | −32 | $1.4497^{20}$ | [15] |
| $(Me_2SiNH)(Me_2SiNSiMe_3)_3$ | 133/3 | −55 | $1.4582^{20}$ | [15] |

[a] *R. E. Burks jr.*, personal communication.

[89] *U. Wannagat* and *S. Surjosubandoro*, unpublished.

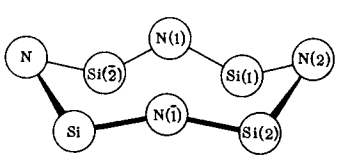
[90] *Th. W. Ray* and *R. E. Burks jr.*, Report 28, Southern Research Institute, Birmingham, Alabama, June 14th, 1963.

[91] *R. Schaeffer, L. Ross, M. Thompson*, and *R. Wells*, US-Dept. Comm. Office Tech. Serv. AD 263749 (1960); Chem. Abstr. *57*, 16120 (1962).

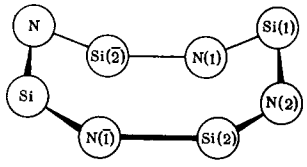
## 1.2.4. Structure of the Cyclotri- and Cyclotetrasilazanes

Electron diffraction measurements [26, 27] indicate that hexamethylcyclotrisilazane *(7e)* has a puckered ring structure (Si-N = 1.78 ± 0.03 Å, Si-C = 1.87 ± 0.05 Å, SiNSi = 117 ± 4 °, NSiN = 111 ± 5 °). From infrared measurements, on the other hand, a planar configuration was deduced [92]. Calculations of the SiNSi angle in *(7e)* (118.5 °) [*] appear to confirm the results of the electron-diffraction measurements [93].

A careful X-ray analysis has been carried out on octamethylcyclotetrasilazane $[(CH_3)_2SiNH]_4$ *(8b)* [94]. The compound forms monoclinic crystals of the space group P2/c in the "chair" (A) and "boat" (B) forms (in the ratio 1:1 in the crystal).



A



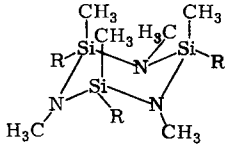
B

*(8b)*

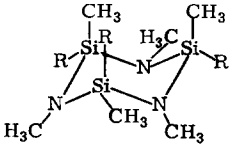
| | | | |
|---|---|---|---|
| Si(1)N(1) | 1.788 Å | Si(1)N(1) | 1.708 Å |
| Si(1)N(2) | 1.746 Å | Si(1)N(2) | 1.741 Å |
| Si(2)N(2) | 1.734 Å | Si(2)N(2) | 1.687 Å |
| Si(2)N($\bar{1}$) | 1.727 Å | Si(2)N($\bar{1}$) | 1.750 Å |
| Si(1)N(1)Si($\bar{2}$) | 132.4 ° | Si(1)N(1)Si($\bar{2}$) | 130.1 ° |
| Si(1)N(2)Si(2) | 132.3 ° | Si(1)N(2)Si(2) | 133.1 ° |
| N(1)Si(1)N(2) | 112.5 ° | N(1)Si(1)N(2) | 110.3 ° |
| N(2)Si(2)N($\bar{1}$) | 110.5 ° | N(2)Si(2)N($\bar{1}$) | 110.3 ° |

*Yokoi* and *Yamasaki* [26, 27] found a value of 123 ± 4 ° for the SiNSi angle in *(8b)* (electron diffraction).

Hexamethyl-2,4,6-triphenyl- *(7f)* and hexamethyl-2,4,6-tri-*p*-anisylcyclotrisilazane *(7g)*, like the structurally similar silicon/sulfur and silicon/oxygen rings [95–97], occur as two structural isomers, for which the structures A and B have been deduced from proton magnetic resonance data [79].



A



B

*(7f)* m.p. 153–154 °C; R=$C_6H_5$ m.p. 84–88 °C
*(7g)* m.p. 176–177 °C; R=*p*-$CH_3OC_6H_4$ m.p. 114–116 °C

The infrared skeletal stretching vibration $\nu_{as}$-SiNSi in *N*-unsubstituted [46, 48, 92, 98] and substituted [79, 85] trimeric and tetrameric cyclosilazanes, as in the disilazanes [99], occurs at

[92] *H. Kriegsmann*, Z. anorg. allg. Chem. *298*, 223 (1959).

[*] This angle was calculated with the aid of an expression for non-linear three-body models (cf. *G. Herzberg*: Infrared and Raman Spectra of Polyatomic Molecules. Van Nostrand, Princeton 1959, p. 168).

[93] *C. Krüger* and *E. G. Rochow*, Inorg. Chem. *2*, 1295 (1963).

[94] *G. S. Smith* and *L. E. Alexander*, Acta crystallogr. *16*, 1015 (1963).

[95] *R. N. Lewis*, J. Amer. chem. Soc. *70*, 1115 (1948).

[96] *V. Chvalovsky* and *V. Bazant*, Chem. Listy *49*, 894 (1955).

[97] *E. Campaigne, N. F. Chamberlain*, and *B. E. Edwards*, J. org. Chemistry *27*, 135 (1962).

[98] *G. V. Tsitsishvili, G. D. Bagratishvili, K. A. Andrianov, L. M. Khananashvili*, and *M. L. Kantariya*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1962*, 1197; Chem. Abstr. *58*, 2026 (1963).

[99] *R. Fessenden*, J. org. Chemistry *25*, 2191 (1960).

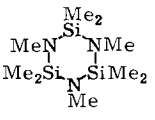
925–950 $cm^{-1}$, with a slight increase in frequency on transition from trimeric to tetrameric and from *N*-unsubstituted to *N*-substituted rings. $\nu_{sym}$-SiNSi occurs at 618–620 $cm^{-1}$. *N*-Silylated or *N*-alkylated cyclotrisilazanes exhibit strong infrared absorption between 1005 and 1055 $cm^{-1}$ [15,79,87], which has not so far been assigned. (For NMR spectra of hexamethylcyclotrisilazane, see [100]).

*Osthoff* and *Kantor* [57] measured the dipole moment of *(7e)* as well as other electrical properties. The ability of *(7e)* and *(8b)* to act as electron donors was studied by *Jarvie* and *Lewis* [101].

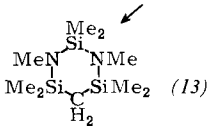
An interesting question, which has not yet been conclusively answered, is that of a pseudoaromatic resonance effect of the nitrogen $\pi$ electrons in cyclotrisilazanes, *i.e.* a displacement of the $\pi$ electrons, which are already partly delocalized in the silazane linkage ($d_\pi$-$p_\pi$ bond) [102,103], through the silicon [104].

*Lienhard* and *Rochow* [85] have demonstrated the absence of aromaticity in nonamethylcyclotrisilazane *(7a)*. They found that the chemical shifts of the proton resonance of the $Si(CH_3)_2$ group in *(7a)* and that of the $Si(CH_3)_2$ group indicated in *(13)* are the same.

*(7a)*



*(13)*



Since the resonance of the $\pi$ electrons in *(13)* is interrupted, there should be a marked difference in the chemical shifts.

Thermodynamic considerations oppose a quasi-aromatic bond system [105]. The electronic structure of the cyclosilazanes can best be explained in terms of localized 3-center $\pi$ bonds. The ultraviolet spectra of cyclotrisilazanes with vinyl substituents on the silicon atoms indicate that the $Si_3N_3$ ring skeleton cannot participate in the conjugation of groups attached to the silicon atom [48]. *Gaidis* and *West* [106] recently reported evidence of the participation of the Si-N bond in the aromatic system in 10,10-dimethyl-9,10-azasiladihydrophenanthrene *(59)*.

### 1.2.5. Properties and Reactions

Cyclotri- and -tetrasilazanes are thermally very stable, apart from compounds having the formula $(RHSiNH)_{3\text{ or }4}$ wich are stable only up to about 200 °C [107]. Decomposition, polymer and oligomer formation, or rearrangements are observed only above 300 °C [107]. The thermal stability is considerably increased by substitution of the silazane hydrogen by alkyl or trialkylsilyl groups.

Cyclosilazanes are relatively stable to water and alkali (cf. [31]), but they are sensitive to acids and alcohols, which cause rapid breakdown into silanol and ammonia or amine, the trimers reacting faster than the tetramers [108].

The stability of the compounds generally increases with the size of the groups attached to the silicon [109]. Cyclosilazanes with mixed substituents are less stable than peralkylated compounds, even when large groups are present [79,110]. The stability is considerably increased by the replacement of NH by NR [79].

Reactions carried out on cyclotri- and -tetrasilazanes have so far been largely confined to acid- and base-catalysed cleavage of the SiN ring structure, which proceeds rapidly and generally in high yields.

Alcohols [33,111–114] and organic acids cause ring cleavage with formation of dialkoxy- or diaryloxytrisilazanes or -disilazanes, or else complete breakdown [112,113,115] of the cyclic silazane to give bisorganyloxy- and bisacyloxysilanes.

Cleavage of cyclotri- and -tetrasilazanes in ether or benzene by stoichiometric quantities of hydrogen chloride leads to 1,3-dichlorosilazanes [33]. Diols react to give low-melting polymers, which are stable up to about 300 °C [116]. An excess of alcohol causes breakdown of the silazane skeleton into nitrogen-free –SiOC– polymers [117].

Transamination of *(7e)* and *(8b)* with aniline leads to bisdianilinodiorganosilane [59] *(5a)* and 1,3-diphenyl-2,2,4,4-tetramethylcyclodisilazane *(3c)* [80,81,29]. The reaction with n-amylamine stops at the stage of 1-amyl-2,2,4,4,6,6-hexamethylcyclotrisilazane (b.p. 85–87 °C/1 mm Hg), whereas the simultaneous action of aniline and ammonia on dimethyldichlorosilane [intermediate formation of *(7e)* and *(8b)*] leads to the 1-phenyl analogue (m.p. 37 °C) [80]. *Andrianov et al.* [118] obtained a (probably linear) polymer of low molecular weight by single ring cleavage in *(7e)* with an aromatic diamine.

[100] *G. R. Holzmann, P. C. Lauterbur, H. J. Anderson,* and *W. Koth,* J. chem. Physics *25,* 172 (1956).

[101] *S. W. Jarvie* and *D. Lewis,* J. chem. Soc. (London) *1963,* 4758.

[102] *D. P. Craig, A. Maccoll, R. S. Nyholm, L. E. Orgel,* and *L. E. Sutton,* J. chem. Soc. (London) *1954,* 332.

[103] *E. A. V. Ebsworth* and *H. J. Emeléus,* J. chem. Soc. (London) *1958,* 2150.

[104] Cf. *I. Haiduc,* Studia Univ. Babes-Bolyai, Ser. 1, No. 2, 9 (1961); Chem. Abstr. *57,* 8151 (1962).

[105] *L. May* and *G. Ya. Rumba,* Latvijas PSR Zinatnu Akad. Vestis, Khim. Ser. *1964,* 23.

[106] *J. M. Gaidis* and *R. West,* J. Amer. chem. Soc. *86,* 5699 (1964).

[107] *D. Ya. Zhinkin, E. A. Semenova, M. V. Sobolevskii,* and *K. A. Andrianov,* Plasticheskie Massy *1963,* No. 12, p. 16; Chem. Abstr. *60,* 8055 (1964).

[108] *K. A. Andrianov* and *G. Ya. Rumba,* Zh. obshch. Khim. *31,* 4038 (1961); Chem. Abstr. *57,* 8600 (1961).

[109] *D. Ya. Zhinkin, E. A. Semenova,* and *K. A. Andrianov,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963,* 1989; Chem. Abstr. *60,* 5535 (1964).

[110] *K. A. Andrianov* and *G. Ya. Rumba,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963,* 290; Chem. Abstr. *58,* 13980 (1963).

[111] *M. M. Morgunova, D. Ya. Zhinkin,* and *M. V. Sobolevskii,* Plasticheskie Massy *1963,* No. 4, p. 23; Chem. Abstr. *58,* 14111 (1963).

[112] *K. A. Andrianov, V. V. Astakhin,* and *V. B. Losev,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963,* 950; Chem. Abstr. *59,* 7552 (1963).

[113] *K. A. Andrianov* and *V. V. Astakhin,* Zh. obshch. Khim. *32,* 2316 (1962); Chem. Abstr. *58,* 9113 (1963).

[114] *M. M. Morgunova, D. Ya. Zhinkin,* and *M. V. Sobolevskii,* Zh. obshch. Khim. *33,* 3269 (1963); Chem. Abstr. *60,* 4174 (1964).

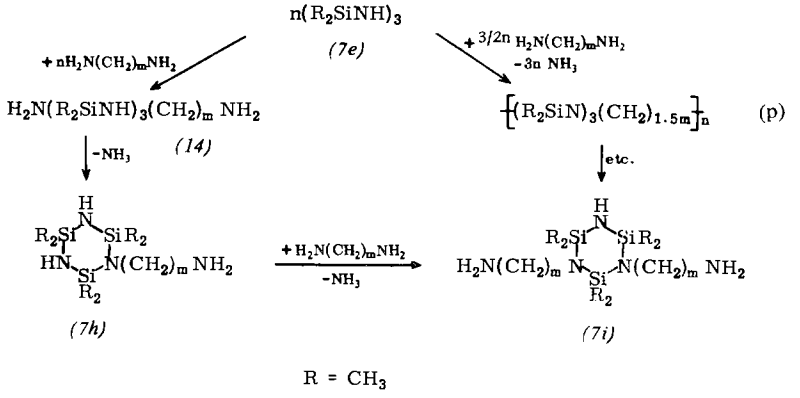
[115] *K. A. Andrianov* and *V. V. Astakhin,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963,* 2206; Chem. Abstr. *60,* 9305 (1964).

[116] *M. M. Morgunova, D. Ya. Zhinkin,* and *M. V. Sobolevskii,* Plasticheskie Massy *1963,* No. 3, p. 26; Chem. Abstr. *58,* 14111 (1963).

[117] *V. B. Losev* and *V. V. Astakhin,* Plasticheskie Massy *1964,* No. 4, p. 26; Chem. Abstr. *61,* 1953 (1964).

[118] *K. A. Andrianov, G. A. Kurakov, L. M. Khananashvili,* and *T. A. Lomonosova,* Zh. obshch. Khim. *33,* 1294 (1963); Chem. Abstr. *59,* 10105 (1963).

*Morgunova et al.* [119,120] synthesized cross-linked polymers by transamination of hexamethylcyclotrisilazane *(7e)* with aliphatic diamines (m = 2 to 6), in accordance with equation (p).




These authors assume that the reaction proceeds by repeated cleavage of the $Si_3N_3$ ring skeleton to form a silazane chain *(14)*, and subsequent ring closure to form *(7h)*; after renewed cleavage, this reacts with further amine *via (7i)* to form the polymer [121].

Ring cleavage in hexamethylcyclotri- *(7e)* and octamethylcyclotetra-silazane *(8b)* can be brought about by a number of other compounds. Metal and metalloid halides react with *(7e)* in the same manner as with disilazanes [122–126], with cleavage of the Si–N bonds. Diorganoboron chloride can open the ring in *(7e)*, or can break it down completely [122].

The reaction of *(7e)* with $Al_2Cl_6$ leads to products containing Si–N and Al–N bonds, which have not been characterized in any detail [33]; $CuCl_2$ and $CoCl_2$ also react [127], but the results reported are contradictory [128]. Whereas dimethyldichlorosilane degrades doubly metalated *(7e)* to 1,3-bischlorosilylcyclodisilazane [25] [cf. equation (f)], the reaction with *(7e)* or *(7a)* leads to equilibria [70,75] [*e.g.* equation (q)].

$$Me_2SiCl_2 + (MeNSiMe_2)_n \leftrightarrows ClMe_2Si(NMeSiMe_2)_{n-1}NMeSiMe_2Cl \qquad (q)$$

The equilibration of *(7e)* with hexamethylsilazane [37] (with ammonium chloride as catalyst) leads to octamethyltrisilazane *(15)*, R = $(CH_3)_3Si$, n = 1. Ammonia at 140 °C/4 atm [68] gave a linear silazane (R = H, n ≈ 15).

$$R_2NH + (Me_2SiNH)_3 \rightarrow RNH(SiMe_2NH)_nR$$
*(7e)* *(15)*

Organic isocyanates also react with *(7e)* and *(8b)* causing complete degradation of the rings [129] (see Section 4.4).

Base- and acid-catalysed polymerization of cyclosilazanes, with ring cleavage, to give linear polysilazanes generally are impossible [68]. Rearrangement and polycondensation leads to the formation of cross-linked polymers.

*Zhinkin et al.* [130,131] and *Andrianov* and *Rumba* [71] have achieved ring expansions in hexamethylcyclotrisilazane *(7e)*. The compound is quantitatively rearranged to octamethylcyclotetrasilazane *(8b)* by small quantities of concentrated sulfuric acid [0.5 mole-%, based on *(7e)*] [130,131], and in poorer yields by $(CH_3)_3SiCl/NH_3$, ammonium chloride, iodine [71], and other electrophiles [131a]. Remarkably, hexaethylcyclotrisilazane cannot be rearranged with acids.

Ring expansions occur as side reactions in transaminations [80,81], in the reaction of *(7e)* with organic acids and alcohols [121,116], and in the reaction of *(7e)* with ammonia [68].

Ring contractions are also known. Thus *(8b)* undergoes rearrangement at 350 to 450 °C to give an 80% yield of *(7e)* [107,132], and poorer yields of *(7e)* are obtained by rearrangement with $H_2SO_4$ or $AlCl_3$ [131a]. Permethylated *N*-trimethylsilylated cyclotri- and cyclotetrasilazanes also tend to ring contraction, as well as rearrangement and disproportionation, at high temperatures and/or under the influence of lithium chloride [15].

The polycondensation of 2,2,4,4,6,6-hexaphenylcyclotrisilazane at 450 °C without catalyst, with elimination of benzene, was reported by *Groszos* and *Hall* [133]. The

[119] *M. M. Morgunova, D. Ya. Zhinkin,* and *M. V. Sobolevskii,* Plasticheskie Massy *1963*, No. 6, p. 24; Chem. Abstr. *59*, 11674 (1963).

[120] USSR-Pat. 157107 (1963), inventors: *M. M. Morgunova, D. Ya. Zhinkin,* and *M. V. Sobolevskii*; Chem. Abstr. *60*, 5664 (1964).

[121] Cf. the short summary in: *D. Ya. Zhinkin, E. A. Semenova, M. M. Morgunova,* and *M. V. Sobolevskii,* Plaste u. Kautschuk *10*, 387 (1963); Chem. Abstr. *59*, 15396 (1963).

[122] *H. Nöth,* Z. Naturforsch. *16b*, 618 (1961).

[123] *M. Becke-Goehring* and *H. Krill,* Chem. Ber. *94*, 1059 (1961).

[124] *H. Schmidbaur* and *M. Schmidt,* Angew. Chem. *74*, 327 (1962); Angew. Chem. internat. Edit. *1*, 327 (1962).

[125] *H. Jenne* and *K. Niedenzu,* Inorg. Chem. *3*, 68 (1964).

[126] *K. A. Andrianov, V. V. Astakhin,* and *D. A. Kochkin,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1962*, 1852; Chem. Abstr. *58*, 9115 (1963).

[127] *R. Weiss,* US Dept. Comm. Office Tech. Serv. AD 263737 (1961); Chem. Abstr. *57*, 14691 (1962).

[128] *J. M. Maselli,* US Dept. Comm. Office Tech. Serv. AD 274520 (1962); Chem. Abstr. *58*, 10311 (1963).

[129] *W. Fink,* Chem. Ber. *97*, 1424 (1964).

[130] *D. Ya. Zhinkin, E. A. Semenova, M. V. Sobolevskii,* and *K. A. Andrianov,* Plasticheskie Massy *1963*, No. 1, p. 16; Chem. Abstr. *60*, 5538 (1964).

[131] USSR-Pat. 154273 (1963), inventors: *D. Ya. Zhinkin, E. A. Semenova,* and *M. V. Sobolevskii*; Chem. Abstr. *60*, 4183 (1964).

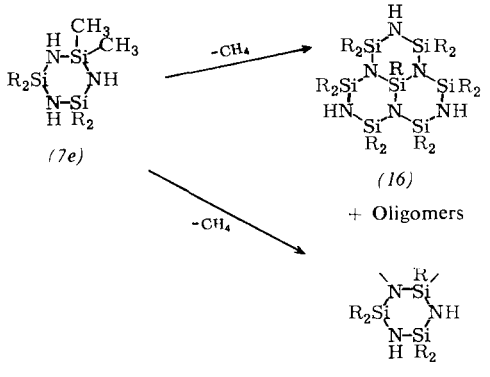
[131a] *K. A. Andrianov, B. A. Ismailov, A. M. Kononov,* and *G. V. Kotrelev,* J. organomet. Chemistry *3*, 129 (1965).

[132] USSR-Pat. 144173 (1962), inventors: *D. Ya. Zhinkin* and *E. A. Semenova*; Chem. Abstr. *57*, 11236 (1962).

[133] US-Pat. 2885370 (1959); American Cyanamid Comp., inventors: *St. J. Groszos, D. Hall,* and *J. A. Hall*; Chem. Abstr. *53*, 16585 (1959).

polymer is highly cross-linked, is stable up to 500 °C, and suffers little attack by acids [134].

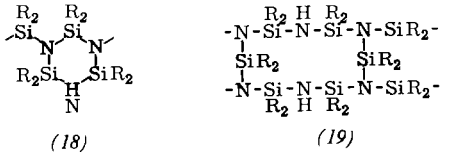
The elimination of methane was observed [135] during attempts to obtain linear polysilazanes by heating *(7e)* and *(8b)* with 1% of solid KOH. Sometimes crystalline polycyclic oligomers (of which the tricyclic compound *(16)*, m.p. 165–167 °C, has been isolated [136]) were obtained at 160 to 260 °C, and partially cross-linked, brittle polymers *(17)*, for which a structure containing intact $Si_3N_3$ units was postulated, at 330 °C.



*(7e)* *(16)* + Oligomers *(17)*

R = $CH_3$

Waxy polymers of unknown structure are obtained by elimination of ammonia from cyclosilazanes having the formula $(C_6H_5HSiNH)_{3 \text{ or } 4}$ in the presence of Pd/C catalysts above 200 °C [39]. *Krüger* and *Rochow* [137–138a] studied the polycondensation of hexamethylcyclotrisilazane *(7e)* and octamethylcyclotetrasilazane *(8b)* with ammonium salts, *e.g.* $NH_4Br$. When equimolar quantities of catalyst are used, the reaction above 160 °C is complete within 6 to 7 hours, and yields a polymer *(18)* or *(19)*, which is cross-linked *via* tertiary nitrogen (oligomers are also formed).



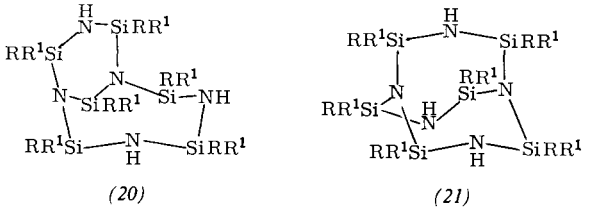
*(18)* *(19)*

R = $CH_3$

Structure *(18)* is more likely, owing to the tendency of the silazanes to undergo ring contraction. The preferred catalysts are ammonium halides (effect: Cl < Br < I). Trimeric cyclosilazanes react more readily than the tetramers.

The waxy to polyethylene-like polymers, which have a maximum crystallinity of 50%, are thermally stable up to 400 °C. Their molecular weight is over 10000. They are resistant to alkali solutions, but are rapidly broken down by acids. The freedom of rotation in these polymers is greatly reduced by "back-coordination" between silicon and nitrogen, formation of small rings, and a high degree of cross-linking in comparison with that in siloxanes [139].

Polymers assumed to have the structure *(18)* [140], as well as bicyclic compounds [38, 140], have been isolated as by-products in the preparation of cyclosilazanes [reaction (i)]. The bicyclic compounds are thought to have the structure *(20)*, though the structure *(21)* is also possible.



*(20)* *(21)*

*(20a)* R=R¹=$CH_3$; b.p. 250–275 °C; $n_D^{20}$ = 1.4684 [140]

*(20b)* R=H, R¹=$CH_3$; b.p. 116 °C/1.5 mm; $n_D^{20}$ = 1.4860 [38]

## 2. Heterocycles with SiN–N Linkages in the Ring

### 2.1. 1,2,4,5-Tetraza-3,6-disilacyclohexane

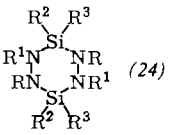
Substituted hydrazines *(22)* react with diorganodichlorosilanes *(23)* at high dilutions in ether to give substituted diorganodihydrazinosilanes *(25)*, which are not particularly stable, and which readily condense to form *(24)* [143, 144].

$$2\ R^2R^3SiCl_2 + 8\ HR^1N\text{-}NRH \longrightarrow$$

*(23)* *(22)*

$$2\ HR^1N\text{-}NR\text{-}SiR^2R^3\text{-}NR\text{-}NR^1H + 4\ HR^1N\text{-}NHR \cdot HCl$$

*(25)*



*(24)*

| R | R¹ | R² | R³ | M.p. (°C) | Ref. |
|---|---|---|---|---|---|
| H | H | Ph | Ph | 168–172 | [143, 144] |
| H | Ph | Ph | Ph | 254–257 | [144] |
| H | Ph | Me | Me | visc. oil | [143] |
| Ph | Ph | Ph | Ph | 329–330 | [145] |
| Ph | Ph | Me | Ph | 240–243 | [145] |

As in ammonolysis, cyclic products are formed by hydrazinolysis in preference to linear ones. If the N–H bonds do not react with the silicon-halogen bond, ring closure can be effected *via* the metalated hydrazines [144, 145] (M = Li, Na).

$$2\ M\text{-}NR\text{-}NR^1\text{-}M + 2\ R^2R^3SiCl_2 \rightarrow (24) + 4\ MCl$$

[134] *R. E. Burks jr.* and *Th. W. Ray*, cf. Quarterly Rep., Southern Research Inst. Birmingham, Alabama, 15th August 1962, p. 32.

[135] *K. A. Andrianov* and *G. Ya. Rumba*, Vysokomolek. Soyedin. *4*, 1060 (1962); Chem. Abstr. *58*, 12683 (1963).

[136] *K. A. Andrianov* and *G. Ya. Rumba*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1962*, 1313; Chem. Abstr. *58*, 2466 (1963).

[137] *C. R. Krüger* and *E. G. Rochow*, Angew. Chem. *74*, 588 (1962); Angew. Chem. internat. Edit. *1*, 458 (1962).

[138] *C. R. Krüger* and *E. G. Rochow*, J. Polymer. Sci. *A 2*, 3179 (1964).

[138a] *E. G. Rochow*, Mh. Chem. *95*, 750 (1964).

[139] *J. R. Barrante* and *E. G. Rochow*, J. org. Chemistry *1*, 273 (1964).

[140] *K. A. Andrianov*, *I. Haiduc*, and *L. M. Khananashvili*, Zh. obshch. Khim. *34*, 912 (1964).

[141] *K. Hedburg*, J. Amer. chem. Soc. *77*, 6491 (1955).

[142] *J. Goubeau* and *J. Jimenez-Barbera*, Z. anorg. allg. Chem. *303*, 217 (1960).

[143] *U. Wannagat* and *H. Niederprüm*, Angew. Chem. *70*, 745 (1958).

[144] *U. Wannagat* and *H. Niederprüm*, Z. anorg. allg. Chem. *311*, 270 (1961).

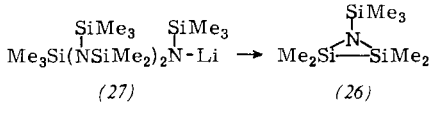
[145] *M. V. George*, *D. Wittenberg*, and *H. Gilman*, J. Amer. chem. Soc. *81*, 361 (1959).

Compounds *(24)* with $R = R^1 = H$ are very readily solvolysed, and are sensitive to oxidation, whereas those with $R = R^1 = C_6H_5$ are more stable[144]. The compounds *(24)* are characterized by an infrared absorption at 890 $cm^{-1}$ [144].

## 3. Heterocycles with Si–SiN Linkages in the Ring

### 3.1. 1-Trimethylsilyl-2,2,3,3-tetramethyl-1-azadisilacyclopropane

An azasiliridine derivative *(26)* (yield 7–12%) has been obtained among other products by the pyrolysis of the lithiosilazane *(27)* at 180–195 °C/100–110 atm[13].

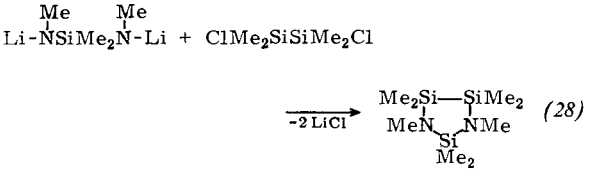


*(27)* *(26)*

Compound *(26)* (b.p. 172 °C, m.p. −37 °C, $n_D^{20} = 1.4375$, $d_4^{18} = 0.827$) has a remarkable thermal stability; the ring is cleaved by bromine at the disilane bond. The ring Si–N bond is weaker than that in cyclodisilazane *(3a)* (ring strain), and the exocyclic Si–N bond is very strong[28]. Compound *(26)* is probably planar.

### 3.2. Octamethyl-1,3-diaza-2,4,5-trisilacyclopentane

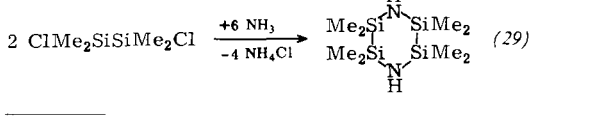
The compound was synthesized *via* doubly metalated bis(methylamino)dimethylsilane with 1,2-dichlorotetramethyldisilane (b.p. 70 °C/13 mm, m.p. −18 °C)[146].



*(28)*

### 3.3. 2,2,3,3,5,5,6,6-Octamethyl-1,4-diaza-2,3,5,6-tetrasilacyclohexane

The compound *(29)*, which is isosteric with 1,4-dioxa-2,3,5,6-tetrasilacyclohexane[147], was obtained by *Wannagat* and *Brandstätter*[148] (who also isolated the 1,4-dithia compound[149]) by ammonolysis of 1,2-dichlorotetramethyldisilane in petroleum ether (b.p. 61 °C/2 mm, m.p. 1 °C, $n_D^{20} = 1.4760$, $d_4^{20} = 0.8458$).



*(29)*

[146] *U. Wannagat*, Angew. Chem. *76*, 234 (1964); Angew. Chem. internat. Edit. *3*, 318 (1964).

[147] *M. Kumada, M. Yamaguchi, Y. Yamamoto, J. Nakajima,* and *K. Shiina*, J. org. Chemistry *21*, 1264 (1956).

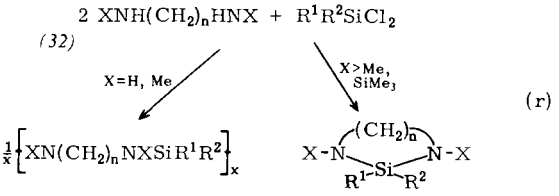
[148] *U. Wannagat* and *O. Brandstätter*, Angew. Chem. *75*, 345 (1963); Angew. Chem. internat. Edit. *2*, 263 (1963).

[149] *U. Wannagat* and *O. Brandstätter*, Mh. Chem. *94*, 1090 (1963).

## 4. Heterocycles with N–SiN–$(C)_n$ Linkages in the Ring

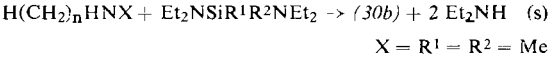
### 4.1. 1,3-Diaza-2-silacyclopentanes and -hexanes

Ethylenediamine *(32)* n = 2, X = H, and *N,N'*-dimethylethylenediamines *(32)*, n = 2, $X = CH_3$, react with polyfunctional organochlorosilanes to form polydiorganosilylethylenediamine. *N,N'*-Disubstituted ethylenediamines with X > Me, on the other hand, tend to form cyclic silylamine derivatives with the 1,3-diaza-2-silacyclopentane skeleton *(30)* [Scheme (r)].



*(30)* n = 2
*(31)* n = 3

Attempts to isolate *(30a)* with X = H[151] and to prepare *(30b)* with $X = R^1 = R^2 = CH_3$ in accordance with Scheme (r) have been unsuccessful. However, the latter compound can be obtained by transamination [equation (s)] (b.p. 132–133 °C/747 mm)[152]. (When $R^1 = R^2 = H$, $X = CH_3$, only polymers are isolated. Ring closure to *(30)* is possible when $R^1 = R^2 = H$ beyond $X = C_2H_5$[84]).



The formation of *(30)* is strongly favored when $X = SiR_3$. No polymers are formed in this case.

The ring in *(30)* is planar with either trigonally hybridized or rapidly inverting nitrogen[150].

The influence of the substituent X on the nitrogen is undoubtedly not only steric in nature. It is surprising that the ring closure of *N,N'*-dimethylethylenediamine *(32b)* does not occur in accordance with equation (r), but can be achieved by transamination in accordance with (s), *i.e.* in a system containing no ammonium salts. From a comparison with the permethylated cyclodisilazane *(3b)*, it appears that the stability principle observed with the cyclodisilazanes is also valid for the 1,3-diaza-2-silacyclopentanes. It is not impossible that the first step in Scheme (r) is ring formation, and that this is followed by ring cleavage by ammonium salts and polymerization.

*Henglein* and *Lienhard*[152] isolated a 1,3-diaza-2-silacyclopentane *(30c)* ($R^1 = R^2 = CH_3$, $X = (CH_3)_3Si$) which has high thermal stability.

Compounds *(30)* in which the ring silicon atom and/or the silyl groups are peralkylated or partially or completely phenylated can be prepared from ethylenediamine and triorganosilanes between 80 and 240 °C[153]. The reaction is catalysed

[150] *D. Kummer* and *J. D. Baldeschwieler*, J. physic. Chem. *67*, 98 (1963).

[151] *D. Kummer* and *E. G. Rochow*, Z. anorg. allg. Chem. *321*, 21 (1963).

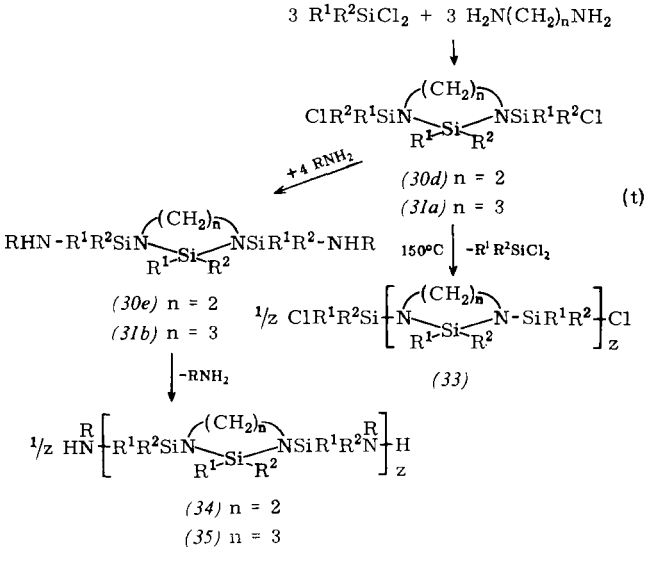
[152] *F. A. Henglein* and *K. Lienhard*, Makromolekulare Chem. *32*, 218 (1959).

[153] *W. Fink*, Chem. Ber., *99*, 2267 (1966).

by NaH. The closure of the 1,3-diaza-2-silacyclopentane ring is accompanied by the cleavage of an Si-phenyl or Si-alkyl bond (elimination of RH).

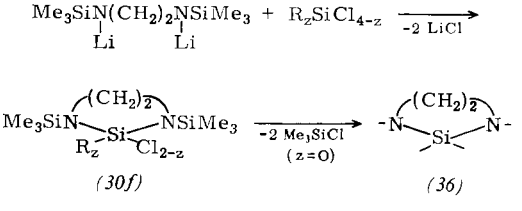
*Henglein* and *Lienhard*[152] and *Breed et al.*[154,155] have described 1,3-diaza-2-silacyclopentanes *(30d)* with monochlorinated silyl groups in positions 1 and 3. Ethylenediamine reacts with excess dialkyl- or alkylaryldichlorosilanes to give good yields of *(30d)* [Scheme (t)]. The reaction with diaryldichlorosilane leads only to disubstituted amines[155].

At higher temperatures the compounds *(30d)* condense, with loss of chlorosilane, to give polymers *(33)*[152,*]. Ammonolysis and aminolysis of *(30d)* leads to the amino compounds *(30e)*[154,155]. These condense at 140 °C in the presence of acidic catalysts (preferably ammonium sulfate) to give polymers with 1,3-diaza-2-silacyclopentane units *(34)*[154,155]. The polymers are soluble in organic solvents, have low melting points, and are sometimes rather elastic; they have molecular weights of up to 15000[154].



(t)

*Kummer* and *Rochow*[151] prepared compounds such as *(30f)* [equation (u)].

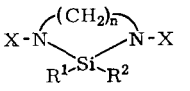


(u)

When heated, they condense (particularly readily in the presence of LiCl) to highly cross-linked polymers *(36)*[151], *e.g. (30f)* with z = 0, possibly in accordance with equation (u). The compounds *(30f)* can react further with ethylenediamine. When z = 1, two heterocycles condense *via* an ethylenediamine bridge[151].

1,3-Diaza-2-silacyclopentanes give a pronounced infrared band at 1340 $cm^{-1}$, which is assigned to the 5-membered ring[151,152].

Table. 6. 1,3-Diaza-2-silacyclopentanes *(30)*, (n = 2) and -hexanes *(31)*, (n = 3).



| X | $R^1$ | $R^2$ | B.p. (°C/mm) | M.p. (°C) | Ref. |
|---|---|---|---|---|---|
| n = 2 | | | | | |
| $Me_3Si$ [a] | Me | Me | 105–107/17 | | [151, 152] |
| $Me_2PhSi$ [b] | Me | Me | 145–146/0.03 | | [153] |
| $MePh_2Si$ | Me | Ph | 262/0.05 | 96 | [153] |
| $Ph_3Si$ | Ph | Ph | | 315–320 | [153] |
| $ClMe_2Si$ [c] | Me | Me | 84/0.03 | 38 | [152, 154, 155] |
| ClMePhSi | Me | Ph | 199–238/0.2–4 | | [155] |
| ClMeViSi | Me | Vi | 95/0.2 | | [155] |
| $Me_3Si$ | Me | Cl | 53/1 | 28–30 | [151] |
| $Me_3Si$ | Cl | Cl | | 82–83 | [151] |
| $H_2NMe_2Si$ [d] | Me | Me | 83/0 3 | | [155] |
| $(MeNH)Me_2Si$ [e] | Me | Me | 76/0.1 | | [155] |
| $(n\text{-}BuNH)Me_2Si$ [f] | Me | Me | 109/0.09 | | [155] |
| $(PhNH)Me_2Si$ | Me | Me | | 41–44 | [155] |
| (MeNH)MePhSi | Me | Ph | 198/0.09 | | [155] |
| (n-BuNH)MePhSi [g] | Me | Ph | 213/0.1 | | [155] |
| (MeNH)MeViSi [h] | Me | Vi | 99–101/0.1 | | [155] |
| n = 3 | | | | | |
| $MePh_2Si$ | Me | Ph | 254/0.04 | | [153] |
| $Ph_3Si$ | Ph | Ph | | 302–324 | [153] |
| $ClMe_2Si$ | Me | Me | 83/0.1 | | [154, 155] |
| ClMePhSi | Me | Ph | 205–225/0.1 | | [154, 155] |
| $H_2NMe_2Si$ [i] | Me | Me | 74/0.2 | | [154, 155] |
| $(MeNH)Me_2Si$ [j] | Me | Me | 84/0.1 | | [154, 155] |
| $(n\text{-}BuNH)Me_2Si$ [k] | Me | Me | 123/0.1 | | [155] |
| $(PhNH)Me_2Si$ | Me | Me | | 41–44 | [155] |
| (MeNH)MePhSi | Me | Ph | 190–230/0.2 | | [155] |

[a] $n_D^{20}$ = 1.4432, $d_4^{20}$ = 0.8623 [152]; [b] $n_D^{20}$ = 1.5343 [153]; [c] $n_D^{20}$ = 1.4383, $d_4^{20}$ = 0.8260 [152; [d] $n_D^{25}$ = 1.4620, $d_{20}^{25}$ = 0.9530 [155]; [e] $n_D^{26}$ = 1.4582, $d_{20}^{26}$ = 0.9304 [155]; [f] $n_D^{28}$ = 1.4566, $d_{20}^{28}$ = 0.9108 [155]; [g] $n_D^{28}$ = 1.5431, $d_{20}^{28}$ = 1.0434 [155]; [h] $n_D^{28}$ = 1.4848, d = $d_{20}^{28}$ 0.9676 [155]; [i] $n_D^{26}$ = 1.4689, $n_D^{26}$ = 0.9672 [155]; [j] $n_D^{26}$ = 1.4671, $n_D^{26}$ = 0.9542 [155]; [k] $n_D^{28}$ = 1.4615, $d_{20}^{28}$ = 0.9243 [155].

The reactions leading to the 1,3-diaza-2-silacyclopentanes are also suitable for the preparation of 1,3-diaza-2-silacyclohexanes *(31)*[153]. Chlorodimethylsilylated compounds *(31a)* can be obtained in moderate yields in accordance with equation (t)[154,155]. The derivatives *(31a)* occur as intermediates in the synthesis of polymers *(35)*, which are obtained from the diamino compounds *(31b)* by condensation with ammonium sulfate[154,155].

Some examples of 1,3-diaza-2-silacylopentanes *(30)* and -hexanes *(31)* are given in Table 6.

### 4.2. 2-Silabenzimidazolines

Compounds *(37)* with readily hydrolysed Si–N bonds are obtained[158] *via* *N,N'*-bis(trimethylsilyl)-*o*-phenylenediamine *(38)* by reaction with polyfunctional chlorosilanes. Whereas the ring closure with methyldichlorosilane is accompanied by elimination of HCl, the reaction of dialkyldichloro- and alkyltrichlorosilanes leads to cleavage of the N–$Si(CH_3)_3$ bond [equation (v)] [*(37a)*,

[154] *L. W. Breed, R. L. Elliott*, and *A. F. Ferris*, J. org. Chemistry *27*, 1114 (1962).

[155] *L. W. Breed, R. L. Elliott*, and *A. F. Ferris*, J. Polymer Sci. *A 2*, 45 (1964).

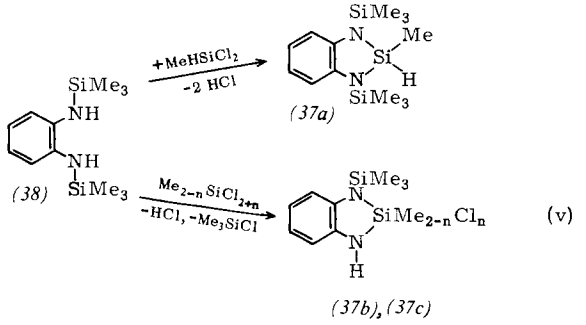
[*] Polymers of similar structure have been synthesized [156,157] by condensation of ethylenediamine with dimethyldichlorosilane. The polymer is at first largely linear but rearranges *via* several intermediate stages to give *(33)* as a result of aging or heat treatment or, more rapidly, by the elimination of ethylenediamine with catalysis by copper salts.

[156] *E. G. Rochow* and *R. N. Minné*, J. Amer. chem. Soc. *82*, 5625, 5628 (1960).

[157] US-Pat. 3098830 (1963), General Electric Co., inventor: *E. G. Rochow*.

[158] *D. Kummer* and *E. G. Rochow*, Angew. Chem. *75*, 207 (1963); Angew. Chem. internat. Edit. *2*, 152 (1963).

b.p. 86 °C/1 mm, $n_D^{20} = 1.5278$; *(37b)*, n = 0, m.p. 91–93 °C; *(37c)*, n = 1, m.p. 99 °C].

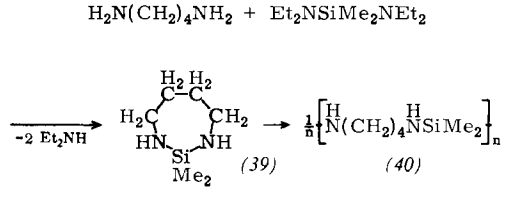



(v)

The *Si*-phenylated compounds *(37)*, which cannot be obtained in this way, can be prepared in good yields by the catalytic silylation of *(38)* or of *o*-phenylenediamine with one or three moles, respectively, of phenylsilane [29,153].

### 4.3. 1,3-Diaza-2-silacycloheptane

Rings with more than six members and containing Si–N bonds are unstable (apart from the stable rings containing only alternating Si and N atoms), and tend to undergo polymerization with ring cleavage. This is clearly seen with compound *(39)* (b.p. 57.5 °C/16 mm), which polymerizes even at room temperature to form polydimethylsilyltetramethylenediamine *(40)* [152].

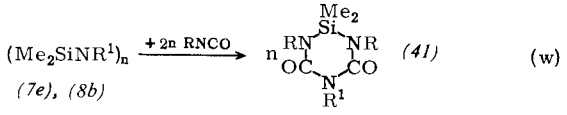



### 4.4. 2,2-Dimethyl-1,3,5-triaza-2-silacyclohexane-4,6-diones

The reactivity of the Si–N bond towards organic isocyanates, reflected in easy cleavability and formation of silylureas [159–162], can be utilized in the synthesis of the 1,3,5-triaza-2-silacyclohexane-4,6-dione.

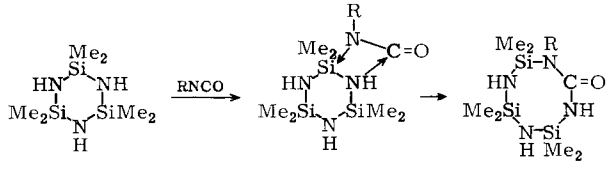
Hexamethylcyclotri- *(7e)*, n = 3, and octamethylcyclotetrasilazanes *(8b)*, n = 4, react with organic isocyanates in solution at 60 to 90 °C to give derivatives of 1,3,5-triaza-2-silacyclohexanedione *(41)* [129,163]. [*(41a)*, R = $C_6H_5$, $R^1$ = H, m.p. 188–190 °C; *(41b)*, R = *p*-Br–$C_6H_4$, $R^1$ = H, m.p. 215 °C].

The structure of *(41)* was found by hydrolysis (which leads to 1,5-diphenylbiuret when $R^1$ = H, R = $C_6H_5$), $^1$H–NMR studies, and X-ray analysis [164].



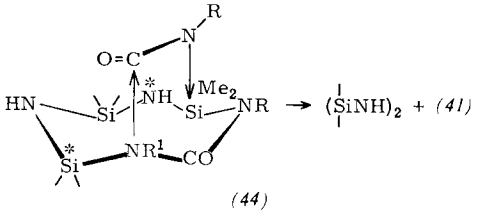

(w)

The reaction (w) can be formulated as a cycloaddition of one molecule of isocyanate (the silazane ring is degraded in stages) to an SiN bond in *(7e)* or *(8b)*.



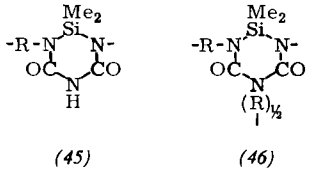

The cleavage of the bond and the ring expansion are facilitated by the weakening of the Si-N bond (suppression of the $d_\pi$-$p_\pi$ bond component owing to occupation of the silicon d orbitals by electrons from the isocyanate nitrogen).

The 8-membered ring *(43)* can add another isocyanate molecule [*(44)*], whereupon the transannular interaction between *silicon and *nitrogen leads to constriction of the ring and to the formation of *(41)* and a cyclosilazane with one less Si-N unit (*i.e.* in this case n = 2), which can then repeat the sequence of reactions.




The reaction of isocyanate with 1,3-disubstituted *(41)* at 120 to 160 °C leads *via* large, unstable rings to 1,3,5-trisubstituted 2,2-dimethyl-1,3,5-triaza-2-silacyclohexane-4,6-diones [129] (*e.g. (41c)* with R = $R^1$ = $C_6H_5$, m.p. 213–215 °C; *(41d)* with R = $R^1$ = $C_2H_5$, m.p. 92–93 °C; *(41e)* with R = $R^1$ = n-$C_4H_9$, b.p. 110–118 °C/0.015 mm).

Transparent, elastic, essentially linear polymers *(45)* containing *(41)* as a structural unit can be synthesized by the reaction of hexamethylcyclotrisilazane *(7e)* with (preferably aliphatic) diisocyanates below 110 °C [29].




Above 110 °C, these rearrange with elimination of $(HNCO)_x$ to form highly cross-linked polymers *(46)* which possess excellent stability towards acids.

[159] *G. Oertel, H. Malz*, and *H. Holtschmidt*, Chem. Ber. *97*, 891 (1964).

[160] *W. Fink*, Chem. Ber. *97*, 1433 (1964).

[161] *J. F. Klebe, J. B. Bush*, and *J. E. Lyons*, J. Amer. chem. Soc. *86*, 4400 (1964).

[162] *D. Ya. Zhinkin, M. M. Morgunova, K. K. Popkov*, and *K. A. Andrianov*, Dokl. Akad. Nauk SSSR *158*, 641 (1964); Chem. Abstr. *62*, 583 (1965).

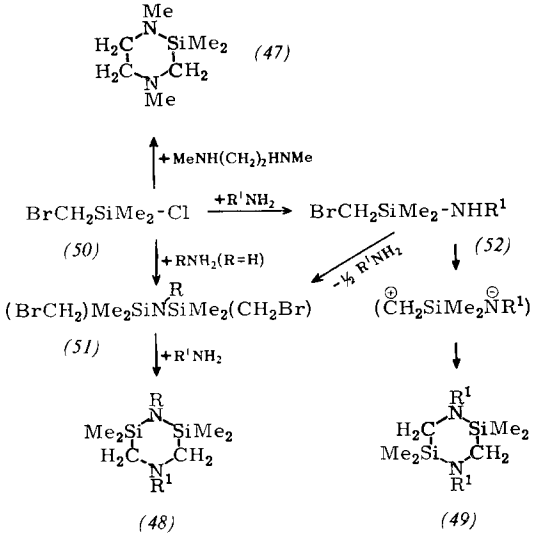
[163] *Th. W. Ray* and *R. E. Burks jr.*, cf. Report 31, Southern Research Inst., Birmingham, Alabama, 17th Sept. 1963.

[164] *J. J. Daly* and *W. Fink*, J. chem. Soc. (London) *1964*, 4958.

## 5. Heterocycles with C–SiN–Si or C–SiN–C Linkages in the Ring

### 5.1. Silapiperazines

The mono- *(47)* and disilapiperazines, the second of which can occur as 2,6- *(48)* and 2,5-isomers *(49)*, are derived formally from the piperazine ring structure [*(47)*: b.p. 64 °C/53 mm; $n_D^{20} = 1.4508$].




*Simmler*[165] obtained 1,2,2,4-tetramethyl-2-silapiperazine *(47)* in small yields by dropwise addition of bromomethyldimethylchlorosilane *(50)* to an excess of *N,N'*-dimethylethylenediamine at 0 °C.

The 2,6- and 2,5-disilapiperazines have also been synthesized from *(50)*[166]. 1,3-Bisbromomethyl-1,1,3,3-tetramethyldisilazane *(51)* [from the ammonolysis of *(50)*, which also yields *(48)* with R = $R^1$ = H] reacts with primary amines to give 4-alkyl-2,6-disilapiperazines *(48)*, and with an excess of amine (transamination) to give 1,4-dialkyl-2,6-disilapiperazines. The direct reaction of *(50)* with excess of primary aliphatic amines leads to inseparable mixtures of 2,6- and 2,5-isomers. (For the preparation of pure *N,N'*-bis-(2-methoxyethyl)-2,2,5,5-tetramethyl-2,5-disilapiperazine, b.p. 115–117 °C/4 mm, $n_D^{21.5} = 1.4605$, cf.[167]).

The proportion of 2,5-isomer *(49)* increases with the size of the group attached to the nitrogen. This indicates that owing to steric factors, the 2,5-disilapiperazines are formed *via* the silylamine *(52)*. Table 7 shows some examples of 2,6-disilapiperazines.

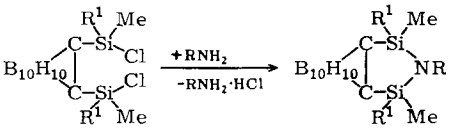
Table 7. 2,6-Disilapiperazines *(48)*.

| R | $R^1$ | B.p. (°C/mm) | $n_D^{20}$ |
|---|---|---|---|
| H | H | [a] | |
| H | Me | 66/51 | 1.4503 |
| H | n-Pr | 81/11 | 1.4505 |
| H | All | 48/0.3 | 1.4625 |
| Me | Me | 74/18 | 1.4516 |
| n-Pr | n-Pr | 118/13 | 1.4572 |
| All | All | 113/15 | 1.4740 |

[a] Decomp. p. of hydrobromide 270 °C.

### 5.2. 2'-Aza-1',3'-disilacarboranes

These compounds, which are remarkable for their thermal and hydrolytic stability, were obtained by ammonolysis or hydrazinolysis of bis(chlorodimethylsilyl)- *(54a)* or bis[(dichloro)methylsilyl]carboranes *(54b)* [168, 169].




*(54a)*: $R^1$ = Me
*(54b)*: $R^1$ = Cl

*(53)*

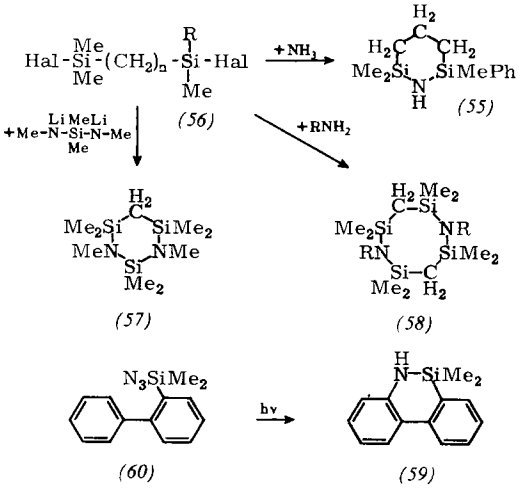
| Derived from: | $R^1$ | R | M.p. (°C) |
|---|---|---|---|
| *(54a)* | Me | H | 190–192 |
| *(54a)* | Me | $NH_2$ | 163–165 |
| *(54a)* | Me | Me | 156–158 |
| *(54a)* | Me | Ph | 183–185 |
| *(54b)* | $NH_2$ | H | 189–191 |
| *(54b)* | NHMe | Me | 128–129 |

The compounds *(53)* are stable up to 500 °C; the Si–N bond, which is normally readily solvolysed, is surprisingly stable in *(53)*.

### 5.3. 1-Aza-2,6-disilacyclohexane and Similar Compounds

2,2,6-Trimethyl-6-phenyl-1-aza-2,6-disilacyclohexane *(55)* (b.p. 100 °C/3 mm, $n_D^{20} = 1.5194$, $d_4^{20} = 0.9736$), which is isosteric with the 1-oxa-2,6-disila compound[170], has been prepared by ammonolysis of the chlorosilyl derivative *(56)* (n = 3, R = $C_6H_5$)[170].

Octamethyl-1,3-diaza-2,4,6-trisilacyclohexane *(57)* (b.p. 46 °C/3 mm, m.p. −18 °C, $n_D^{20} = 1.4573$) and octamethyl-1,5-diaza-2,4,6,8-tetrasilacyclooctane *(58)* (R = H: b.p. 82 to




[165] *W. Simmler*, Chem. Ber. *96*, 349 (1963).

[166] *H. Niederprüm* and *W. Simmler*, Chem. Ber. *96*, 965 (1963).

[167] *H. Pfleger*, US Dept. Comm. Office Tech. Serv., AD 263736 (1961); Chem. Abstr. *58*, 2466 (1963).

[168] *St. Papetti* and *T. L. Heying*, Inorg. Chem. *2*, 1105 (1963).

[169] *St. Papetti, B. B. Schaeffer, H. J. Troscianiec*, and *T. L. Heying*, Inorg. Chem. *3*, 1444 (1964).

[170] *Chi-Tao Wang, Hsin-Chung Chon*, and *Mau-Shui Hung*, Acta chim. sinica (Hua Hsueh Hsueh Pao) *30*, 91 (1964); Chem. Abstr. *61*, 1888 (1964).

84 °C/3.5 mm, m.p. 35 °C; R = $CH_3$: b.p. 97 °C/3 mm, m.p. 44–45 °C) were synthesized [17,85,171] by the reaction of *(56)* (n = 1, R = $CH_3$, Hal = Br) with *N,N'*-dilithiodi(methylamino)dimethylsilane [for *(57)*] and with ammonia or methylamine [for *(58)*].

10,10-Dimethyl-9,10-dihydro-9,10-azasilaphenanthrene *(59)* (m.p. 143 °C) can be prepared by photolysis of 2-(azidodimethylsilyl)biphenyl *(60)* [106]. The ultraviolet spectrum of *(59)* is remarkably similar to that of phenanthrene; this similarity has been interpreted as resulting from aromatization of the ring containing the Si-N bond.

n = 1 [172–181], 2 [172,175,176,178,179], 3 [175,176,179], 4 [178,179], and 5 [178,179]. Some examples are shown in Table 8.

Compounds with n = 6 to 10 do not give cyclic siloxazanes, but instead form polymeric siloxazanes with low thermal stabilities [180].

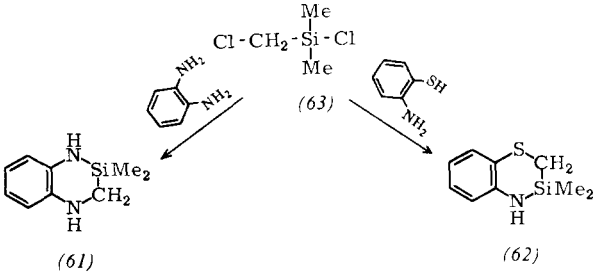
The cyclization of *(67)* to form *(65)* and *(66)* proceeds very readily for $R^2$ = H and n < 6 [*(67)* cannot be isolated]. When $R^2$ = alkyl, *(67)* is stable [175–179], but can be cyclized to *(65)* or

Table 8. Cyclic siloxazanes.

| n | R | $R^1$ | $R^2$ | B.p. (°C/mm) | M.p. (°C) | $n_D^{20}$ | Ref. |
|---|---|---|---|---|---|---|---|
| *(65)* | | | | | | | |
| 2 | Me [a] | Me | H | 151/760 | 9.5 | 1.4068 | [172,175,176,179] |
| 2 | Me | Ph | H [j] | 169–172/0.25 | | | [179] |
| 2 | Me | Ph | H [k] | | 113–115 | | [179] |
| [b] | | | | 119–135/0.05 | 100 | | [179] |
| 2 | Me [c] | Me | Et | 41/1–2 | | 1.4153 | [178] |
| 2 | Me | Me | n-Bu | 78/5 | | | [179] |
| 3 | Me [d] | Me | H | 190–191/760 | 20 | 1.4151 | [175,176,179] |
| 3 | Me | Ph | H | 192–202/0.15 | | | [179] |
| 4 | Me [e] | Me | H | 81–83/3 | | 1.4125 | [179, 181] |
| 5 | Me [f] | Me | H | 64–65/0.1 | | 1.4122 | [179, 181] |
| *(66)* | | | | | | | |
| 1 | Me | Me | H | 206–208/760 | 37 | | [172–176, 179] |
| 1 | Me | Ph | H | 200–206/0.1 | | | [179] |
| 1 | Me | Me | n-Bu | 95–98/0.25 | | | [179] |
| 1 | MeO | MeO | H | 173–175/0.05 | | | [177] |
| [g] | | | | 70/0.5 | >20 | 1.4308 | [172, 173] |
| 1 | Me [b] | Me | Et | 95–96/1–2 | | 1.4410 | [177] |
| 2 | Me [i] | Me | H | 148–150/2 | –12 | 1.4269 | [172, 179] |

[a] $d_4^{20}$ = 0.9313 [172]; [b] 2,2,4,4-Tetramethyl-6,6-diphenyl-1,5-dioxa-3-diaza-2,4,6-trisilacyclohexane; [c] $d_4^{20}$ = 0.9343 [178]; [d] $d_4^{26}$ = 0.9921 [175,176]; [e] $d_4^{20}$ = 0.9683 [180]; [f] $d_4^{20}$ = 0.9690 [180]; [g] 4,4,8,8-Tetramethyl-2,2,6,6-tetraethyl-1,5-dioxa-3,7-diaza-2,4,6,8-tetrasilacyclooctane; [h] $d_4^{20}$ = 0.9470 [178]; [i] $d_4^{20}$ = 0.9756 [172]; [j] Configuration not determined; [k] *meso*-Form.

2,2-Dimethyl-1,2,3,4-tetrahydro-1,4-diaza-2-silanaphthalene *(61)* (b.p. 142–144 °C/4 mm, m.p. 52 °C) and 3,3-dimethyl-1,2,3,4-tetrahydro-1-thia-4-aza-3-silanaphthalene *(62)* (b.p. 151–154 °C/8 mm) have been prepared by the reaction of *o*-phenylenediamine and *o*-aminothiophenol with chlorochloromethyldimethylsilane *(63)* [171a].




*(61)* *(62)*

## 6. Heterocycles with O–SiN–Si Linkages in the Ring

### 6.1. Cyclosiloxazanes

Rings with O–SiN–Si linkages [172,173] are generally prepared by ammonolysis or aminolysis of α,ω-dichloro-α,ω-tetraorgano(preferably methyl)siloxanes *(64)* with *(66)* with the aid of acidic catalysts (*e.g.* ammonium sulfate [179]) if the amine formed is simultaneously removed from the equilibrium. The conversion of *(65)* or *(66)* into *(67)* with cleavage of the siloxazane ring is also known. With excess of ethylamine in the presence of $C_2H_5NH_2 \cdot HCl$, the reaction proceeds almost quantitatively even at –20 °C, *e.g.* when $R^2 = C_2H_5$, R = $R^1$ = $CH_3$, n = 2 [178]. Compound *(67)* is probably not formed strictly in accordance with equation (x), but *via* cyclic siloxazanes, which immediately undergo ring cleavage under the conditions of the reaction (excess of amine).


[171] *K. Lienhard* and *E. G. Rochow*, Angew. Chem. *75*, 980 (1963); Angew. Chem. internat. Edit. *2*, 691 (1963).

[171a] *M. Wiberg* and *M. Schmidt*, J. organomet. Chemistry *1*, 22 (1963).

[172] *N. N. Sokolov*, Symposium Appl. Organosilicon Compds., Proc., Leningrad 1958, *2*, 130; Chem. Abstr. *54*, 8603 (1960).

[173] *N. N. Sokolov*, Zh. obshch. Khim. *29*, 258 (1959); Chem. Abstr. *53*, 21622 (1959).

[174] See [64], p. 38.

[175] *C. R. Krüger* and *E. G. Rochow*, Angew. Chem. *74*, 491 (1962); Angew. Chem. internat. Edit. *1*, 455 (1962).

[176] *C. R. Krüger* and *E. G. Rochow*, Inorg. Chem. *2*, 1295 (1963).

[176a] French. Pat. 1357957 (1964), Compagnie Française Thomson-Houston, inventor: *J. G. Murray*.

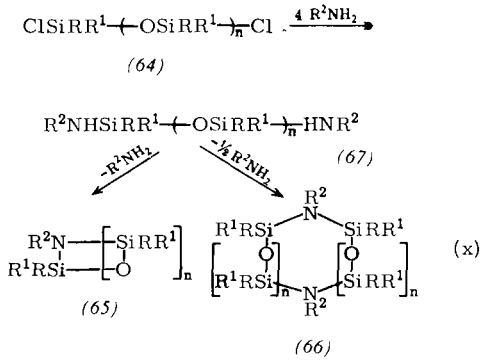
[177] *O. Schmitz-DuMont*, *D. Merten*, and *D. Eiching*, Z. anorg. allg. Chem. *319*, 362 (1963).

[178] *K. A. Andrianov*, *T. V. Vasil'eva*, and *I-Ming Li*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963*, 1847; Chem. Abstr. *60*, 2999 (1964).

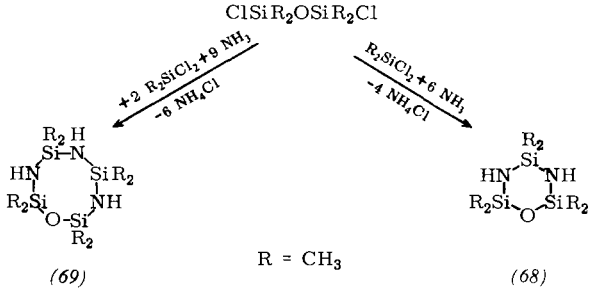
[179] *J. G. Murray* and *R. K. Griffith*, J. org. Chemistry *29*, 1215 (1964).

[180] *K. A. Andrianov*, *L. M. Volkova*, and *V. N. Talanov*, Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963*, 2045; Chem. Abstr. *60*, 5534 (1964).

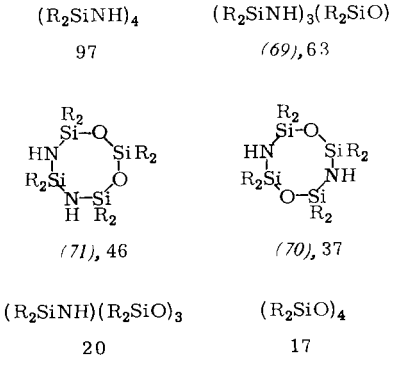
[181] *K. A. Andrianov*, *I. Haiduc*, and *L. M. Khananashvili*, Zh. obshch. Khim. *33*, 2790 (1963); Chem. Abstr. *59*, 15300 (1963).



*Andrianov et al.*[181,182] prepared 6-membered *(68)* and 8-membered *(69)* cyclic siloxazanes by co-ammonolysis of 1,3-dichlorotetramethyldisiloxane and dimethyldichlorosilane (ratio 1:1 and 1:2, respectively) [*(68)*, R = $CH_3$, m.p. 47 °C; *(69)*, R = $CH_3$, m.p. 63 °C].



The same authors[182] isolated the 1,3-dioxa-5,7-diaza isomer *(71)* of 2,2,4,4,6,6,8,8-octamethyl-1,5-dioxa-3,4-diazacyclooctane *(70)*[173–176] from the products obtained by ammonolysis of a 1:1 mixture of 1,5-dichlorohexamethyltrisiloxane and dimethyldichlorosilane (Scheme 3).



Scheme 3. Transitions between cyclotetrasilazanes and cyclotetrasiloxanes. The figures under the formulae are the melting points (°C); R = $CH_3$.

Siloxazanes can be polymerized with ammonium halides, with partial decomposition, to siloxanes, and with alkaline catalysts to polymers and oligomers which are cross-linked *via* triply silylated nitrogen[176,176a]. The N–H bond in siloxazanes is not metalated by organometallic compounds or $NaNH_2$, but the Si–O bonds are broken instead[176].

Whereas the SiOSi bond angle in *(65)* with n = 2 (R = $R^1$ = $CH_3$, $R^2$ = H) corresponds to that in hexamethylcyclotrisiloxane, the angle of the SiNSi bond (133 °C) is considerably larger than in hexamethylcyclotrisilazane (117 °C)[176]. The abnormally low hydrolytic stability of 6-membered cyclosiloxazanes [*(65)* with n = 2] may be due to the ring strain in these compounds. The Si-N bonds in 8-membered cyclosiloxazanes [*(66)* with n = 1], on the other hand, are appreciably more stable than those in cyclosilazanes[179]. Cyclosiloxazanes [*e.g. (66)* with n = 1, R = $R^1$ = $CH_3$, $R^2$ = H] combine outstanding thermal stability with a wide liquid range. They are more stable at 450 °C than cyclotetrasiloxanes or cyclotrisilazanes[183,185].

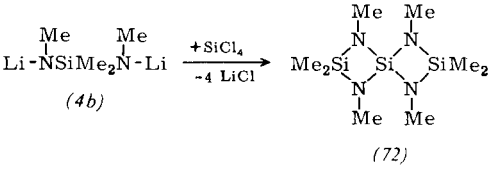
The relative thermal stabilities of a number of heterocycles containing Si, N, or O at 450 °C[183,184] are listed below

| Compound | *(66)*, n = 1 R = $R^1$ = $R^2$ = Me | *(7a)* $(MeNSiMe_2)_3$ | *(7e)* $(HNSiMe_2)_3$ | $(OSiMe_2)_4$ |
|---|---|---|---|---|
| ml of gas/g [*] | 0.10 | 0.24 | 0.58 | 0.82 |

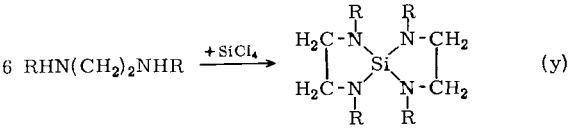
[*] ml of gas formed in 1.5 h/g of substance.

## 7. Spiranes with SiN Linkages

Spirosilazanes can, in principle, be prepared by condensation of a tetrahalogenosilane with a diamine or diaminosilane (possibly in the form of the dilithium compound). Thus octamethylspiro[3.3]trisilazane *(72)* (b.p. 39 °C/4 mm, m.p. 34 °C) is obtained in this way from silicon tetrachloride and *(4b)*[18]



and 1,4,6,9-tetraza-5-silaspiro[4.4]nonane *(73)*, like the 5-germaspiranes, is obtained in accordance with equation (y).



| R | B.p., °C/mm (M.p., °C) | $n_D^{28}$ |
|---|---|---|
| *(73a)* Me | 75/8 | 1.4640 |
| *(73b)* Et | 123/7 | 1.4677 |
| *(73c)* p-Toy | (300–304) | |
| *(73d)* $Me_3Si$ | (206) [151] | |

Whereas *N,N'*-dialkylethylenediamines react smoothly in benzene at 40 to 60 °C to give *(73)*, the arylated diamines react only with difficulty, and give poor yields. It is concluded from NMR data that the rings in the alkylated 1,4,6-tetraza-5-silaspiro[4.4]nonanes *(73)* are planar[185].

The spiro compound *(74)* (m.p. 200 °C), in which only two nitrogen atoms are trimethylsilylated, can be pre-

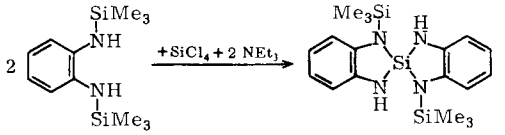
[182] *K. A. Andrianov, I. Haiduc,* and *L. M. Khananashvili,* Izvest. Akad. Nauk SSSR, Otd. Khim. Nauk *1963*, 1701; Chem. Abstr. *59*, 15299 (1963).

[183] See [64], p. 11.

[184] *Th. W. Ray* and *R. E. Burks jr.*, cf. Annual Rep., Southern Research Inst., Birmingham, Alabama, 28. Feb. 1962, p. 42.

[185] *C. H. Yoder* and *J. J. Zuckerman,* Inorg. Chem. *3*, 1329 (1964).

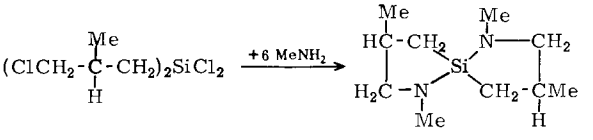
pared from *N,N'*-bis(trimethylsilyl)-*o*-phenylenediamine *(38)* [158]. Silicon tetrachloride reacts both with the N–H and with the N–Si bond [cf. equation (v)].



*(38)* *(74)*

1,4,6,9-Tetrakis(trimethylsilyl)-1,4,6,9-tetraza-5-silaspiro[4.4]nonane *(73d)* has been isolated from the products obtained by the reaction of 1,3-bis(trimethylsilyl)-2,2-dichloro-1,3-diaza-2-silacyclopentane with ethylenediamine/trimethylchlorosilane [151]. The compound is remarkably resistant to hydrolysis.

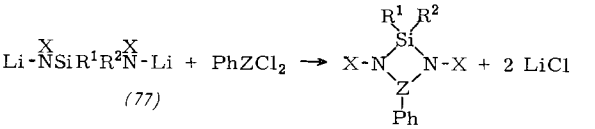
The preparation of tetramethyl-1,6-diaza-5-silaspiro-[4.4]nonane *(75)* is described in a patent [186].



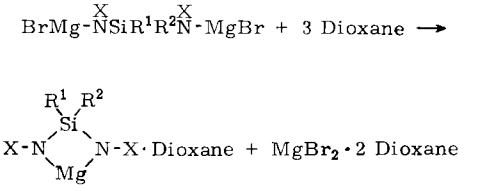
*(75)*

## 8. Miscellaneous

The reaction of monoorganoboron dichlorides or dihalides of trivalent phosphorus with metalated silazane *(77)* leads to diazasilaboretidines *(76a)*, *(76c)* and diazaphosphasiletidines *(76b)*, *(76d)* [12]. Magnesium can be introduced into the ring by means of the di-Grignard compound [29] [X = $(CH_3)_3Si$, $R^1 = R^2 = CH_3$, sublimes at 140 °C/1.5 mm].



*(77)* *(76)*



| X | Z | $R^1$ | $R^2$ | B.p., °C/mm (F.p., °C) | $n_D^{20}$ | Ref. |
|---|---|---|---|---|---|---|
| *(76a)* $Me_3Si$ | B | Me | Me | 90–91/1.22 | 1.4738 | [12] |
| *(76b)* $Me_3Si$ | P | Me | Me | 107/4 | 1.5029 | [12] |
| *(76c)* Ph | B | Ph | Ph | (268–270) | | [29] |
| *(76d)* Ph | P | Ph | Ph | (212) | | [29] |

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Translated by Express Translation Service, London

[186] French Pat. 1330624 (1963), Dow Corning, inventor: *J. L. Speier jr.*

# The Hormonal System of Plants

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*Higher plants generate active substances, termed phytohormones, having the character of tissue hormones. Some of these compounds have been isolated and identified, namely ethylene, heteroauxins, and gibberellic acids. Cell-elongation inhibitors have been detected, but not yet isolated or identified. Natural and synthetic substances with hormone-analogous effects and those with a hormone-antagonistic effect have become known; evidently, they act on the hormonal system of plants which regulates growth, differentiation, and development and can serve as model substances for as yet unknown phytohormones. Certain physiological phenomena suggest the existence of additional phytohormones.*

## I. Introduction

Since 1904 the term hormones has been used to designate substances produced as internal secretions by an organ of an organism and carried in the bloodstream to a different organ, where they act even at very low concentrations, and which are essential for normal metabolism and development [1]. This concept was restricted for about 25 years to animal organisms; however, the discovery in 1929 [2] of similar substances which are transported by the plant tissue juices to the sites of

[1] *W. M. Bayliss* and *E. Starling*, Proc. Roy. Soc. (London) Ser. B *73*, 310 (1904).

[2] *F. W. Went*, Recueil Trav. bot. néerl. *25*, 1 (1929).

action led to an extension to plants. Although many animal hormones are produced by glands, some are formed by tissues (aglandular hormones). Because higher plants, with few exceptions, have no gland organs, plant hormones (phytohormones) must be regarded as aglandular secretions.

There are also noteworthy analogies in regard to hormone action. Animal hormones regulate the intensity of metabolic changes[3] such as the rates of protein, fat, carbohydrate, and basal metabolism (thyroxin), production of other hormones or internal secretions (thyreotropin), production of pigments (pigment-forming hormones), secretion of certain glands, *e.g.* lactation (prolactin), water balance and salt excretion (adiuretin), displacement of substances into certain organs or storage in these (glycogen storage in liver by insulin), contractions of certain tissues (constriction of blood vessels, tachycardiac stimulation of the heart by adrenalin), development of genitalia and secondary sexual characteristics (estradiol, testosterone), and growth and rate of growth (somatotropin, whose absence leads to dwarfing and cessation of development). Analogously in plants, phytohormones control the intensity of metabolism, the production of other phytohormones, production and decomposition of pigments, displacement of certain substances into certain organs or storage in them, elongation of the cell wall, the development of flowers, and also growth and growth rate (with absence of individual hormones leading to dwarfing and inhibition of development). No information is available yet about hormonal control of water balance, salt secretion, and formation of secretions in plants, except that the water uptake of individual cells is influenced by the cell-elongation hormones.

## II. Methods of Detection

The discovery and study of phytohormones (or of synthetic substances with analogous behavior) requires methods allowing investigation of the generation and measurement of hormonal action in numerous plants (to ensure statistical significance), available throughout the year (under standardized conditions) and over the shortest possible period. The test plants are susceptible to hormones only during a certain stage in their development, the determination of which in general is tedious. In addition, the specimens must be deprived as much as possible of their native hormones.

These conditions are given in growth reactions which become evident very soon after the hormone takes effect. An example of such a reaction is the epinastic downward movement of leaves under the influence of gases which promote the longitudinal growth of cells; the upper side of the leaf stem is stimulated to an increased rate of growth (the top surface of the stem is more susceptible than the underside; curving occurs even if the concentration of active agent, *e.g.* tobacco smoke[4] or ethylene[5] is the same on either side). One-sided application of a substance promoting cell elongation to a uniformly reactive organ, *e.g.* cereal coleoptiles, also can produce measurable curving and permits a quanitative evaluation of the activity. This is the basis of *Went*'s auxin test[6] and numerous analogous methods[7]. More expedient is a measurement of length after uniform exposure to the test solution[9], because transport of a component applied on one side to the untreated side can produce errors[8].

Measurable effects are obtained at a similar rate during germination of various plant seeds. Inhibition of germination[10] or inhibition of root growth of the germinated seed[11] are possible test criteria. Since nonspecific or toxic substances can also produce inhibition, the use of an inhibition test to detect phytohormones is not as convincing as a stimulation test.

Slower methods of detection, suitable for higher hormone concentrations, are based on the influencing or initiation of callus formation, root formation, bud formation on grafted plants or rhizome disks[12] on transplants, or on callus tissue of plant tissue cultures[13] and also on the emergence of morphological changes (or malformations) especially in dicotyledons[14]. Retardation of the degradation of chlorophyll in leaves can also serve for the detection of hormones[15]. Certain hormonal effects influence the overall habit of the plant (rosette or elongated form), *i.e.* the internodal length[16–19].

## III. Historical

*Küster*[20] showed as early as 1909 that substances formed by plant organisms can exert physiological effects on other plants, but this effect is due partly to the action of nutrients or vitamin-like substances or of metabolites of one organism on the metabolic system of another.

The observations of *Molisch*[4] showed that certain plants respond very sensitively to tobacco smoke with epinastic growth. Subsequently, *Ricinus communis* leaves, for example, were found to react epinastically to

[3] *R. Abderhalden*: Vitamine, Hormone, Fermente. 4th Edit., Schwabe, Basel 1953.

[4] *H. Molisch*, S.-B. Akad. Wiss. Wien., math.-naturwiss. Kl., Abt. I, *120*, July 1911.

[5] *E. M. Harvey*, Bot. Gaz. *56*, 439 (1913).

[6] Cf. [2].

[7] *H. Linser* and *O. Kiermayer*: Methoden zur Bestimmung pflanzlicher Wuchsstoffe. Springer, Vienna 1957.

[8] *H. Linser*, Planta *28*, 227 (1938); *29*, 392 (1939).

[9] *O. Kiermayer*, Planta *47*, 527 (1956).

[10] *M. Evenari*, Bot. Rev. *15*, 153 (1949).

[11] *F. Moewus*, Biol. Zbl. *68*, 58 (1949).

[12] *H. Linser*, Österr. bot. Z. *95*, 95 (1948).

[13] *F. Skoog*, see [130].

[14] *H. Linser*, *W. Frohner*, and *R. Kirschner*, Pyton (Argentina) *3*, 53 (1953).

[15] *K. Mothes*, Naturwissenschaften *47*, 337 (1960).

[16] *E. Kurosawa*, Trans. nat. Hist. Soc. Formosa *16*, 213 (1926).

[17] *T. Yabuta* and *Y. Sumiki*, J. agric. chem. Soc. Japan *14*, 1526 (1938).

[18] *N. E. Tolbert*, J. biol. Chemistry *235*, 475 (1960).

[19] *H. Linser*, *H. Mayr*, and *G. Bodo*, Bodenkultur *12*, 279 (1961).

[20] *E. Küster*: Vorträge und Aufsätze über Entwicklungsmechanik der Organismen. Engelmann, Leipzig 1909, Vol. 6, p. 1.

ethylene ($1:10^7$ in air)[5]. It was further established that ripening apples can cause potatoes stored in the same room to form sprouts with inhibited longitudinal growth but of increased thickness[21], to increase their sugar content, and to increase the catalase and oxidase activity. Moreover, ripening apples were observed to produce ethylene (in mesocarp and endocarp) and to eliminate it into the air[22]. It therefore seemed reasonable to assign hormonal character to ethylene.

Meanwhile, in 1929, *Went* had demonstrated with *Avena* coleoptiles[6] that during phototropic growth the coleoptile tip liberates substances which regulate the longitudinal growth of the underlying cells. The auxin subsequently obtained by *Kögl* from urine[23] could not be re-isolated later. The cell-elongating hormone (for which the term auxin was retained) of plants is indole-3-acetic acid (heteroauxin)[24]. Cell-elongation inhibitors[23] with as yet unknown structures were also found. In addition, numerous synthetic substances with cell-elongation promoting or inhibiting action are known (cf.[7]).

In 1926 it was discovered that cell-free filtrates of *Gibberella fujikuroj* culture media cause the same Bakanae disease in rice plants as the fungus itself[16]. In 1938 the active component was isolated and its constitution elucidated. Since then the term gibberellins, originally introduced in 1935, has been employed to designate this compound and similar substances.

## IV. Ethylene

Ethylene is formed above all by ripening fruit, but leaves[26] (rhubarb, calla, marshmallow, peony, asparagus) and flowers (dandelion) also liberate gases which can produce epinasty[27,28].

The formation of ethylene during metabolism is inhibited by respiratory poisons[28a]. It is considered to be related to the citric acid cycle[28b], but pyruvic acid is a better starting material than fumaric acid[28c]. Ethylene can be formed enzymatically also from linolenic acid and from methionine in the presence of copper and ascorbate[28d]. The degradation of lipids of the mitochondria caused by age likewise yields ethylene[28e].

The formation of ethylene in plant organs is induced or stimulated by auxins, the rate of formation depending on the promoter content of the relevant organ. Asymmetric distributions of auxin, as in tropisms, are also expressed in the rate of production of ethylene[29].

*Crocker et al.*[25] found an epinastic reaction in 80 out of 202 investigated species when ethylene was allowed to act on the stem. Further effects of ethylene are inhibition (in very small concentrations promotion) of the longitudinal growth of elongating organs, stimulation of root formation, acceleration of fruit ripening (respiration, chlorophyll degradation, color changes, *etc.*), chlorophyll degradation in leaves and shedding of leaves and flowers, promotion (in higher concentrations inhibition) of the sprouting of buds, promotion of callus formation, and inhibition of anthocyanin formation[28].

Ethylene chlorohydrin, acetylene, propylene, and carbon monoxide act similarly to ethylene, but the latter is 500 times more active than acetylene and propylene, and about 5000 times more active than carbon monoxide[30]. The opposite action, retardation of ripening and aging, is shown by ethylene oxide, which inhibits the formation of ethylene in the plant and acts as an ethylene antagonist[31].

Fresh, pure ethylene behaves somewhat differently towards the plant than does aged material (after storage or after regeneration following adsorption on mercury(II) perchlorate). The plants absorb ethylene stomatally, cuticularly, lenticellularly, and through other surfaces, and experiments with $^{14}C$-ethylene have shown that aged ethylene is taken up in larger quantities than the fresh gas[32].

Referred to 1 g dry substance, older plants take up more ethylene than younger ones, but the youngest leaves absorb more ethylene than older ones. More ethylene is also absorbed when the plant is kept in the dark. About two-thirds of the absorbed amount (which reaches a maximum after about 2 hours) can be removed by heating the plant. Eighteen metabolites have been detected in the residue by radiochromatography[33]. Three of these appear in the ether-soluble fraction together with carotenes[34]; the bulk of the reaction products are alcohol-soluble and are contained in the cell wall. Products of esterification with phosphoric acid are probably present[31], but there is no indication that the ethylene causes decoupling of the oxidative phosphorylation[31].

The ripening-promoting action of ethylene is utilized in the banana trade. Unripe bananas treated for 5 days with $10^{-4}$ parts of ethylene in air at 20–22 °C ripen 20 days sooner than untreated fruit. The yellow, mature color of harvested tobacco leaves can likewise be produced by treatment with ethylene (1:5000)[35].

[21] *O. H. Elmer*, Science (Washington) *75*, 103 (1932).

[22] *R. Gane*, Nature (London) *134*, 1008 (1934).

[23] *F. Kögl, A. J. Haagen-Smit*, and *H. Erxleben*, Hoppe-Seylers Z. physiol. Chem. *214*, 241 (1933).

[24] *F. Kögl, A. J. Haagen-Smit*, and *H. Erxleben*, Hoppe-Seylers Z. physiol. Chem. *228*, 90 (1934).

[25] *W. Crocker, P. W. Zimmermann*, and *A. E. Hitchcock*, Contrib. Boyce Thompson Inst. *4*, 177 (1932).

[26] *H. K. Pratt*, Plant Physiol. *29*, 16 (1954).

[27] *F. E. Denny* and *P. Miller-Lawrence*, Contrib. Boyce Thompson Inst. *7*, 97 (1935).

[28] *H. Molisch*: Der Einfluß einer Pflanze auf die andere, Allelopathie. Fischer, Jena 1937, p. 44.

[28a] *M. Meheriuk* and *M. Spencer*, Nature (London) *204*, 43 (1964).

[28b] *S. P. Burg* and *E. A. Burg*, Nature (London) *203*, 869 (1964).

[28c] *M. S. Gibson*, Dissertation, Purdue University, 1963.

[28d] *M. Liebermann* and *L. W. Mapson*, Nature (London) *204*, 343 (1964).

[28e] *M. Spencer* and *A. O. Olson*, Nature (London) *205*, 699 (1965).

[29] *F. B. Abeles* and *B. Rubinstein*, Plant Physiol. *39*, 963 (1964).

[30] *W. Crocker*, Bot. Gaz. *77*, 322 (1924).

[31] *M. Liebermann, S. Asen*, and *L. W. Mapson*, Nature (London) *204*, 756 (1964).

[32] *W. C. Hall, C. S. Miller*, and *F. A. Herrero* in: Proc. 4th International Conference on Plant Growth Regulation. Iowa State University Press 1961, p. 751.

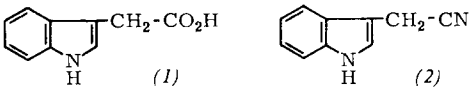
[33] *D. R. Buhler, E. Hansen*, and *S. H. Wang*, Nature (London) *179*, 48 (1957).

[34] *L. Genevois*, VIII. Congrés International Botanique, Rapports et Communications, Pierre André, Paris 1954. Section 11/12, p. 403.

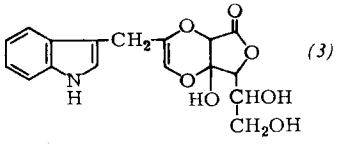
[35] Arbeiten der landwirtschaftlichen Versuchsstation Limburgerhof (1939), p. 241.

## V. Auxins

Auxins occur in all plants. They are found predominantly in pollen seeds, in the developing seedling, in the latter's endosperm, coleoptile and root tips, and also in the bud vegetation points of older plants. The most important auxin, invariably present, is heteroauxin [36], indole-3-acetic acid *(1)* [37,38]. Many plants also contain indole-3-acetaldehyde, indole-3-butyric acid, indole-3-acetonitrile *(2)* and further indole derivatives [39] such




as 2-hydroxyindole-3-acetic acid and ethyl indole-3-acetate, with similar cell-elongating action. Indole-3-acetonitrile is ten times as active as indole-3-acetic acid in the paste test. Indole-3-acetic acid is formed from tryptophan *via* ascorbigen *(3)* [39,39a].




Numerous authors produced evidence that cell-elongation hormones other than indole derivatives exist, but did not isolate them. Mixtures of unsaturated and saturated $C_{20}$ and $C_{22}$ fatty alcohols with cell-elongating action have been found in tobacco plants [40].

The physiological effects of indole-3-acetic acid are [41–43]:

1. In small concentrations promotion, in large concentrations inhibition of longitudinal cell growth and the related water absorption of the cells;
2. Promotion of cell division of the meristematic tissue (stem, hypocotyl);
3. Promotion of root formation even on tissues which do not normally form roots, but inhibition of root growth, except in smallest concentrations;
4. Promotion of callus formation and callus growth;
5. Inhibition of budding and growth of auxiliary buds and bud formation;
6. Influencing of leaf, flower, and fruit shedding;
7. Influencing of flower formation;
8. Formation of parthenocarpic fruit (infertile seedless fruit) [43a];
9. Promotion of respiration and protein formation.

The concentration *vs.* activity curves exhibit a maximum [7,8], *i.e.* there is promotion at small concentrations, and inhibition at larger concentrations (Fig. 1). The optimum concentration for root growth is $10^{-10}$, for bud growth $10^{-8}$, for stem growth $10^{-5}$, and for flower promotion $10^{-4}$ M [44]. Optimum root formation occurs at concentrations which almost completely inhibit the longitudinal growth of the roots formed.

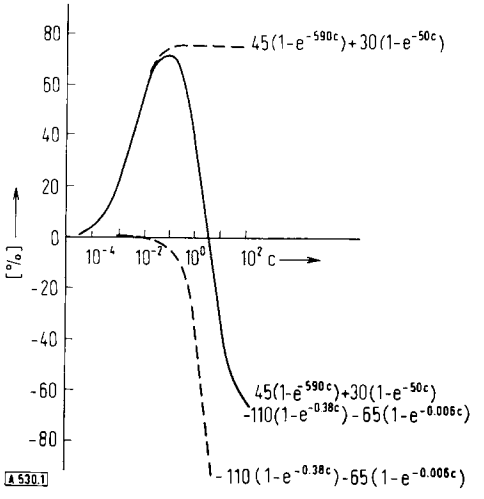
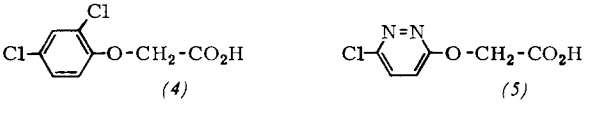



Fig. 1. Concentration—activity curve of indole-3-acetic acid (full line) and the derived promotion (top) and inhibition components (bottom, broken lines).
Ordinate: Increase in coleoptyl length in % relative to untreated coleoptyls;
Abscissa: Concentration of indole-3-acetic acid, wt-%.

Certain synthetic substances have an effect similar to that of the auxins; these include α-naphthylacetic acid, 2,4-dichlorophenoxyacetic acid *(4)* and other phenoxyacetic acid derivatives, 6-chloropyridazine-3-yloxyacetic acid *(5)*, and carboxymethyl *N,N*-dimethyldithiocarbamate [44].




Like indole-3-acetic acid, these compounds show maxima in their concentration-activity curves. In contrast, eosin, tetrachlorofluorescein, tetraiodofluorescein, 2 3,5-triiodobenzoic acid, β-naphthoxyacetic acid, and 2,4,6-trichlorophenoxyacetic acid yield decreasing concentration *vs.* activity curves without a maximum [45].

In order to show auxin activity a molecule evidently must possess certain dimensions [46]; a distance of 5.5 Å is postulated to be necessary between the hydroxyl oxygen in the carboxyl group and an atom in the phenyl or indolyl ring or in a corresponding radical able to take up a positive charge [47] (Fig. 2).


[36] *F. Kögl* and *D. G. F. Kostermans*, Hoppe-Seylers Z. physiol. Chem. *228*, 113 (1934).

[37] *A. J. Haagen-Smit*, *W. B. Dandliker*, *S. H. Wittwer*, and *A. E. Murneck*, Amer. J. Bot. *33*, 118 (1946).

[38] *L. C. Post*, Dissertation, Universität Utrecht, 1959.

[39] *C. H. Fawcett*, Ann. Rev. Plant Physiol. *12*, 345 (1961).

[39a] *G. v. Raussendorf-Bargen*, Planta *58*, 471 (1962).

[40] *A. J. Vlitos* and *D. G. Crosby*, Nature (London) *184*, 462 (1959).

[41] *F. F. Went* and *K. v. Thimann*: Phytohormones. MacMillan, New York 1937.

[42] *H. Söding*: Die Wuchsstofflehre. Thieme, Stuttgart 1952.

[43] *L. J. Audus*: Plant Growth Substances. 2nd Edit., Leonard Hill, London 1953.

[44] *K. V. Thimann* in *W. W. Nowinski*: Fundamental Aspects of Normal and Malignant Growth. Elsevier, Amsterdam 1960, p. 748.

[45] *H. Linser*, Mh. Chem. *85*, 196 (1954).

[46] *H. Linser* and *R. Kirschner*, Naturwissenschaften *47*, 254 (1960).

[47] *W. L. Porter* and *K. V. Thimann*: Abstracts of the 9th International Botanical Congress, Montreal. University of Toronto Press, Toronto 1959, p. 305.

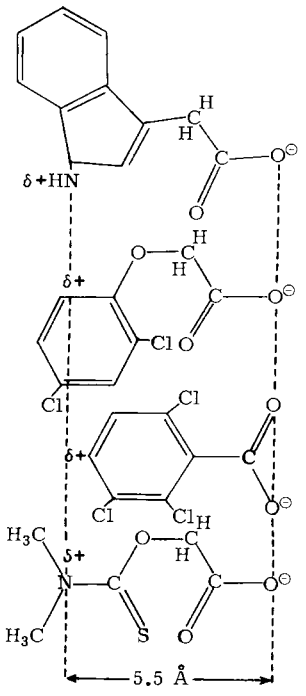


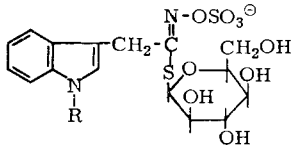

Fig. 2. Distance between atoms of opposite charge in indole-3-acetic acid and in the most active auxins of three other series.

In structure and size, bis-(2,4-dichlorophenoxy)acetic acid resembles eosin, tetrachlorofluorescein, and tetraiodofluorescein, and possesses an inhibitory character [48]. The recently discovered active substance methyl 2,7-dichloro-9-hydroxyfluorene-9-carboxylate [49] has a similar molecular structure. Despite numerous attempts, the relationship between constitution and activity has not yet been elucidated.

Since longitudinal growth is linked closely with protein synthesis, inhibitors of the latter, such as chloramphenicol, also inhibit the former [49a].

All parts of the plant rapidly take up auxins from external sources. Absorption is frequently augmented when the side-chain of the molecule is esterified with a lower alcohol, *e.g.* with butanol. Evidently, the auxins can then also be absorbed from the cell boundary layers *via* the lipid phase. The distribution in the plant is predominantly in the basal direction and is faster at 25 to 30 °C than at 15 °C [50]; apical transport is small and little hormone is moved transversally. This is the reason for the curving observed after one-sided application of the growth agent. Changes in the magnitude of the transverse transport lead to so-called tropistic growth curvatures. On this basis, phototropism can be interpreted as the action of light not on auxin itself but on its distribution downwards from the coleoptile tip, with the auxin content of the illuminated side remaining smaller than that of the unexposed side [51].

During metabolism indole-3-acetic acid is decarboxylated by an indole-3-acetic acid oxidase and loses its activity. Auxin oxidase is inhibited by chlorogenic acid [52]. Indole-3-acetic acid taken up from outside was found partly as *N*-indolylacetyl aspartate and partly as 1-(indolylacetyl)-β-D-glucose. Analogous derivatives are formed after absorption of α-naphthylacetic acid [51a]. Binding to protein has also been observed [52]. Indolylacetylglucose is formed from indole-3-acetic acid and uridine diphosphoglucose. In the biosynthesis of indolylacetyl aspartate an energy-rich compound, perhaps indolylacetyl-CoA, is a likely intermediate [53]. In *Brassica* species, large quantities of indole-3-acetic acid [8] are present in the inactive form as glucobrassicin *(6)* and neoglucobrassicin *(7)* [53]. At pH 4 these are rapidly split enzymatically into indole-3-acetonitrile, glucose, sulfate, sulfur, and hydrogen sulfide, and at pH 7 glucose, sulfate, thiocyanate, and 3-hydroxymethylindole are formed. The last-named compound combines with ascorbic acid to form ascorbigen *(3)* [54].



*(6)*, R = H
*(7)*, R = $OCH_3$

Synthetic substances of the auxin type have been used in agriculture since 1941 in England and the United States, and since 1946 also in continental Europe to combat weeds (cf. [55]). In particular, 2,4-dichlorophenoxyacetic acid and some of its derivatives and analogues have been used successfully to combat dicotyledous weeds in cereal cultures. In horticulture, auxins are used to promote root formation on grafted plants and to produce parthenocarpic fruit, and in orchards for thinning out flowers and fruit and for prevention of premature fruit dropping.

## VI. Gibberellins

Gibberellins are produced not only by fungi but also by higher plants. For example, gibberellins $A_1$, $A_5$, $A_6$ and $A_8$ [*(8)*, *(12)*, *(13)*, and *(15)*] have been isolated from the seed of *Phaseolus multiflorus* [56]. Substances with gibberellin-like action but of unknown structure have been detected in numerous plants and plant organs [57].

[48] *H. Linser* in *R. L. Wain* and *F. Wightman*: The Chemistry and Mode of Action of Plant Growth Substances. Butterworths, London 1956, p. 141.

[49] *G. Schneider*, Naturwissenschaften *51*, 416 (1964).

[49a] *L. D. Nodeen* and *K. V. Thimann*, Plant Physiol. *40*, 193 (1965).

[50] *Y. Vardar*, Ber. schweizer. bot. Ges. *74*, 229, 236 (1964).

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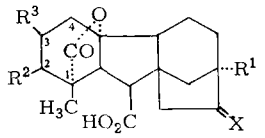


| | | X | $R^1$ | $R^2$ | $R^3$ | |
|---|---|---|---|---|---|---|
| *(8)* | $A_1$ | $=CH_2$ | OH | OH | H | |
| *(9)* | $A_2$ | $-OH$ | H | OH | H | |
| | | $-CH_3$ | | | | |
| *(10)* | $A_3$ | $=CH_2$ | OH | OH | H | $\Delta^{3,4}$ |
| *(11)* | $A_4$ | $=CH_2$ | H | OH | H | |
| *(12)* | $A_5$ | $=CH_2$ | OH | H | H | $\Delta^{2,3}$ |
| *(13)* | $A_6$ | $=CH_2$ | OH | H | H | + 1 OH |
| *(14)* | $A_7$ | $=CH_2$ | H | OH | H | |
| *(15)* | $A_8$ | $=CH_2$ | OH | OH | OH | |
| *(16)* | $A_9$ | $=CH_2$ | H | H | H | |
| *(17)* | $A_{10}$ | $-OH$ | H | H | H | |
| | | $-CH_3$ | | | | |

Rapidly growing tissue always contains particularly high concentrations of gibberellins [58], but unripe seeds contain about 100 times as much [59] and also form these substances during growth [60].

2. Promotion of hypocotyl growth [65];

3. Promotion of germination, particularly of light germinators in the dark [66];

4. Promotion of the sexual development of flowers [67];

5. Promotion of flower formation [68];

6. Formation of parthenocarpic fruit and promotion of fruit flesh growth [69];

7. Interruption of the rest period of buds and underground storage organs [70, 73a];

8. Influencing of flower formation [71] and the photoperiodic behavior of flowering plants [72];

9. Influencing of the shape and size of the leaves [73, 73a];

10. Promotion of cell division in the cambial zone [74];

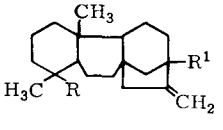
11. Influencing of the activity of α- and β-amylase, protease, and catalase [75], lessening of the activity of indole-3-acetic acid oxidase [76].

Ten gibberellins are known [77, 78], the activities of which differ in different plants and in different physiological systems (Table 1). Evidently, the gibberellins are

Table 1. Relative effectiveness of gibberellins $A_1$—$A_9$ relative to $A_7$ = 100 % [80].

| Gibberellin | Dwarf pea, stem growth | Dwarf maize, leaf shedding | Lettuce, hypocotyl | Cucumber, hypocotyl | Lettuce, seed germination in the dark | Cucumber, formation of male flowers on female plants | Tomatoes, parthenocarpy |
|---|---|---|---|---|---|---|---|
| $A_1$ *(8)* | 100 | 33 | 2 | 2 | 3 | 8 | 50 |
| $A_2$ *(9)* | 33 | 5 | 2 | 2 | 0 | 40 | 11 |
| $A_3$ *(10)* | 330 | 50 | 50 | 2 | 10 | 27 | 33 |
| $A_4$ *(11)* | 16 | 50 | 16 | 100 | 100 | 80 | 100 |
| $A_5$ *(12)* | 33 | 100 | 2 | 0.2 | 3 | 2 | 330 |
| $A_6$ *(13)* | 33 | 5 | 0.5 | 0.2 | 0 | 3 | 25 |
| $A_8$ *(15)* | 3 | 0.5 | 0 | 0.02 | 0 | 2 | 3 |
| $A_9$ *(16)* | 0 | 100 | 16 | 100 | 0 | 40 | 20 |

Gibberellins are formed from mevalonic acid [62, 63]. Kaurene *(18)*, kauranol, and steviol *(19)* are metabolized to gibberellic acid [63a,b].



*(18)*, R = $CH_3$, $R^1$ = H
*(19)*, R = $CO_2H$, $R^1$ = OH

The essential physiological effects of the gibberellins (0.05–0.5 ppm) are [61]:

1. Increase of the internodal length of growing plants even in hereditary rosette or dwarf growth, so that the plants attain the normal elongated habit [64];

not only species-specific but also system-specific. Methods of detecting gibberellins are given by *Knapp* [79a].

The acetyl, diacetyl, monobenzoyl, and butyryl derivatives of gibberellin, as well as the sodium, potassium,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and calcium salts are particularly active when administered *via* the leaves. Ethyl, butyl, isopropyl, and octyl gibberellates, which are effective when administered to the roots, develop no activity when given *via* the leaf[79]. The plant absorbs gibberellins from aqueous solutions and lanolin pastes, and distributes them in their tissues also in the apical direction, *i.e.*, translocates them in a nonpolar manner[82].

Synthetic substances with analogous effects are not yet known. 2-Chloroethyltrimethylammonium chloride (chlorocholine chloride) reduces the internodal length[81], and therefore seems to represent a gibberellin antagonist but probably inhibits its synthesis[81a,b].

Longitudinal growth of pea seedlings growing in complete darkness is not promoted by gibberellins[83], but the latter do eliminate the inhibitory effect of red light[84] and also that of infrared light in tomatoes[85]. Red light inhibits the lengthening of the stem and the hypocotyl but is a requisite for growth promotion by gibberellins[86]. Inhibitions by blue or green light are also eliminated by gibberellins[87].

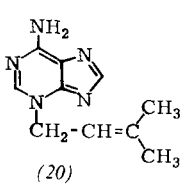
Little is known about the metabolism of the gibberellins and about possible inactive representatives.

General application of gibberellins in agriculture and horticulture is limited by their high cost. They accelerate germination of barley, reduce the malting process by 48 hours, and decrease shrinkage during malting by 1 %[88,89]. After the sowing of grasses characterized by early competition, gibberellins are able to prevent disadvantageous effects on individual species and to eliminate their summer cessation of growth[90], but practical successes have been small[91]. Widespread use is made of gibberellins in dwarf plant culture[61,92–94] (improvement in flower quality, number of flowers, time of flowering) and in fruit growing and horticulture for parthenocarpic fruit formation (*e.g.* pears) or modifying the size of the fruit[95,96].

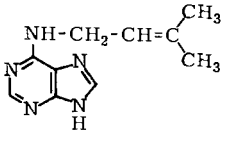
## VII. Kinins

Kinins are phytohormones which initiate cell division in tissues, including those whose cells do not divide in the absence of kinins even when optimally nourished and supplied with other phytohormones[97]. Since the term kinin has a different meaning in animal physiology, *Thimann* proposed the name cytomin, but this has not been adopted.

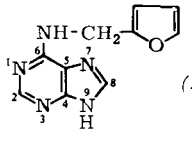
Kinins occur in the endosperm of maize[98] and coconut[99,100], and in other plant organs[97]. Studies by *Mothes* and *Engelbrecht*[101] have demonstrated that these substances are formed in the root and are only then transported to the leaves. Pea seedlings were found to contain a substance which on chromatography behaves like kinetin[102]. The growth factor in maize was found to be 6-(4-hydroxy-3-methyl-2-butenyl)aminopterine and was termed zeatin[103]. An inactive compound, triacanthine, 6-amino-3-(γ,γ-dimethylallyl)-purine *(20)*[104,105], occurs in *Gleditschia triacanthos*. On being heated in an autoclave *(20)* rearranges to 6-(γ,γ-dimethylallylamino)purine *(21)*, which is about 10 times as active as kinetin, 6-furfurylaminopurine *(22)*[107,108], which is formed from nucleic acid-containing material[106] and has not yet been found in



*(20)*



*(21)*



*(22)*

plants[97]. Kinetin can be prepared in large quantities, and its effects, which have been studied in detail, are[109]: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1. Acceleration of cell division and the related DNA synthesis;

2. Acceleration [110–112] or inhibition [113,114] of cell enlargement in leaves;

3. Promotion of leaf bud formation [115, 116] and elimination of the related polarity [117], as well as the mutual inhibition of longitudinal growth [118];

4. Promotion of root growth and root formation; occasionally inhibition;

5. Influencing of leaf shape [119] and leaf pigments [120, 121];

6. Promotion of germination [109];

7. Interruption of the rest period [122, 123];

8. Increase in respiration [112] and of RNA and DNA synthesis [124, 125];

9. Inhibition of protein degradation, rejuvenation of the leaves [126];

10. Translocation of low-molecular nitrogen compounds [127] but not of inorganic ions [128].

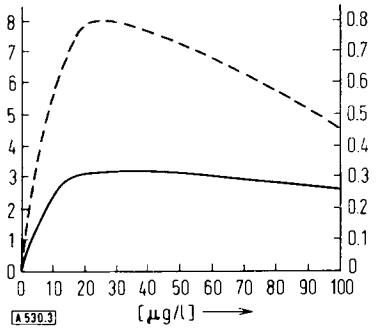


Fig. 3. Concentration–activity curves of kinetin (kinetin callus test after [129]).

Abscissa: Kinetin concentration, µg/l;
Left-hand ordinate and broken curve: Fresh substance (g/callus);
Right-hand ordinate and continuous curve: Dry substance (g/callus).

The sometimes contradictory results on the cell elongation response and the course of the concentration-activity curves (Fig. 3) [129] show that the promoting effect at low concentrations is countered by inhibition of the same processes at high concentrations. Tests for kinins are described by *Miller* [129a].

No kinetin antagonists are known; chloramphenicol inhibits protein synthesis and hence kinetin action, but the relation is probably indirect.

Adenine has similar effects to kinetin on bud formation [130], suggesting that the intact purine ring is essential to the activity. However, 8-azakinetin has also been found to be active [131, 132]. The amino group is not essential, and can be replaced by sulfur [109]. Moreover, the furan ring of the kinetin can be replaced by a benzene ring without loss in activity. Tetrahydrofurfuryl, pyridyl, naphthyl, cyclohexyl, piperidyl, and other rings also yield active compounds, and even 6-alkylaminopurines are active [109]. It is therefore reasonable to assume that the side chain and its ring linked to the amino group impart lipid affinity to the molecule. The methylene group between the amino group and the furan ring can also be dispensed with. The position of the amino group on C-6 seemed to be essential, but 1-benzoylaminopurine and 1-(γ,γ-dimethylallylamino)-purine are also active [133].

No reliable evidence is available whether triacanthin [134], an alkaloid of *Holarrhena floribunda* and *Chidlovra sanguinea* occurring in amounts of up to 0.7 % of the dry substance [129], can be converted enzymatically into an active kinin. Possibly it plays a role similar to that of glucobrassicin in the case of auxins.

## VIII. Morphological Regulators

One effect produced by synthetic auxin analogues of the 2,4-dichlorophenoxyacetic acid type was omitted from the discussion of this class of compounds, because it is absent in natural auxins or at any rate has not been achieved with indole-3-acetic acid. This property is the change in the shape of leaves, flowers, or fruit [14], which can lead to malformations but frequently also to regular and more balanced forms. The process involves an alteration of the morphological characteristics which are normally used to characterize and demarcate species, and which are considered as genetically fixed. In *Erodium*, leaf shapes are produced that are not species-characteristic and could belong to a new species [135]. Substances which produce this effect are

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called morphological regulators. They include 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, 2,3,5-triiodobenzoic acid, and some similar substances; also, because of their action on the species- and type-conditioned habit, the gibberellins and their antagonists. Although no morphological regulators have so far been obtained from plants, it is reasonable to assume that the plant normally uses hormones to produce its characteristic leaf and flower form.

## IX. Hormones of Unknown Constitution

The sex of fungi and flower formation in higher plants presumably is determined by hormonal factors. Sexual process-regulating glucoproteins acting as hormones have been found in the alga *Chlamydomonas* [136]. *Raper* [137] has shown that four hormones (A,B,C,D) are involved in the sex differentiation of *Achlya*. The number and growth of the antheridial hyphae is determined by hormone A. The male hyphae then produce hormone B which causes formation of oogonia or primordial ova of the female sexual organs. For some time, the mature oogonia form hormone C, which stimulates the male hyphae to chemotropic growth and results in formation of the gametangium. The fully differentiated antheridium finally forms hormone D, which in turn causes formation of female gametes. This interplay of hormones in lower plants suggests that several hormones may be involved also in flower formation. Grafting tests also indicate the existence of flower-forming hormones. Flowers have been produced in plants in the non-flowering state with extracts of plants about to flower [138–144], but so far no specific flower-forming hormone is known.

Hormones probably participate in the photoperiodic behavior of plants, being formed in dependence on the lighting conditions with their relative quantities determining the physiological effect. Possibly, short-day conditions lead to the formation of a substance K, while long days lead to a substance L [145]. It seems that K is formed and decomposed more quickly than L, and that the K:L ratio governs flower formation. In many respects, gibberellins act similarly to substance L, but the identity of the two factors has not been proved.

## X. Outlook

The great expectations of increased crop yields raised by the term "growth substances" have not been fulfilled. Auxins can accelerate certain development processes, but these accelerators generally produce no effect on the overall yield. Any aggregate increase in the yield of cultured plants by phytohormones is due not so much to an influence on growth, but to control of the differentiation steps by which the yield-determining factors (assimilated area, organ formation, habit, life span of leaves) or morphological and physiological properties of the plants are altered.

Externally applied hormones are subject to widely different conditions in the individual types of plants in regard to absorption and endogenic hormone relations, so that widely varying reactions can ensue. A precise study of these relationships before application of phytohormone-analogous substances is necessary.

Absence of suitable tests makes the detection and study of individual hormones, particularly those participating in differentiation processes, very difficult and in some cases impossible. Study of the effect of synthetic hormone analogues is simpler than that of native plant hormones, but it is the investigation of these latter substances which is essential for the elucidation of the mechanism of plant development with respect to shape and yield.

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# Multienzyme Complexes

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In 1948 *D. E. Green*[2] termed the mitochondrial enzymes the *cyclophorase complex*, in order, as he later commented[3] "... to signify that the complex was a unit of enzyme action and not a chance mixture of several hundred enzymes. ... this complex was visualized as an organized mosaic of enzymes in which each of the large number of component enzymes was uniquely located to permit efficient implementation of consecutive reaction sequences".

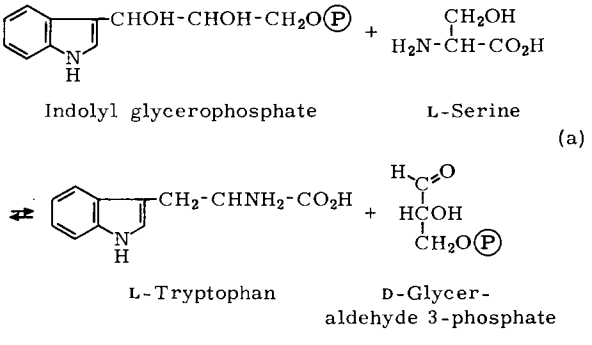
These words contain the concept of the multienzyme complex: ordered association (not involving peptide linkages) of various enzymes that catalyse successive steps in a reaction sequence. The present paper deals with recent findings regarding the properties of such complexes, and the question whether the concept represents a biological principle is discussed.

Predominantly protein-chemical aspects of the association of enzymes were recently described by *Sund* and *Weber*[4], and the "macromolecular organization of enzyme systems" by *Reed* and *Cox*[5].

## I. Multienzyme Complexes in a Narrower Sense

### 1. Tryptophan Synthetase

A clear and relatively simple example is the tryptophan synthetase from *Escherichia coli*. In the presence of pyridoxal phosphate, the enzyme catalyses the last step [Eq. (a)] in the reaction chain leading to the biosynthesis of tryptophan:




It can also[6,7] bring about the cleavage

indolyl glycerophosphate $\rightleftarrows$ indole + D-glyceraldehyde 3-phosphate (b)

and the condensation

indole + L-serine $\rightleftarrows$ L-tryptophan (c)

The extensive investigations by *Yanofsky* and coworkers, which made this enzyme a component of one of the best-known gene enzyme systems, also showed that the synthetase consists of two sub-units, the proteins A and B. The isolated crystallizable protein A (molecular weight about 30000[8]) consists of only one polypeptide chain $\alpha$[9], while the protein B ($M$ = 117000) consists of two chains ($\beta_2$)[10].

The physiological reaction (a) can take place only when the proteins A and B are in contact with each other; indole does not occur as a free intermediate[6,11].

Isolated protein A is inactive in reactions (a) and (c), but can bring about reaction (b) (not requiring pyridoxal phosphate, as expected) with about 1 % of the activity exhibited in the presence of B[12]. On the other hand, isolated B containing pyridoxal phosphate (2 moles of coenzyme per mole of protein) does not catalyse reactions (a) and (b), but catalyses the condensation (c) with 3 to 10 % of the activity exhibited in the presence of A[12]. It was later found that protein B can also act as an L-serine deaminase[13]

L-serine $\rightleftarrows$ pyruvate + $NH_3$ (d)

Addition of A causes almost complete inhibition of B in reaction (d).

There is strong evidence that the catalytically active centers of the respective complementary proteins are not involved in the activation of A in reaction (b) and in that of B in reaction (c). Protein B which has lost its enzymatic activity as a result of mutation can activate A in reaction (b) in the same way as unaltered protein B, while the reverse is true of A which has been inactivated by mutation. Moreover, the activity of B in reaction (c) is increased by a factor of about 20 in the presence of a high concentration of $NH_4^+$ ions[14]. Finally, *Hatanaka*

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[2] *D. E. Green, W. F. Loomis,* and *V. H. Auerbach,* J. biol. Chemistry *172,* 389 (1948).

[3] *D. E. Green,* Harvey Lectures *52,* 177 (1958).

[4] *H. Sund* and *K. Weber,* Angew. Chem. *78,* 217 (1966); Angew. Chem. internat. Edit. *5,* 231 (1966).

[5] *L. J. Reed* and *D. J. Cox,* Annu. Rev. Biochem. *35,* in press.

[6] *I. P. Crawford* and *C. Yanofsky,* Proc. nat. Acad. Sci. USA *44,* 1161 (1958).

[7] *I. P. Crawford,* Biochim. biophysica Acta *45,* 405 (1960).

[8] *U. Henning, D. R. Helinski, F. C. Chao,* and *C. Yanofsky,* J. biol. Chemistry *237,* 1523 (1962).

[9] *B. C. Carlton* and *C. Yanofsky,* J. biol. Chemistry *237,* 1531 (1962).

[10] *D. A. Wilson* and *I. P. Crawford,* Bacteriol. Proc. USA *1964,* 92.

[11] *C. Yanofsky* and *M. Rachmeler,* Biochim. biophysica Acta *28,* 640 (1958).

[12] *C. Yanofsky,* Bacteriol. Rev. *24,* 221 (1960).

[13] *I. P. Crawford* and *J. Ito,* Proc. nat. Acad. Sci. USA *51,* 390 (1964).

[14] *M. Hatanaka, E. A. White, K. Horibata,* and *I. P. Crawford,* Arch. Biochem. Biophysics *97,* 596 (1962).

and *Crawford*[15] have isolated a mutant of *E. coli* producing a defective protein B, which by itself is inactive in reaction (c); in the presence of A, however, the activities of all three tryptophan synthetase reactions are observed.

The two proteins are only loosely associated[16]. L-Serine and pyridoxal phosphate are essential to the complex formation between A and B. Centrifugation of a mixture of A and B in a sucrose density gradient leads to practically complete separation of the components A (2.7 S) and B (5.1 S), while the associated A–B complex (6.4 S) appears after incubation of the mixture with L-serine and coenzyme[16]. The completely associated A–B complex, tryptophan synthetase, contains two moles of A to one mole of B, and its probable polypeptide-chain formula is therefore $\alpha_2\beta_2$[16,17].

The enzymatic activities of the components change, by several orders of magnitude in some cases, on complex formation. The activation by $NH_4^+$ and the behavior of the various proteins which have become inactive as a result of mutation provide very strong evidence that complex formation *per se* is responsible for the change in enzymatic activity. Association presumably involves changes in the conformation of the proteins, for which the active site of the complementary component is not directly responsible.

It is interesting to compare the tryptophan synthetase of *E. coli* (or other enterobacteria) with that of *Neurospora*. The neurospora enzyme[18,19] ($M$ = 135000) so far has not been dissociated into enzymatically active sub-units. On reduction with mercaptoethanol in 5 M guanidinium chloride, the protein dissociates into four sub-units, possibly made up of two identical pairs[19]. This result led *D. M. Bonner*[20] to assume that the two tryptophan synthetases represent two different stages of evolution. It is conceivable that the tryptophan synthetase reaction initially proceeded in separate steps, with indole as a free intermediate. With the development of the association of the two proteins, indole is no longer liberated; the binding of the two proteins may have become "tighter" during the further evolution.

## 2. Pyruvate and α-Ketoglutarate Dehydrogenases

In animal tissues, as well as in many fungi and bacteria, the principal route for the degradation of the two α-keto acids is by oxidative decarboxylation:

$$R{-}COCO_2H + CoASH + NAD^+ \rightarrow R{-}COSCoA + CO_2 + NADH + H^+ \quad (e)$$

It is now known[5,21] that this overall reaction (e) proceeds *via* the steps (f) to (k).

$$R\text{-}CO\text{-}CO_2H + TPP\text{-}E1 \rightleftarrows R\text{-}CHOH\text{-}TPP\text{-}E1 + \underline{CO_2} \quad (f)$$

$$R\text{-}CHOH\text{-}TPP\text{-}E1 + \text{S—S (E2)} \rightleftarrows TPP\text{-}E1 + \text{SH S-CO-R (E2)} \quad (g)$$

$$\text{SH S-CO-R (E2)} + CoA\text{-}SH \rightleftarrows \text{SH SH (E2)} + \underline{R\text{-}CO\text{-}SCoA} \quad (h)$$

$$\text{SH SH (E2)} + FAD\text{-}E3_{ox.} \rightleftarrows \text{S—S (E2)} + FAD\text{-}E3_{red.} \quad (i)$$

$$FAD\text{-}E3_{red.} + NAD^+ \rightleftarrows FAD\text{-}E3_{ox.} + \underline{NADH + H^+} \quad (k)$$

The best-known case is that of the pyruvate dehydrogenase of *E. coli*, which has been isolated as a homogeneous protein ($M = 4.8\times10^6$)[22]. Electron micrographs[23] of the complex show (Fig. 1) a polyhedral structure with a diameter of 300 to 350 Å.

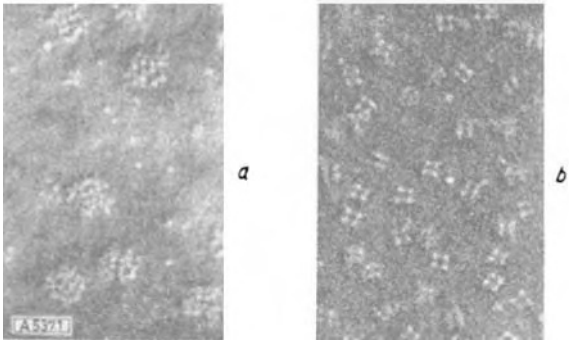


Fig. 1a). Pyruvate dehydrogenase complex from *E. coli*. Magnification factor 260000. b) Lipoate reductase transacetylase component of the enzyme complex, same magnification. The tetrad structure of the component is visible in the center of the complex (1a). In these projections, the diameter of the complex is about 300 Å and that of the components is about 120 Å. Both samples were obtained by negative staining with phosphotungstic acid.

The complex can be dissociated, under mild conditions, into three proteins[24], to which the activities of reactions (f) to (k) could be assigned with the aid of model reactions: the thiamine pyrophosphate(TPP)-dependent pyruvate decarboxylase (E1), the lipoate reductase transacetylase (E2) containing lipoic acid, and the flavoprotein dihydrolipoate dehydrogenase (E3). The proteins re-associate spontaneously *in vitro*[24]; E1 does

[15] *M. Hatanaka* and *I. P. Crawford*, Bacteriol. Proc. USA *1965*, 88.

[16] *T. Greighton* and *C. Yanofsky*, J. biol. Chemistry *241*, 980 (1966).

[17] *D. Wilson* and *I. P. Crawford*, J. biol. Chemistry *240*, 4018 (1965).

[18] *W. C. Mohler* and *S. R. Suskind*, Biochim. biophysica Acta *43*, 288 (1960).

[19] *M. Carsiotis, E. Apella, P. Provost, J. Germershausen*, and *S. R. Suskind*, Biochem. biophysic. Res. Commun. *18*, 877(1965).

[20] *D. M. Bonner, J. A. DeMoss*, and *S. E. Mills* in *V. Bryson* and *H. J. Vogel*: Evolving Genes and Proteins. Academic Press, New York 1965, p. 305.

[21] *I. C. Gunsalus* in *W. D. McElroy* and *B. Glass*: The Mechanism of Enzyme Action. Johns Hopkins Press, Baltimore 1964, p. 545.

[22] *M. Koike, L. J. Reed*, and *W. R. Carroll*, J. biol. Chemistry *235*, 1924 (1960).

[23] *H. Fernandez-Moran, L. J. Reed, M. Koike*, and *C. R. Willms*, Science (Washington) *145*, 930 (1964).

[24] *M. Koike, L. J. Reed*, and *W. R. Carroll*, J. biol. Chemistry *238*, 30 (63).

not associate with E3, but E2 binds both E1 and E3. One molecule of the complex contains about twelve molecules of the decarboxylase ($M$ = 1.83×10⁵), one molecule of E2 ($M$ = 1.6×10⁶), and about six molecules of the flavoprotein ($M$ = 1.12×10⁵) [5]. The lipoate reductase transacetylase is probably centrally situated (cf. Fig. 1), and surrounded by the two other enzymes.

The lipoate reductase transacetylase has also been reversibly dissociated; it dissociates at pH 2.6 into subunits having $M \approx 7\times10^4$ [5]. The enzyme contains one mole of lipoic acid per 3.5×10⁴ g of protein, and may therefore consist, not of about 24, but of about 48 polypeptide chains having $M$ = 3.5×10⁴. The composition of the decarboxylase is not yet known; that of the flavoprotein will be discussed below. The lipoic acid is covalently bound to the ε-amino group of a lysine residue [25]. The dithiolan ring of the coenzyme must react with (a) the hydroxyethyl TPP of the decarboxylase, (b) the flavin-adenine dinucleotide (FAD) of the dihydrolipoate dehydrogenase, and (c) the coenzyme A. Since the intermediates of the overall reaction remain bound to the enzyme, there appear to be steric difficulties opposing the interaction of one and the same lipoic acid residue with all the prosthetic groups mentioned. The lipoic acid:FAD ratio in the complex is about 4:1. The lipoic acid linkage forms a "flexible arm" (about 14 Å long), and the coenzyme may be able to rotate about the α-C atom of the lysine residue in the enzyme complex [24, 26]. It was shown that all the lipoic acid residues can take part in the oxidation of pyruvate. It was therefore suggested [24] that different lipoic acids could participate in the various reaction steps (Fig. 2), which indeed would be a remarkable type of electron transport in a protein molecule.

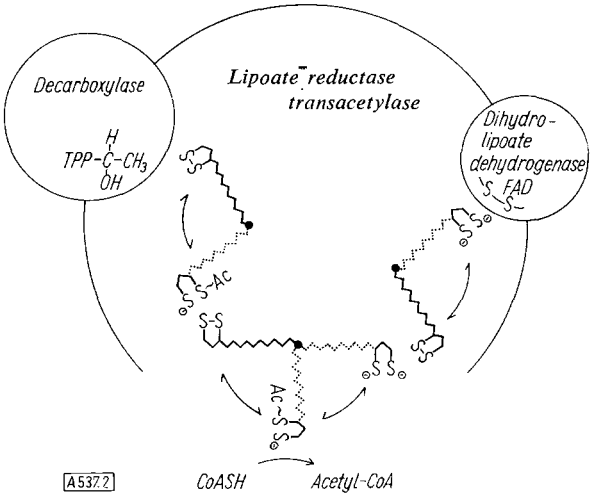
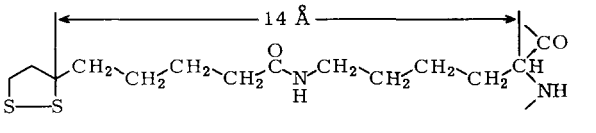



Fig. 2. Scheme of the hypothetical interaction between the coenzymes of the pyruvate dehydrogenase [24]. The lipoic acid residue pivots about the α-C atom of a lysine residue.




[25] *H. Nawa, W. T. Brady, M. Koike,* and *L. J. Reed,* J. Amer. chem. Soc. *82,* 896 (1960).

[26] *R. M. Bock* and *R. S. Criddle,* quoted in *D. E. Green,* Comparat. Biochem. Physiol. *4,* 81 (1962).

A similar situation is found with the α-ketoglutarate dehydrogenase of *E. coli* ($M$ = 2.4×10⁶) [22, 24]. This also could be reversibly dissociated into α-ketoglutarate decarboxylase, lipoate reductase transsuccinylase, and dihydrolipoate dehydrogenase. The flavoproteins of the two α-ketoacid dehydrogenases are functionally interchangeable, that of the pyruvate dehydrogenase being bound by the lipoate reductase transsuccinylase and *vice versa*; no "hybrid" binding of the decarboxylases takes place [27].

It is possible that the two flavoproteins are identical [5, 28]. If this were the case, it would raise an interesting problem in connection with the regulation of the synthesis of the dihydrolipoate dehydrogenase, since the syntheses of the pyruvate and α-ketoglutarate dehydrogenases are not regulated by the same mechanism [29].

It is not yet known whether the structure of the enzyme complex in the cell is the same as that in which it is obtained after purification. However, since the intermediates of the overall reaction (e) remain bound to the enzyme, some form of association of the enzymes is necessary. It is conceivable that the large complex isolated is an artifact resulting from the aggregation of smaller complexes that were bound to other structures in the cell. There are several arguments against this view; *e.g.*, mutants in which the decarboxylase component has lost its enzymatic activity were found to contain a "partial" complex consisting of the lipoate reductase transacetylase and the flavoprotein [30]. This partial complex appears to be the same as that obtained by the removal of the decarboxylase from the pyruvate dehydrogenase complex *in vitro*.

Concerning the α-keto acid dehydrogenases from animal cells in which the enzymes are components of mitochondria, the reader is referred to the review by *Reed* and *Cox* [5].

### 3. Fatty Acid Synthetase

A similar organization of structure and function is found in the synthesis of unbranched saturated fatty acids. Investigations by *Lynen et al.* [31] have shown that the overall reaction (l)

$$CH_3{-}CO{-}SCoA + n\ HO_2C{-}CH_2{-}CO{-}SCoA + 2n\ NADPH + 2n\ H^+ \rightarrow CH_3(-CH_2-CH_2-)CO{-}SCoA + n\ CO_2 + n\ CoASH + 2n\ NADP^+ + n\ H_2O \quad (n = 7 \text{ for palmityl-CoA}) \quad (l)$$

in yeast is catalysed by a homogeneous protein ($M$ = 2.3×10⁶), the principal products being palmityl and stearyl CoA. The net reaction takes place on the fatty acid synthetase in the following steps. The acetyl transfer [Eq. (m)] is the initiation reaction.

[27] *B. B. Mukherjee, J. Matthews, D. L. Horney,* and *L. J. Reed,* J. biol. Chemistry *240,* PC 2268 (1965).

[28] *U. Henning, G. Dennert, R. Hertel,* and *S. W. Shipp,* Cold Spring Harbor Symp. Quant. Biol. *31,* in press.

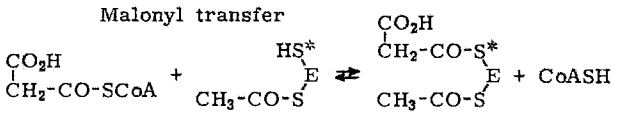
[29] *U. Henning* and *G. Deppe,* unpublished work.

[30] *U. Henning, C. Herz,* and *K. Szolyvay,* Z. Vererbungslehre *95,* 236 (1964).

[31] *F. Lynen,* Angew. Chem. *77,* 929 (1965).

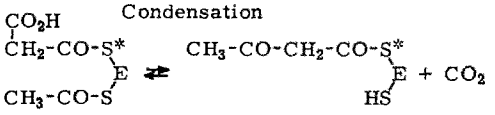
The five subsequent reactions lead to lengthening of the chain; they begin with the malonyl transfer [Eq. (n)].

Malonyl transfer



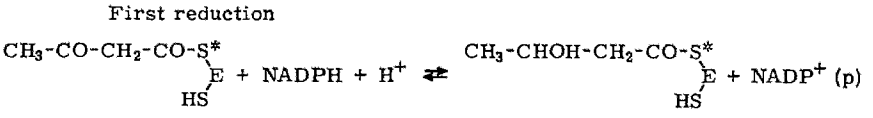
(n)

Condensation



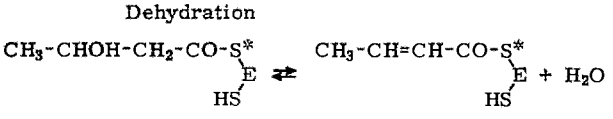
(o)

First reduction



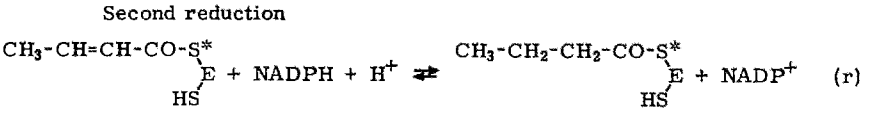
(p)

Dehydration



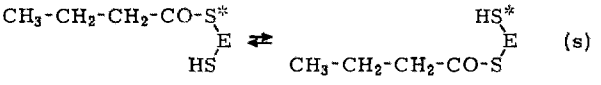
(q)

Second reduction



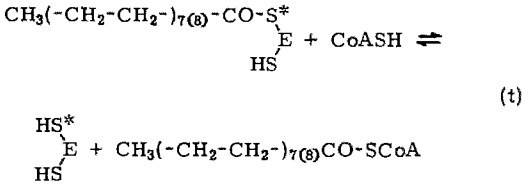
(r)

The SH group which accepts the malonyl residue is then liberated by the butyryl transfer [Eq. (s)].



(s)

Finally, when the chain length becomes $C_{16}$ to $C_{18}$, the stearyl or palmityl CoA is formed.



(t)

The existence of the functionally different SH groups (HS*-, HS–) has been demonstrated [32]. As with the other enzyme complexes, all intermediates remain enzyme-bound.

The seven reaction steps (m) to (s) apparently correspond to seven sub-units in the synthetase; however, dissociation of the enzyme into enzymatically active sub-units has not been achieved. An electron micrograph [33] of the synthetase (Fig. 3) shows its ordered structure in particles having a diameter of 200 to 250 Å. As in the case of tryptophan synthetase, the enzyme system from *E. coli* which carries out the fatty acid synthesis easily can be separated into enzyme fractions with different functions [34].

Details of bacterial and animal systems cannot be discussed here. The electron micrographs, and the fact that the synthetase from yeast can be dissociated into inactive sub-units only under fairly drastic conditions strongly indicate that the isolated enzyme is not an artifact produced during purification.

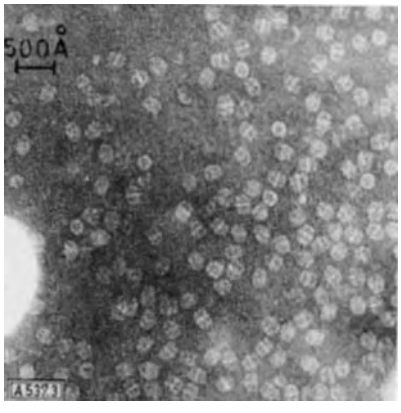



Fig. 3. Fatty acid synthetase from yeast [33]. (Preparation as in Fig. 1, magnification factor 250000).

## 4. Other Multienzyme Complexes

The examples described undoubtedly are not special cases of little general importance. There is evidence that a number of other reaction sequences are catalysed by a functional complex. This is true of the four enzymes that synthesize valine from pyruvate and isoleucine from pyruvate and α-ketobutyrate in *Neurospora* [35,36], and also of the synthesis of isoleucine in *Salmonella* [37].

[32] *F. Lynen* in *M. Sela*: New Perspectives in Biology. B.B.A Library Vol. 4, Elsevier Publishing Comp., Amsterdam-London-New York 1964, p. 132.

[33] *A. Hagen* and *P. H. Hofschneider* in *M. Titlbach*: Electron Microscopy 1964 (Proc. 3rd European Regional Conference). Publishing House Czechoslovak Acad. Sci., Prague 1964, Vol. 13, p. 69.

[34] *P. R. Vagelos*, Annu. Rev. Biochem. *33*, 139 (1964).

[35] *K. Kiritani, S. Narise, A. Bergquist*, and *R. P. Wagner*, Biochim. biophysica Acta *100*, 432 (1965).

[36] *R. P. Wagner, A. Bergquist*, and *T. Barbee*, Biochim. biophysica Acta *100*, 444 (1965).

[37] *C. S. Cronenweit* and *R. P. Wagner*, Proc. nat. Acad. Sci. USA *54*, 1643 (1965).

Three enzymes involved in the biosynthesis of tryptophan appear to act as a functional unit in *Neurospora* [38], as do three enzymes involved in the biosynthesis of histidine in *Neurospora* [39]. In the last case, since the three enzymes in question correspond, not to consecutive reaction steps, but to the second, third, and tenth steps, it is reasonable to suspect that *all* relevant enzymes *in vivo* are associated in a functional unit.

The features common to all these examples are readily recognized, and have been characterized by *Lynen* [32] as "strict compartmentalization in the smallest possible space". If enzymes that operate in sequence are also physically adjacent, the activity of the overall reaction sequence presumably may be greater than if these enzymes were separated. In the latter case the action would be optimal only when the concentrations of diffusing intermediates reach certain values. Moreover, reaction chains in which the intermediates are bound to the enzyme avoid competition between different enzymes for the same intermediate.

The specific activities of the fatty acid synthetase from yeast and of the pyruvate dehydrogenase are high; one synthetase complex can catalyse the conversion of $2.4\times10^3$ molecules of malonyl CoA per minute into fatty acid [32], and one pyruvate dehydrogenase complex at 30 °C can produce at least $1.25\times10^4$ molecules of acetyl CoA per minute from pyruvate.

One might conclude that the concept of the multienzyme complex represents an example of the biological principle of "increasing the efficiency". However, this view probably is still too narrow. In higher organisms at least, the large enzyme complexes discussed are localized in the mitochondria. The same is true of the above mentioned enzymes of the biosyntheses of valine and isoleucine in *Neurospora* [35, 36]; the isoleucine system in *Salmonella* [37] occurs in the membrane fraction. It appears reasonable to combine enzyme systems physically when they are bound to large cell structures, even if they are not also components or "supply" enzymes of further processes (*e.g.* the respiratory chain). Another interesting speculative aspect [39a] is that the structure-bound enzymes could greatly increase their surface if the substrate can be retained by the structure (*e.g.* membrane) and can migrate along the latter to the enzyme.

## II. Extension of the Concept: Homofunctional and Heterofunctional Enzyme Complexes

With regard to the enzyme protein, the definition of the multienzyme complex as described in the introduction is really teleological, and therefore is too specialized. This can be seen particularly well with hemoglobin and myoglobin [41–43], which *Frieden* [40] aptly described as "perfect" enzymes, since they permit the study of the enzyme-substrate interaction without the formation of interfering products. The four heme groups, and hence the four active sites, corresponding to the four polypeptide chains of hemoglobin, are situated in "pockets" in each of the two $\alpha$ and $\beta$ chains on the surface of the molecule, without being in contact with one another. The tertiary structure (and also the position of the heme) of myoglobin, which consists of only one polypeptide chain, is extremely similar to the tertiary structure of each of the hemoglobin chains, and in this sense myoglobin may be regarded as a naturally-occurring sub-unit of hemoglobin. The activities of all the polypeptide chains are the same. In contrast to myoglobin, however, the binding of $O_2$ by hemoglobin leads to a heme-heme interaction, *i.e.* a co-operation of the binding sites [44–46]. The rate of reaction of a heme with $O_2$ depends on the state of loading of the other hemes with $O_2$, and increases with the amount of $O_2$ already bound. Thus the association of different sub-units leads (in a wider sense) to an increase in efficiency.

The question arises whether the fact that a protein molecule consists of several sub-units, *i.e.* the presence of a quarternary structure, is enougn to constitute a multienzyme complex. It may be assumed that this is not the case, but that the cell also makes use of the association to *produce* an active site. This appears to be the situation with the dihydrolipoate dehydrogenase [cf. reactions (i) and (k)], as *Massey*'s investigations [47,48] have shown in the case of the pig's heart enzyme.

The enzyme consists of two probably identical polypeptide chains, each with $M = 50000$; 2 moles of FAD and 4 moles of cystine units (as well as 12 cysteine units) are present per mole of enzyme. The intermediate is the reduced enzyme [reaction (i)], in which, in contrast to several other dehydrogenases containing FAD, the flavin coenzyme takes up only one electron. The difference spectrum of the resulting reduced enzyme is similar to that of the semiquinoid form of FMN which occurs as a charge-transfer complex in an equilibrium mixture of FMN and $FMMH_2$. This form ("red" enzyme) has been obtained by the action of NADH or dihydrolipoic acid on stoichiometric quantities of the dehydrogenase. However, spectrophotometric titration of this last reaction with either of the substrates shows that the red form of the protein corresponds to the uptake of two electrons per FAD. This discrepancy was resolved when a disulfide was discovered as a second prosthetic group of the enzyme, and it was found by amperometric titration that the addition of NADH leads to the formation of a dithiol. When the NAD formed in a mixture of NADH and enzyme is removed with an NADase (which does not attack NADH), the enzyme is completely reduced and becomes colorless; four electrons are taken up per FAD. The colorless enzyme can react with NAD to give again the red form.

The dihydrolipoic dehydrogenase in the oxidized yellow state is unusually stable towards urea (in 6.5 M urea at 0 °C only

[38] *J. A. De Moss* and *J. Wegman*, Proc. nat. Acad. Sci. USA *54*, 241 (1965).

[39] *A. Ahmed, M. E. Case*, and *N. H. Giles*, Brookhaven Symp. Biol. *17*, 53 (64).

[39a] *M. Delbrück*, personal communication.

[40] *C. Frieden*, Brookhaven Symp. Biol. *17*, 98 (1964).

[41] *J. C. Kendrew*, Angew. Chem. *75*, 595 (1963).

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[43] *G. Braunitzer, K. Hilse, W. Rudloff*, and *U. Hilschmann*, Advances Protein Chem. *19*, 1 (1964).

[44] *R. Benesch* and *R. E. Benesch*, J. molecular Biol. *6*, 489 (1963).

[45] *H. Muirhead* and *M. F. Perutz*, Cold Spring Harbor Symp. Quant. Biol. *28*, 451 (1963).

[46] *R. E. Benesch, R. Benesch*, and *G. McDuff*, Proc. nat. Acad. Sci. USA *54*, 535 (1965).

[47] *V. Massey, T. Hofmann*, and *G. Palmer*, J. biol. Chemistry *237*, 3820 (1962).

[48] *V. Massey* in *P. D. Boyer, H. L. Lardy*, and *K. Myrbäck*: The Enzymes. Academic Press, New York, 1963, Vol. 7, p. 275.

about 30 % of the enzyme activity is lost after one month); the red form of the enzyme also retains its activity in urea. In the presence of excess NADH or dihydrolipoic acid in 6.5 M urea, the spectrum is initially that of the semi-reduced enzyme, but this soon gives way to that of the fully reduced protein. The completely reduced enzyme is unstable in the urea solution. The $FADH_2$ (or FAD after the admission of air) becomes separated from the protein and dialysable; the protein becomes insoluble when the urea concentration is decreased to less than 2 M, and the molecular weight of the resulting reduced dehydrogenase falls to half that of the native protein.

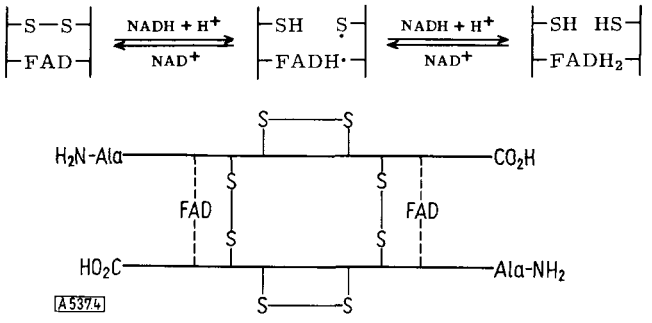


Fig. 4. Scheme of the dihydrolipoate dehydrogenase [47]. Model representation of the steps of the enzyme reduction as described in the text.

Figure 4 shows the model derived by *Massey* from these and other data. Both polypeptide chains appear to be involved, with the disulfide bridges, in the catalysis. The active sites literally are situated *between* the polypeptide chains, since at least cystine residues of both chains act as components of one active site. However, it is not known whether other amino acid residues belonging to one active site originate from both chains.

The example described is not intended to show implicitly that enzymes of this type must necessarily consist of identical polypeptide chains. An association of different polypeptide chains can give almost the same catalytic activity, as is well known from various forms of lactic dehydrogenase [49,50]. These can consist either of four identical chains (the so-called isozymes I and V, consisting of chains H and M) or mixtures of integral molar quantities of chains H and M (isozymes II, III, and IV: 1H2M, 2H2M, 1H3M). *Holbrook* [51] recently reported results that led him to conclude that the active sites in this case also are composed of parts of adjacent sub-units. A similar possibility exists for aldolase, which has only one active site, but consists of at least three (or six) polypeptide chains [52–55].

However, the direct participation of several sub-units of an enzyme molecule in one active site is hypothetical. If this hypothesis is true, it remains to be seen whether it is correct to classify such enzymes separately, since the transition to proteins of the tryptophan synthetase type may be continuous. (Incidentally, it would not be easy to give a good account for the biological evolution of enzymes with "mixed"centers of activity, as dihydrolipoate dehydrogenase).

From the examples described, it appears that a protein may be regarded with certainty as a multienzyme complex if the centers of activity for various steps in an overall reaction chain are situated on different sub-units. As far as the protein is concerned, however, there is no fundamental difference between such complexes and enzymes in which similar active centers are also present in their sub-units and are not formed only by the combination of the sub-units in such a manner that two or more sub-units contribute in forming an active site. If a classification is desired, it appears more reasonable to distinguish between *homofunctional* and *heterofunctional* multienzyme complexes, depending on whether the sub-units and active centers are identical or different.

The so-called allosteric effect [56,57], for which association is evidently a prerequisite, fits in easily with the "heterofunction" on association. An example is the heme-heme interaction in hemoglobin described earlier. Another extreme case was reported in the aspartate transcarbamylase (ATC) of *E. coli* [58].

The enzyme initiates the biosynthesis of cytidine triphosphate (CTP) with the reaction: carbamyl phosphate + aspartate → carbamyl aspartate. It is regulated by feed-back, its activity being inhibited by CTP. The ATC ($M \approx 3\times10^5$) consists of enzymatically inactive regulatory sub-units ($M \approx 3\times10^4$) and enzymatically active sub-units ($M \approx 9\times10^4$); only the first type binds CTP. The enzymatically active sub-unit, when dissociated from the regulating sub-unit, is not inhibited by CTP.

It may be concluded that multienzyme complexes as defined initially do not occupy a special position in enzyme structures. It remains to be seen whether the concept of homofunctional and heterofunctional complexes provides a better insight, since the organization of enzymes is more elaborate than has been described here. We have not considered systems which act at the level of large cell structures, *e.g.* the vectorial enzymes of the transport system on membranes or the mechanochemical systems of contractile or other mobile structures.

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[57] *J. Monod, J. Wyman*, and *J. P. Changeux*, J. molecular. Biol. *12*, 88 (1965).

[58] *J. C. Gerhart*, Brookhaven Symp. Quant. Biol. *17*, 222 (1964).

# Complex Formation and Flower Colors

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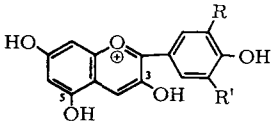
*The pigment of the blue cornflower, protocyanin, is a complex of high molecular weight. Iron(III) and aluminum ions combine with the anhydro base of the cyanin to form deep-blue complexes, which are stable in the physiological pH range. Complexes of this type also have been synthesized. Alkali metal salts play no part in blue flower pigments. Formation of blue complexes can be prevented by sequestration of the metal ions with stronger complexing agents, e.g. flavonols. The variation of flower colors can be explained to a large extent on the basis of the complex formation of anthocyanins. In delphinidin glycosides, the color base or anhydro base is stable even in slightly acidic media.*

The majority of flower colors are produced by a surprisingly small number of pigments. Apart from the betacyanins, which are confined to a few groups of plants, and the carotenoids, which are important in yellow and orange flowers, mainly the anthocyanins are responsible for the color range from orange to deep blue. Anthocyanins are glycosides of anthocyanidins.

The principal aglycones found in Nature are *(1)* to *(6)*, which occur as their glycosides with sugars on the OH groups attached to C-3 and C-5. The position of the longest-wavelength maximum [3] in the absorption spectra of the aglycones and their glycosides differ at the most by 38 mμ. This difference is not sufficient to explain all the color shades found in Nature. Since *Willstätter*'s classic work, therefore, several hypotheses have been proposed to explain the colors of flowers.

Thus in the investigation of the red rose and of the blue cornflower, *Willstätter* [4] found an example of the




| Compound | R | R' | Name | λmax (mμ) [a] |
|---|---|---|---|---|
| *(1)* | H | H | Pelargonidin | 520 |
| *(2)* | OH | H | Cyanidin | 535 |
| *(3)* | OH | OH | Delphinidin | 544 |
| *(4)* | $OCH_3$ | H | Päonidin | 532 |
| *(5)* | $OCH_3$ | OH | Petunidin | 543 |
| *(6)* | $OCH_3$ | $OCH_3$ | Malvidin | 542 |

[a] In 0.01% methanolic HCl.

presence of the same anthocyanin both in blue and in red flowers. He isolated the same pigment, cyanin, which is a 3,5-diglucoside of cyanidin *(2)*, from the flowers of roses and of cornflowers, and ascribed this to the fact that the red oxonium salts of the anthocyanins, which are stable in the acidic range, are converted into blue-green salts in alkaline media (pH > 8). *Willstätter* concluded that the cornflower, and blue flowers in general, must contain alkali metal salts of anthocyanins in an alkaline medium, whereas red flowers contain the oxonium salts, which are stable only in acidic media (pH < 4). This view was adopted in textbooks of organic chemistry and botany as an established fact, and is found even in a few recent textbooks [5–8].

An unclear point in this hypothesis was the requirement of an alkaline medium in the petals. It has long been known that, owing to the presence of dicarboxylic acids of the citric acid cycle, flower petals are slightly acidic, so that in them phenoxides cannot be stable. This fact was pointed out by *K. Shibata et al.* [9], and later by *G. M.* and *R. Robinson* [10], who therefore assumed that in blue flowers the anthocyanins are fixed or stabilized by colloidal bonding or "copigmentation" with other substances present, whereas *Shibata* and *Hayashi* [9, 11] postulated that the blue color is due to alkaline earth compounds of the anthocyanins.

Two observations led us to check the causes of the blue pigmentation of flowers by anthocyanins: The press juices of blue flowers, *e.g.* cornflowers (*Centaurea cyanea*) have a pH between 3.8 and 5.0. The blue color remains stable in this acidic medium, though no pure

[*] From a lecture to the Symposium "Chemistry of Plant Pigments", Aberdeen University, September 24th, 1965.

[1] *H. Egeter*, Diploma Thesis, Technische Hochschule Karlsruhe, 1960; Dissertation, Technische Hochschule Karlsruhe, 1962.

[2] *K. Nether*, Diploma Thesis, Technische Hochschule Karlsruhe, 1959.

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[5] *L. F.* and *M. Fieser*: Organic Chemistry. Heath, Boston 1950, p. 874.

[6] *K. Freudenberg* and *H. Plieninger*: Organische Chemie. 10th Ed., Quelle u. Meyer, Heidelberg 1963, p. 232.

[7] *F. Klages*: Einführung in die Organische Chemie. 2nd Ed., Walter de Gruyter, Berlin 1965, p. 419.

[8] *H. Walter*: Einführung in die Phytologie. 4th Ed., Eugen Ulmer, Stuttgart 1962, Part I, p. 48.

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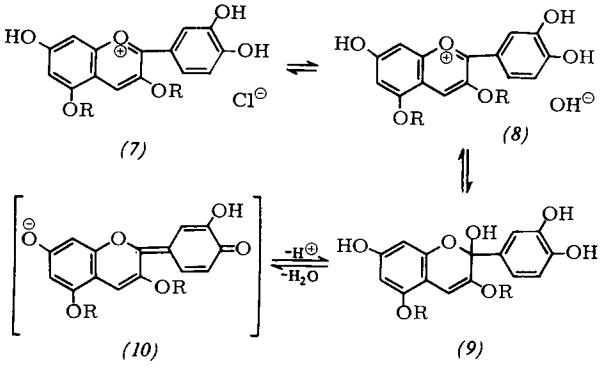
[10] *R. Robinson* and *G. M. Robinson*, J. Amer. chem. Soc. *61*, 1065, 1606 (1939).

[11] *K. Shibata*, *K. Hayashi*, and *T. Isaka*, Acta phytochim. (Tokyo) *25*, 17 (1949).

anthocyanin is blue in this range. According to investigations by *Kuhn* and *Sperling*[12], cyanin gives a blue resonance-stabilized anion *(10)* only in alkaline media (pH > 8). At pH ≈ 4, the oxonium salt *(7)* of the cyanin changes *via* the unstable color base *(8)* into a pale yellowish pseudo-base *(9)*. Thus the stability of the blue pigment of cornflower in acidic media refutes *Willstätter*'s alkali salt hypothesis.



*(7)* *(8)* *(10)* *(9)*

Another observation shows that a special bonding state, and not simply an alkali metal salt of cyanin, occurs in the blue pigment of the cornflower. Thus an enzyme that degrades anthocyanins, cyanin oxidase, has been isolated from *Coleus hybridus*[13]. This enzyme occurs in the green parts of the leaves and is absent from the red parts (the existence of red varieties of plants could be due to the mutative loss of this enzyme[13,14]). Cyanin oxidase attacks only anthocyanins having at least two adjacent free hydroxyl groups on the benzene ring, *i.e.* the glycosides of cyanidin *(2)*, delphinidin *(3)*, and petunidin *(5)*.

Cyanin is degraded by cyanin oxidase in the pH range 5 to 9, *i.e.* also in the range in which the alkali metal salts can exist (Fig. 1). However, the blue cornflower pigment is not degraded, even though it contains cyanin. It may therefore be concluded that the cyanin in the cornflower pigment must be in a special bonding state involving the adjacent hydroxyl groups in the phenyl group.

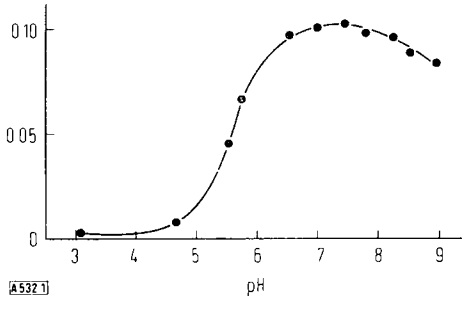



Fig. 1. pH dependence of the activity of cyanin oxidase in the degradation of cyanin. Activity determined in accordance with [13].
Ordinate: Enzyme activity (degraded cyanin per unit weight of enzyme preparation).

[12] *H. Kuhn* and *W. Sperling*, Experientia *16*, 237 (1960).
[13] *E. Bayer* and *K. Wegmann*, Z. Naturforsch. *12b*, 37 (1957).
[14] *K. Paech* and *F. Eberhardt*, Z. Naturforsch. *7b*, 664 (1952).



The only possible solution to this problem was the isolation of the native pigment, which we named protocyanin. The name cyanin (Κυάνεος = blue) was originally derived by *Willstätter* from the color of the cornflower, though cyanin chloride was the pigment from red roses.

In the isolation of protocyanin from garden cornflowers (*Centaurea cyanea polyphemus*), the use of strong acids must be avoided, since the pigment would otherwise be destroyed. This instability of the blue compounds towards acids probably is the reason for the fact that the extraction of the flowers in the earlier work with dilute mineral acids always gave only the oxonium salts, so that the existence of the protoanthocyanins remained undetected.

The isolation of protocyanin was facilitated by two surprising properties: The dye is not dialysable, and it migrates to the anode in an electric field at pH 4.6, *i.e.* it can be separated from accompanying anthocyanins by electrophoresis. Cyanin does not migrate in an acetate buffer at pH 4.6, as is shown by the paper electropherogram in Fig. 2. This fact is a further argument

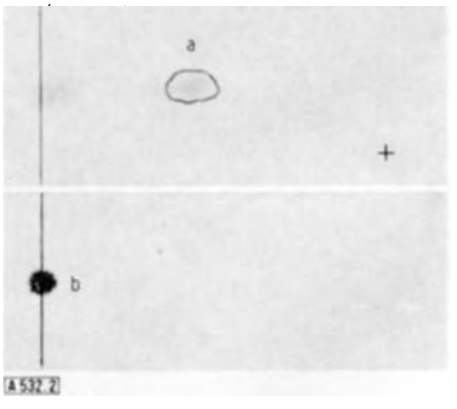



Fig. 2. Paper electropherogram of protocyanin (a) and pure cyanin (b) in 0.2 M acetate buffer (pH 4.45). Voltage: 110 V; migration time: 6 hours; rate of migration of protocyanin: 0.7 cm/hour.

against the presence of alkali metal or alkaline earth metal salts. Electrophoresis generally is a simple method for the detection of blue, complex anthocyanin compounds, since, under the conditions mentioned, the only other flower pigments that migrate are the betacyanins discovered by *Dreiding et al.*[15]. However, since these are yellow to red, they can easily be distinguished from the protoanthocyanins. To isolate the protocyanin, crushed cornflower blooms are pressed, and the resulting ink-blue solutions (pH 4.6) are mixed with alcohol. The blue floccules deposited after a short time are separated from the almost colorless solution. The blue substance, which is soluble in distilled water, is reprecipitated several times with alcohol. The solution is then saturated with ammonium sulfate to remove small quantities of proteins. After a further precipita-

[15] *T. J. Mabry, H. Wyler, G. Sassu, H. Mercier, I. Parikh*, and *A. S. Dreiding*, Helv. chim. Acta *45*, 640 (1962).

tion with alcohol, the product is dialysed against distilled water for 36 hours to remove components of low molecular weight, and the sample is finally purified by preparative electrophoresis without a carrier. The isolation can be simplified by chromatography on Sephadex columns. This procedure gives electrophoretically pure protocyanin as deep-blue platelets. The molecular weight at pH 4.0 is 6200 according to ultracentrifuge measurements, which yield a diffusion coefficient of $11.9 \times 10^{-7}$ cm²/sec at 20 °C.

Protocyanin contains 19.2 % of cyanin and a total of 1 equivalent [*] of iron(III) and aluminum(III) per mole of cyanin [16]. Spectral analysis showed that our product contained only traces of other metals. Protocyanin also is stable towards heat. The macromolecular substance that accounts for about 80 % of protocyanin is therefore not a protein, but a polysaccharide, the main component of which, apart from arabinose and glucose, is galacturonic acid. Thus the macromolecular component is a pectin-like substance. This discovery confirms the hypothesis of *G. M.* and *R. Robinson* [10] that the anthocyanins are bound to macromolecular "carrier substances" [16a].

The color depends, however, on the presence of the metal ions in protocyanin, probably in the form of iron and aluminum chelates. It probably will not surprise gardeners that blue flower colors are due to iron and aluminum complexes of cyanin, since an old gardening trick is to sprinkle red hydrangeas with aluminum or iron alum solution to change their color to blue.

In order to clarify further the bonding of the metal ions, it was necessary to prepare model complexes and to compare their properties with those of protocyanin.

## Chelate Formation of Anthocyanins

Anthocyanins containing at least two hydroxyl groups in the phenyl group can be qualitatively recognized by the blue color that arises on reaction with iron(III) salts. The molar ratios of anthocyanin to metal ion at which complex formation occurs can be established by the method of continuous variation [17]. Spectroscopic measurements have shown that various types of complexes are formed with both aluminum and iron(III) ions at the metal ion: anthocyanin ratios of 1:1, 1:2, and 1:3 [16]. No intensely colored chelates are formed with bivalent ions of transition metals, and no complex can be isolated. If the synthetic and the natural complexes are the same, the synthetic ones containing iron and aluminum ions should also be stable at pH 4 to 6, and must be intensely colored. Figure 3 shows the absorption of the synthetic metal complexes at 590 mμ and at various pH values in comparison with the absorption of protocyanin. Measurements on complexes containing bivalent cobalt, nickel, calcium, magnesium, and barium ions are also shown. It can be seen from the diagram that neither the alkaline earth metal nor the cobalt or nickel complexes of cyanin are stable and blue at pH 4 to 6. Their extinctions are almost 100 times lower, *i.e.* blue complexes are not formed. This is also true of the bivalent ions of other transition elements. The synthetic iron and aluminum complexes, on the other hand, are deeply colored, and their behavior with variation of the pH is similar to that of protocyanin (cf. Fig. 3). Deep-blue chelates stable at pH 4 to 7 are formed, not only with iron(III) and aluminum, but also

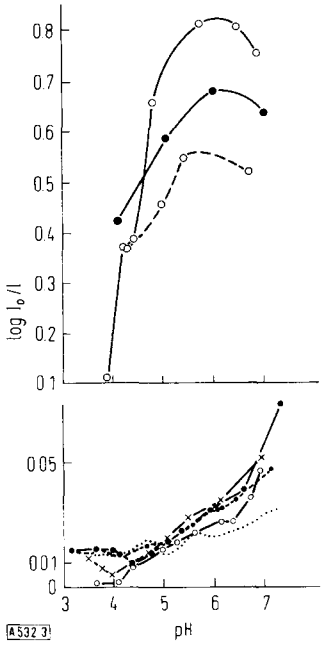



Fig. 3. Top: pH-stability of iron(III) and aluminum complexes of cyanin (o---o) and o—o) and of protocyanin (●—●).

Bottom: Behavior of cyanin in the presence of nickel(II) (x—x), cobalt(II) (●—●), calcium (---), barium (●---●), and magnesium (o—o) acetates.

The concentration of the protocyanin was 0.97 mg in 1 ml of 0.2 M acetate buffer. Cyanin was mixed with the metal salts in the molar ratio of 1:2. The mixtures were taken up in 0.2 M acetate buffer so that the cyanin concentration was $5 \times 10^{-4}$ M.

Ordinate: Extinction at 590 mμ.

by Sn(IV), Ti(III), Cr(III), and $UO_2^{2+}$. However, tin, titanium, chromium, and uranium occur in plants only as trace elements. It is therefore unlikely that any metals other than iron and aluminum are involved in the formation of blue flower pigments.

The complexes of cyanin and cyanidin with iron and aluminum have also been isolated on a preparative scale [18]. The tricyanidinoiron(III) or aluminum complexes *(11a)* and the dicyanidinoiron(III) or aluminum complexes *(12a)* are relatively easy to obtain. In the case of cyanin, the 2:1 complex, which also contains an anion, is formed preferentially. Analysis and structural elucidation show that the complexes are derived from

[*] While the ratio Fe:Al in the protocyanin of garden cornflowers is about 2:1, the protocyanin of wild cornflowers contains mainly Fe together with a little Al.

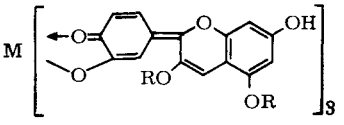
[16] *E. Bayer*, Chem. Ber. *91*, 1115 (1958).

[16a] *Note added in proof*: The presence of the macromolecular component in the protocyanin of the wild cornflower has been confirmed recently by *N. Saito* and *K. Hayashi*, Sci. Rep. Tokyo Kyoiku Daigaku Sect. B *12*, 39 (1965).

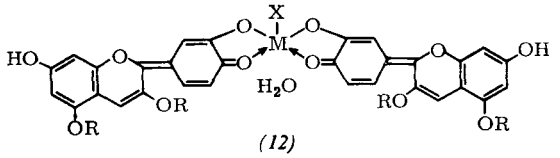
[17] *P. Job*, Ann. Chim. Phys. *9*, 113 (1928).

[18] *E. Bayer, K. Nether*, and *H. Egeter*, Chem. Ber. *93*, 2871 (1960).

the anhydro-base of the anthocyanin. Complex formation involves the two adjacent hydroxyl groups in the phenyl group, since anthocyanins that do not contain two adjacent hydroxyl functions in the phenyl group do not form complexes. This agrees with the facts observed in the enzymatic degradation of protocyanin. Since the



*(11)*



*(12)*

M = $Al^{3+}$, $Fe^{3+}$ *(11a)*, R = H *(11b)*, R = Glucosyl
X = $OH^-$, $Cl^-$ *(12a)*, R = H *(12b)*, R = Glucosyl

metal ion:cyanin ratio in natural protocyanin is 1:2, compound *(12b)* is a synthetic model for the cornflower pigment. The iron complex can be prepared by a simple method that is suitable as a lecture demonstration.

A solution of 16.2 mg of anhydrous iron(III) chloride in 2 ml of water and exactly 52 ml of 0.1 N NaOH are added to a solution of 65 mg of cyanin chloride in 50 ml of 0.1 N HCl. About 150 ml of acetone is added to the resulting blue solution. Blue-black chlorodicyaninoiron(III) precipitates and is filtered off and washed with a very small quantity of methanol. The substance dissolves readily in water to give a deep-blue solution. Yield: 25 mg.

*R. Kuhn* [19] has prepared the aluminum complex *(12a)* as a lacquer in a simple demonstration experiment using our procedure:

100 ml of a thick slurry of $Al(OH)_3$ in methanol is added to 32 mg of cyanidin chloride in 800 ml of methanol. When the mixture has been shaken, the cornflower-blue aluminum complex separates, and the supernatant becomes colorless. The $Al(OH)_3$ should be precipitated from a hot aqueous solution of aluminum sulfate with concentrated ammonia and washed with water until the washings remain neutral. The color of the Al complex then persists for many hours.

The synthetic complex *(12b)* differs from natural protocyanin in the absence of the macromolecular component. Nevertheless, the absorption spectra of the two complexes agree closely (Fig. 4). The weak shoulder at 640 mμ in the spectrum of protocyanin is also hinted at by the marked broadening of the band at 570 mμ in the spectrum of the model complex. The polygalacturonic

[19] *R. Kuhn*, Naturwissenschaften *49*, 1 (1962), cited p. 6.

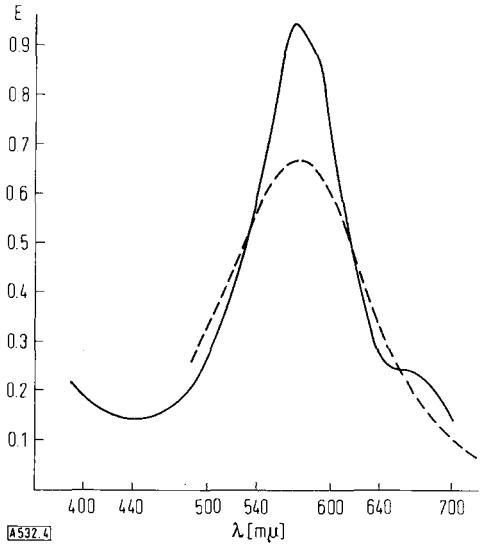
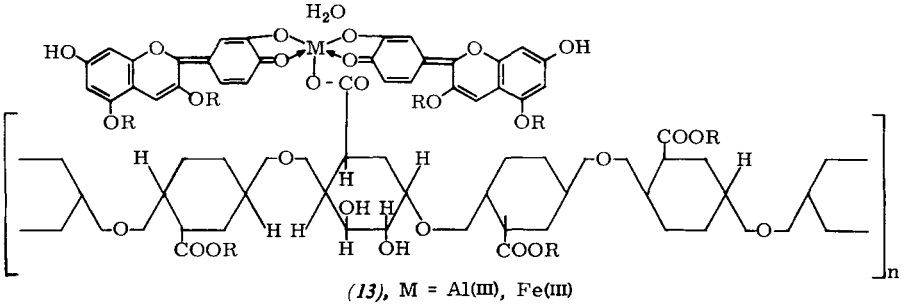



Fig. 4. Absorption spectra of protocyanin (1.25 mg/ml) (—) and of the dicyaninoaluminum complex (0.4 mg/ml) (---) in 0.2 M acetate buffer, pH 6.1.

acid is probably coordinatively bonded by its carboxyl groups to the iron atom in place of the residue X in formula *(12)*, giving the structure *(13)* (molecular weight about 6200). A deep-blue complex containing no chloride can in fact be obtained from apple pectin, cyanin, and iron(III) or aluminum chloride.

As far as we know, protocyanin is the first naturally occurring metal chelate in which the macromolecular carrier has been found to be a polysaccharide instead of a protein. Thus, in addition to the chromoproteins and metal proteides, we now have the chromosaccharides.



*(13)*, M = Al(III), Fe(III)

## The Possibility of the Existence of Blue Roses

According to the investigations on the cornflower pigment, the existence of blue flower pigments can be explained by complex formation, whereas red flower pigments are the oxonium salts. It should therefore be possible, in theory, to produce the cornflower-blue rose that rose-growers have sought in vain, by causing the cyanin in the rose to undergo chelate formation. In the case of hydrangeas, the red variety need only be sprinkled with alum solution to bring about a color change from red to blue. However, this method is unsuccessful with roses. The change to blue in the petals of the hydrangea accompanies the increase in the aluminum content, as can be seen from Table 1. In roses, on the other hand, the aluminum content of the petals does

Table 1. Iron and aluminum content of the petals of hydrangeas and roses.

| | Normal plants | | Cut flowers placed in alum soln. (24 hr) [a] | | Plants sprinkled with alum soln. (7days) [a] | |
|---|---|---|---|---|---|---|
| | Al | Fe | Al | Fe | Al | Fe |
| Hydrangea | 0.17% | 0.12% | 0.52% | 0.20% | 0.35% | 0.15% |
| Rose | 0.41% | 0.12% | 0.59% | 0.14% | 0.43% | 0.11% |

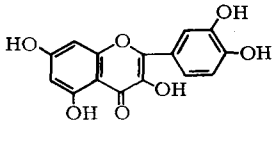
[a] 0.1% aqueous solutions of aluminum alum or iron alum were used.

not increase as a result of this treatment. Roses must therefore possess a "safeguard" which prevents the excessive concentration of metal ions in the petals. However, even the 0.12 to 0.4% of aluminum and iron already present, without further accumulation, should in principle be sufficient for the formation of cyanin complexes. Why, then, does this not occur?

This question could be avoided if it were postulated that the metal ions and the anthocyanin oxonium salts occur in different cell areas. However, it is also conceivable that the Al and Fe in the petals are not free, but are already in the form of complexes. If other complexing agents gave more stable complexes, the failure of the blue color to develop would be understandable. We have now to find such complexing agents in roses. We thought that the most likely substances would be the acids of the citric acid cycle and phenolic components.

Citrate forms more stable complexes than cyanin with iron, as can be shown by the failure of the blue color to develop when cyanin chloride and iron(III) chloride are added to an acetate buffer containing citrate at pH 4.6. However, no notable quantities of citric acid could be detected in the flowers of various types of roses studied by us. Nevertheless, of all the many types of roses that exist, some may contain appreciable quantities of citric acid. For example, *Karrer*[20] reported the presence of 2% of citric acid in one variety. The iron complexes formed by the dicarboxylic acids of the citric acid cycle are less stable than those formed by cyanin.

It has been known for some time that glycosides of flavonols occur in petals as well as anthocyanins. *G. M.* and *R. Robinson*[10,21] assumed that these substances could play some part in determining the tint. These authors[21] made special mention of flavonols in their "copigmentation hypothesis", but did not investigate the matter further. *Karrer*[20] has detected a glycoside of quercetin *(14)* in red roses, but gave no further details about the sugar component. We have confirmed the presence of quercetin glucosides in various types of roses. We also found glycosides of kaempferol *(15)* in red rose petals.



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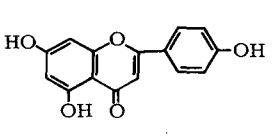


*(15)*

[20] *P. Karrer* and *K. Schwarz*, Helv. chim. Acta *11*, 916 (1928).

[21] *R.* and *G. M. Robinson*, Biochem. J. *25*, 1687 (1931); *26*, 1663 (1932).

The formation of anthocyanin chelates with $Al^{3+}$ and $Fe^{3+}$ is actually suppressed in the presence of quercitrin, and metal ions that have already been incorporated into natural protocyanin can be displaced by the addition of quercitrin, as is shown in Figure 5 by the decrease in intensity of the blue color on addition of

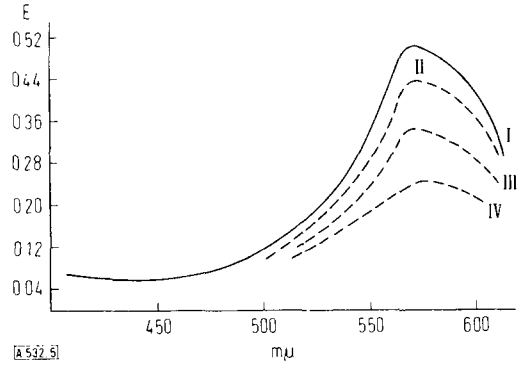
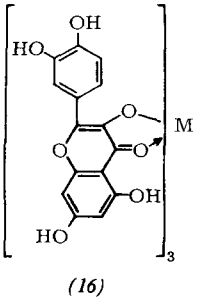



Fig. 5. Exchange of metal ions between blue protocyanin (I) and quercitrin in acetate buffer, pH 4.5. Cyanin concentration: $3.7 \times 10^{-4}$ M. Curves: II: addition of $3.7 \times 10^{-4}$ M quercitrin; III: $1.11 \times 10^{-3}$ M quercitrin; IV: $1.85 \times 10^{-3}$ M quercitrin.

quercitrin. The metal ions are bound by the flavonol glycosides, and the pseudo-base *(9)* is formed. Thus flavonol glycosides could also mask the aluminum and iron ions in the rose, so that, in order to obtain blue roses, it would be necessary to breed plants that do not contain flavones and citric acid. The stronger tendency of flavonols towards complex formation than anthocyanins is due to the presence of the hydroxyketo grouping. *Hörhammer* and *Hänsel*[22,23], who studied the composition of the flavonol chelates by the continuous variation method[17], found that flavonols having a free hydroxyl group in position 3 form both 1:1 and 2:1 chelates, whilst flavonols with a sugar residue attached to C-3 give only 1:1 complexes. We have isolated the Al and Fe chelates of kaempferol, quercetin, and quercitrin and, in agreement with the results obtained by *Hörhammer* and *Hänsel*[22,23], we found three types of complexes for the aglycones *(16)* to *(18)*, and only the 1:1 complex *(21)* for the 3-glycosides. Owing to steric hindrance by the sugar residue adjacent to the carbonyl function, only one flavone molecule can be attached to the central atom in the



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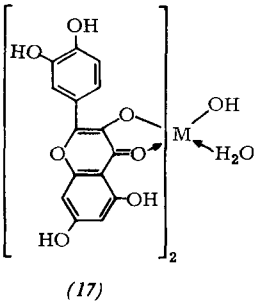


*(17)*

[22] *L. Hörhammer* and *R. Hänsel*, Arch. Pharm. *285*, 438 (1952); *288*, 315 (1955).

[23] *L. Hörhammer* and *R. Hänsel*, Z. analyt. Chem. *148*, 251 (1955).

3-glycosides. The same effect is found even with a methyl group. Thus 3-hydroxy-5,7,3′,4′-tetramethoxyflavone *(19)*, like quercetin, gives three types of complexes, whereas only the 1:1 type can be isolated for 5-hydroxy-3,7,3′,4′-tetramethoxyflavone *(20)*, as with the 3-glycosides rutin *(21)*, R = $C_{12}H_{21}O_9$, and quercitrin *(21)*, R = $C_6H_{11}O_4$.

## Variation of Flower Colors

The question now arises of whether the variation of flower colors in general can be explained by complex formation. It is conceivable that all the hues between deep blue and red are produced by a mixture of blue chelates with red oxonium salts.

We have already mentioned that only the glycosides of cyanidin *(2)*, delphinidin *(3)*, and petunidin *(5)* form deep olue chelates. Glycosides of pelargonidin *(1)*, peonidin *(4)*, and malvidin *(6)* are unable to do so, and should therefore occur as principal components only in red to violet flowers. This is in agreement with the results obtained by *Werckmeister* [24] in chromatographic studies on the anthocyanin contents of various flowers. A few examples are given below.

The cornflower occurs in a red variety as well as in blue. *R.* and *G. M. Robinson* [10] assumed that the red color is due to "copigmentation" with chlorogenic acid. However, the anthocyanin present in the red cornflower is not cyanin, but pelargonin [25], a glycoside of pelargonidin *(1)* with only one hydroxyl group in the phenyl ring, which cannot form blue complexes.

The various types of shrub lupin (*Lupinus polyphemus*) show every shade from pink to violet and deep blue in their flowers. The pigment obtained from the press juices of blue lupins cannot be dialysed and, like the protocyanin of the cornflower, must therefore have a high molecular weight. The pigment of red lupins, on the other hand, passes through the dialysis tube in 30 to 60 minutes [26]. When the press juices of violet lupins are dialysed, the inner solution becomes blue within an hour, *i.e.* the color of violet lupins is produced by a mixture of macromolecular, blue chelates with red, dialysable oxonium salts.

The anthocyanins found in lupins of different colors are shown in Table 2. The red varieties contain only pelargonidin glycosides, which do not form blue complexes. The blue lupins contain glycosides of cyanidin and delphinidin, *i.e.* strong complexing agents. Violet flowers contain the pelargonidin glycosides as well as the delphinidin and cyanidin glycosides.

Table 2. Lupin anthocyanins.

| Anthocyanin | RF in butanol/ $CH_3COOH$/ $H_2O$ (4:1:5) | Lupins red | blue | violet |
|---|---|---|---|---|
| Delphinidin monoglucoside | 0.19 | − | ++ | + |
| Pelargonidin monoglycoside | 0.39 | ++ | − | + − |
| Pelargonin | 0.35 | ++ | − | + |
| Cyanidin glycoside | 0.24 | − | ++ | + |
| Unknown | 0.29 | − | − | + |

The colors of various other flowers can similarly be explained by complex formation. Table 3 shows the properties of the press juices of some flowers; the presence of non-dialysable complexes and the direction of migration in an electric field are indicated.

Table 3. Dialysability and electrophoretic mobility of some flower pigments.

| Plant | Color | Dialysis of press juice | Electrophoretic mobility [a] | pH of press juice |
|---|---|---|---|---|
| Crocus *(Crocus spec.)* | blue | No dialysis in 10 hr | to cathode | 5.75 |
| Sweet violet *(Viola odorata)* | blue | Does not dialyse; blue precipitate after 10 hr | to cathode | 6.3 |
| Grape hyacinth *(Muscari botryoides)* | blue | Dialyses in 8 hr | to anode | 5.4 |
| Tulip *(Tulipa gesneriana)* | red | Dialyses in 2 hr | none | 5.35 |
| Tulip *(Tulipa gesneriana)* | deep-violet | Dialyses in 2 hr | none | 5.25 |
| Iris *(Iris germanica)* | blue | Precipitate after 1 hr | — | 5.4 |
| Columbine *(Aquilegia coerula hybrida)* | blue | No dialysis in 8 hr | — | 5.4 |
| Columbine *(Aquilegia coerula hybrida)* | violet | Violet — blue (in 2 hr) | — | 5.5 |
| Columbine *(Aquilegia coerula hybrida)* | pink | Dialyses in 2 hr | none | 5.6 |
| Pansy *(Viola tricolor)* | blue | No dialysis in 24 hr | to cathode | 5.3 |
| Peony *(Paeonia officinalis)* | red | Dialyses in 5 hr | none | 5.0 |
| Larkspur *(Delphinium consolida)* | blue | Blue precipitate | — | 5.5 |
| Canterbury bell *(Campanula spec.)* | blue | Blue precipitate after 5 hr | to cathode | 5.7 |
| Tufted violet *(Viola cornuta)* | blue-violet | Blue precipitate after 1 hr | — | 6.0 |
| Aster *(Aster spec.)* | red | Dialyses in 3 hr | none | 5.25 |
| Lobelia *(Lobelia spec.)* | blue | No dialysis in 10 hr | to anode | 5.85 |

[a] In 0.2 M acetate buffer, pH 4.62, 400 V.

## Limits of the Complex Formation Theory

Complex formation has been proved for cyanin by the isolation of protocyanin. In the case of delphinidin glycosides, as was already observed by *Willstätter* [27], the decoloration to the leuco-base in dilute solution does not occur so readily as in the case of cyanin. Thus

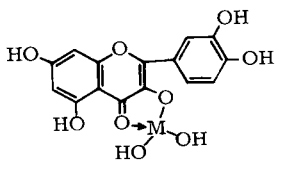
[24] *P. Werckmeister*, Der Züchter *24*, 224 (1954).

[25] *M. Hadders* and *C. Wehmer* in *G. Klein*: Handbuch der Pflanzenanalyse. Springer, Vienna 1932; Vol. III/2, p. 984.

[26] *E. Bayer*, Chem. Ber. *92*, 1062 (1959).

[27] *R. Willstätter* and *T. J. Nolan*, Liebigs Ann. Chem. *408*, 3 (1915).

the violet quinoid anhydro-bases *(22)* of delphinidin glycosides could be stable in weakly acidic to neutral media [12].



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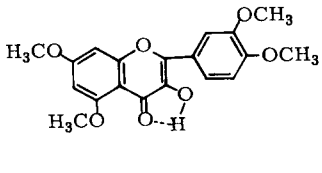

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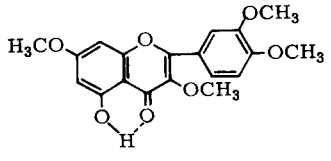

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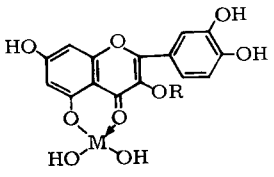

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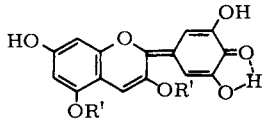

*(22)*

We have therefore studied the question of whether the pigment of the larkspur is an aluminum or an iron complex. This pigment is sparingly soluble in water, and can be extracted from the flowers only with dimethylformamide/water (2:1). Comparison of the absorption spectra (Fig. 6) of a synthetic delphinin-aluminum complex and of the larkspur pigment shows

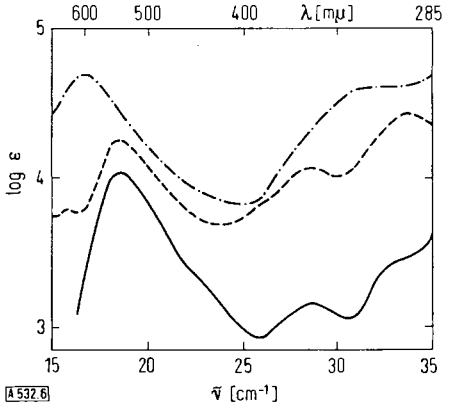


Fig. 6. Absorption spectra of delphinin chloride in 0.01% methanolic hydrochloric acid (—), larkspur pigment in acetate buffer, pH 4.7 (---), and chlorodidelphininoaluminum (·····).

that the latter absorbs at a wavelength 40 to 50 mμ lower, and has a lower maximum extinction than chlorodidelphininoaluminum. The addition of an aluminum salt to the pigment of the larkspur causes a shift towards longer wavelengths and an increase in extinction, owing to complex formation (Fig. 6). Thus the larkspur pigment does not consist primarily of an iron or aluminum complex. Like protocyanin, the pigment of larkspur cannot be dialysed, and so has a high molecular weight. A polysaccharide is again involved. In addition to glucose and arabinose, it contains galacturonic acid. The pigment contains metal ions only in traces, the quantity being about ten times smaller than the stoichiometric amount for chelate formation. Thus the pigment of the larkspur is a compound of a pectin-like polysaccharide and the neutral "anhydro-base" *(22)* of delphinin, without metal ions. This linking of delphinin to pectin to give a non-dialysable molecular complex can also be brought about artificially. When 400 mg of purified apple pectin is added to 19.5 mg of pure delphinin, isolated from larkspur, in 50 ml of water, less than 2% of the delphinin passes through the dialysis tube after dialysis for 20 hours. As the pectin is added, the extinction increases, as shown by Fig. 7. Moreover, the position of the maximum extinction agrees with that of the larkspur pigment maximum. Details of the bonding of the anhydro-base of delphinin to the pectin are not known; hydrogen bonds possibly are involved. Cyanin does not form blue-violet non-dialysable complexes with

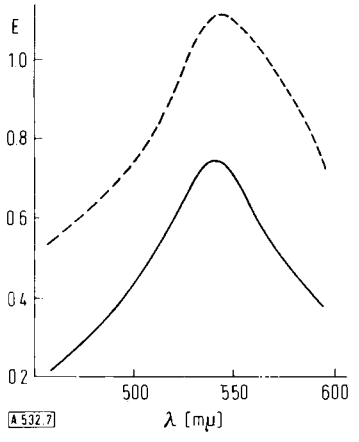


Fig. 7. Increase in the extinction of delphinin in acetate buffer, pH 4.7 (—), on addition of purified apple pectin (---).

Delphinin chloride (18 mg) was dissolved in 6 ml of 0.1% methanolic hydrochloric acid and 2 ml of distilled water. The solution was made up to 50 ml with 0.2 M acetate buffer (pH 4.7), and pectin in acetate buffer (pH 4.7) was then added (40 mg of pectin to 18 mg of delphinin). Before the measurements were made, the reference solution and the samples containing added pectin were allowed to stand for 1 day, and were then centrifuged.

pectins. Moreover, the aglycone delphinidin exhibits neither a deepening of color nor the formation of a macromolecular non-dialysable compound when pectin is added.

These results may explain the observation of *K. Hayashi et al.* [28], who isolated a blue compound containing 1 atom of magnesium per 4 molecules of delphinidin glucoside from *Commelina communis*. This is opposed by the fact that, as with the cyanidin derivatives, spectroscopic studies and attempted isolation have failed to reveal any tendency for delphinin or delphinidin to form complexes with alkaline earth ions at pH 2 to 9 [16, 18, 29]. The attachment of four bidentate anthocyanin ligands would result in a coordination number of 8 for magnesium. Thus this theory is im-

[28] *K. Hayashi, Y. Abe,* and *S. Mitsui,* Proc. Japan Acad. *34,* 373 (1958); *35,* 169 (1959).

[29] *E. Bayer,* Chimia *16,* 333 (1962).

probable from the chemical point of view. However, this conflict would be resolved if the blue color in the commelin, as in the larkspur, were due to the combination of a polysaccharide with the anhydro-base of the delphinidin glycoside, and if the magnesium were simply an impurity that is difficult to remove. It is probable, therefore, that *Hayashi et al.* [28] are the first to have isolated a member of this class of macromolecular pigments.

The bonding of anthocyanins to pectins is probably also involved in the coloring of fruits. Thus it has been known for some time that the pigment of red grapes can be dissolved more easily in order to obtain an intensely red wine if an enzyme that attacks pectins, *e.g.* vinibon [30], is added.

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Translated by Express Translation Service, London

[30] *E. Vogt*: Der Wein. 3rd Ed. Eugen Ulmer, Stuttgart 1595, p. 129.

# Evolutionary Aspects of the Structure of Proteins

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*The evolution of protein structures is discussed using cytochrome c, hemoglobin, and neurohypophyseal hormones as examples. Although these substances have different biological functions, their evolution is controlled by the same general rules: their primary structures vary at the level of the species, order, or class, but this variation is restricted by the fact that the biological activity of the protein must not be impaired. Alterations (i.e. substitutions, deletions, or additions of amino acid residues) can therefore occur only in certain positions of the peptide chains, although with different frequencies. The total number of alterations thus represents only the final state of a protein and does not take into account successive substitutions which may have taken place at the affected sites. It can therefore give only a rough indication of the phylogenetic distance between two species. The nature of the substituting residues, on the other hand, is a useful guide to zoological cognateness, since it allows the identification of transition molecules which simultaneously contain amino acid residues from the protein of the evolutionary ancestor and from the protein of the evolutionary descendant.*

Although normally observed on the morphology of organisms, evolution must ultimately be due to changes at the molecular level, since every hereditary modification in the phenotypes results from a genetic mutation, *i.e.* a change in deoxyribonucleic acid (DNA). This does not mean, however, that the "laws" of the evolution of organisms apply to molecular evolution. Thus, whilst genetic mutations are random and anarchic, the evolution of organisms seems to be oriented in a certain direction by natural selection, which filters the multitude of genetic mutations and makes new beneficial characteristics dominant. The question, however, is to what extent is morphological "orthogenesis" connected with molecular "orthogenesis", *i.e.* to what extent is morphological evolution parallelled by chemical changes. This question can be answered only by selecting the operative molecules from various species and by arranging them in the order attributed to phylogeny. If we can then recognize a stepwise change in the molecules that can be correlated with the steps of anatomical evolution, we can begin the more direct, biochemical investigation of the mechanism of evolution.

The new task in this connection is to examine the chemistry of the genes, which are responsible for the transmission of existing characteristics and for the appearance of new characteristics through mutations. It is now accepted that genes are deoxyribonucleic acids and that their specific action depends on the sequence of the constituent nucleotides. If these deoxyribonucleic acids could be isolated and analysed, we could directly compare the genetic materials of various species. While this is not yet possible, we can isolate and characterize the "products" of the genes, *i.e.* enzymes and, more generally, proteins. It has emerged from the experiments of *Yanofsky et al.* [1] that the sequence of the amino acid residues in proteins corresponds to the sequence of nucleotides in DNA (concept of colinearity). We may therefore study mutations as reflected in the corresponding proteins.

Proteins are characterized not so much by the number and the nature of the constituent amino acids, as by their sequence. Mutational changes in this structure can occur by insertion, deletion, or substitution of the amino acid residues. A unit change can therefore be defined as one which affects a single residue in the chain. We can also determine the variation coefficient,

[1] *C. Yanofsky, B. C. Carlton, J. R. Guest, O. R. Helinski*, and *U. Henning*, Proc. nat. Acad. Sci. USA *51*, 266 (1954).

*i.e.* the ratio of the number of changed residues to the number of unchanged residues. Comparison of homologous proteins of fishes, amphibians, reptiles, and mammals shows that a structural pattern remains unchanged in all these classes. This usually involves the length of the peptide chain, the prosthetic group, and the nature of the amino acids in certain positions. This unchanged structural pattern is probably linked with the biological role of the particular protein.

Interestingly, the length of the peptide chain of homologous proteins is the most stable parameter. All the cytochromes c of the vertebrates so far investigated consist of a chain with 104 amino acid residues, and all the neurohypophyseal hormones of fishes, amphibians, birds, and mammals contain nine amino acid residues. Evolutionary changes seem, therefore, to be restricted to substitutions of amino acid residues in the chain, insertion and deletion occurring only rarely.

Furthermore, investigations of the mutations of tryptophan synthetase[1], hemoglobins[2], and tobacco mosaic virus (TMV)[3] have shown that a genetic change generally affects only one amino acid residue at a time. We may therefore consider an amino acid substitution as a unit evolution. If this is correct, the evolution of the vertebrates should be accompanied by an increase in the number of substitutions. Substitutional similarity will then be a criterion of interspecific kinship, and a scheme of evolution can be based on the number of substitutions (Fig. 1, left), provided that

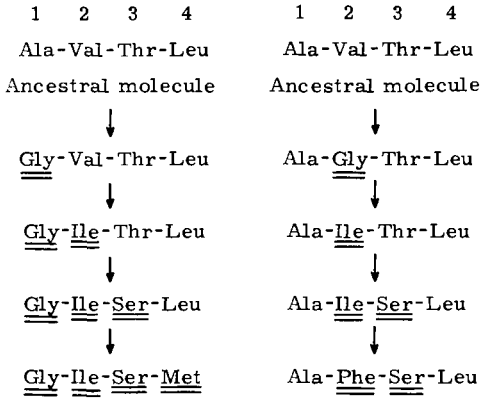


Fig. 1. Evolution of proteins having equal (left) or unequal (right) frequencies of substitution at various sites in the chain (schematic).

mutation affects all positions of a peptide chain with equal probability. However, this is not the case, since in the proteins of vertebrates some positions are never affected while others are involved with various frequencies. The biological function of the molecule does not allow just any substitution, and it is probably the position in the chain which determines whether an amino acid will be a permanent feature or substitutable, and if so, with what probability. The number of immutable positions often is equal to or exceeds the number of the mutable sites. Thus it is not the total number of substitutions in the chain, but the nature of the amino acids on sites with frequent variations that enables us to trace the evolution of a protein, and it should be possible to characterize in certain zoological groups transition molecules with structures intermediate between those of proteins of more primitive species on the one hand, and of more highly evolved ones on the other (Fig. 1, right).

Since the evolution of the vertebrates is the best known, and since proteins from vertebrates are relatively easy to obtain, they have been the subject of most studies. For practical reasons, the proteins selected must be produced by the organisms in sufficient amounts, they must be amenable to rapid purification, and they must have a relatively small molecular weight permitting complete structural analysis in a reasonably short time. Hemoglobins and cytochromes c (abundant and easy to purify), and the neurohypophyseal hormones (structurally simple) fulfil these conditions. Although they have different biological functions, they agree in that their molecules vary from species to species or from class to class.

## I. Cytochrome c

Among the proteins involved in the respiratory chain of aerobic organisms, cytochrome c is one of the easiest to purify, since it is easily soluble and, like most basic proteins, easy to process on cation exchangers. Cytochrome c has been isolated from vertebrates, invertebrates, microorganisms, and some plants. In a number of cases it has been crystallized. Cytochrome c of the heart of vertebrates has been investigated in particular, since this organ contains a relatively large amount of the enzyme. The cytochromes c from various classes of vertebrates all contain 104 amino acid residues, a single prosthetic group (heme), have an isoelectric point close to pH 10 and a redox potential close to +250 mV. Furthermore, they all react with mammalian cytochrome oxidase. Obviously their function has suffered no change in the course of evolution, although their structures have been modified by amino acid substitutions. It has not yet been possible to relate the steps of chemical change with the steps of morphological evolution, although the number of amino acid substitutions increases as we approach the top of the evolutionary ladder.

### 1. The Structural Pattern

We denote by the term "structural pattern" the totality of structural features that do not show any interspecific variation. The structural pattern of the cardiac cytochromes c of 12 species belonging to three classes of vertebrates[4,5] is characterized by a chain of 104 amino

[2] *C. Baglioni* in *J. H. Taylor*: Molecular Genetics. Academic Press, New York, London 1963, Part I, p. 405.

[3] *A. Tsugita* and *H. Fraenkel-Conrat* in *J. H. Taylor*: Molecular Genetics. Academic Press, New York, London 1963. Part I, p. 477.

[4] *E. Margoliasch* and *E. L. Smith* in *V. Bryson* and *H. J. Vogel*: Evolving genes and proteins. Academic Press, New York, London 1965, p. 221.

[5] *E. L. Smith* and *E. Margoliasch*, Fed. Proc. *23*, 1243 (1964).

acid residues, about half of which are identical in all the proteins in question, and by a heme prosthetic group fixed in the 14,17-positions, so that the two thioether bridges of the chain are always separated by two amino acids (see Fig. 2). Though the chain length varies slightly in invertebrates and microorganisms, it is constant in vertebrates, so that evolution operates here only through amino acid substitutions.

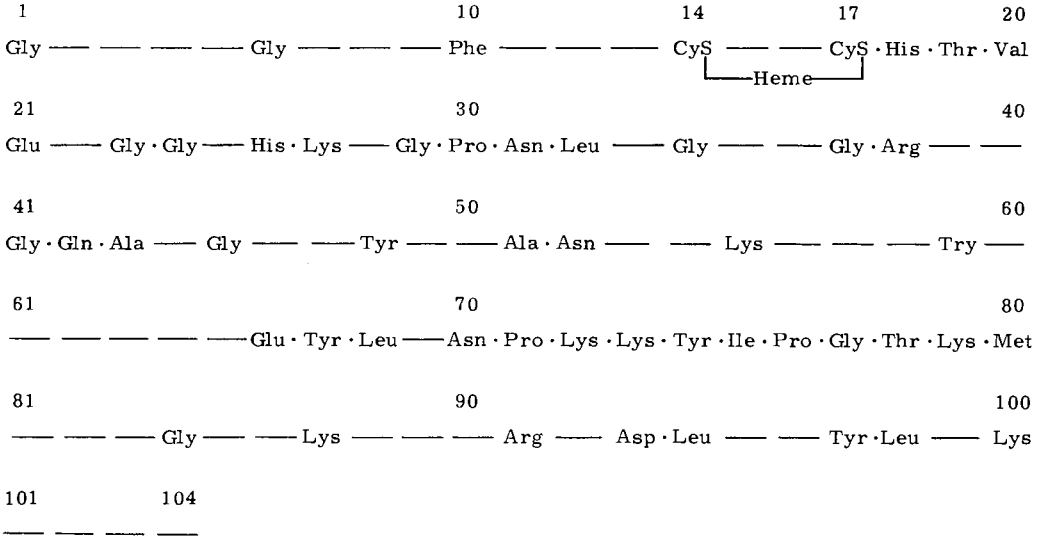


Fig. 2. Structural pattern of the cytochromes c of vertebrates: The dashes represent mutable sites (after [4]).

## 2. Substitutions

### a) Total Number of Substitutions

Figure 2 shows that positions 70 to 80 on the peptide chain are exempt from substitution. This may be because mutations have never affected this region, or because this region is indispensable to the enzymatic activity and the molecules inactivated by substitutions were eliminated during evolution. On the other hand, the substitutable positions outside this region are fairly regularly distributed along the peptide chain, indicating that substitutions affect the sites singly.

Table 1 shows that the difference in the number of substitutions in the cytochromes c is small between mammals of the same order, but significantly greater between mammals of different orders. However, the total number of substitutions is not sufficient for establishing a kinship among various species of vertebrates. Thus, the cytochrome c of the tunny, a bony fish, differs from that of mammals only by 17 to 21 residues, the difference between those of man and horse being as high as 12 residues. Such a comparison takes into account only the "final" states and gives the minimum number of substitutions that must have taken place. The actual number is surely considerably higher, for some sites may have suffered a series of substitutions in the course of evolution, only the last one of which is detected. The observed minimum number of substitutions is thus only a rough indication of interspecific kinship, having a greater validity only within small zoological groups.

Table 1. Number of substitutions in the cytochromes c of some mammals.

| Species compared | Orders compared | Number of substitutions |
|---|---|---|
| Man — ape | Primates — primates | 1 |
| Cow — pig — sheep | *Artiodactyla-Artiodactyla* | 0 |
| Cow — horse | *Artiodactyla — Perissodactyla* | 3 |
| Man — cow | Primates — *Artiodactyla* | 10 |
| Man — horse | Primates — *Perissodactyla* | 12 |
| Man — dog | Primates — *Carnivora* | 10 |
| Man — rabbit | Primates — *Rodentia* | 11 |

### b) Nature of the Substitutions

Depending on whether the substitution involves two chemically equivalent or non-equivalent amino acids, we distinguish between substitutions which preserve and others which alter the chemistry of the chain [4]. Chemically equivalent amino acids are, for example, isoleucine and valine, serine and threonine, or lysine and arginine. Substitution between any of these pairs generally does not change the chemical properties of the protein, its biological properties being changed only to a very small extent. By contrast, the replacement of a charged residue by a hydrophobic residue such as that of lysine by isoleucine, represents a considerable modification and may lead to a molecule with novel properties. Both preserving and modifying substitutions are detectable in the cytochromes c.

Since the prosthetic heme group plays an important part in the electron transfer, substitutions in its neighborhood are of particular interest [6]. Figure 3 shows the preserving and the modifying substitutions affecting these positions in the cytochromes c of 12 vertebrates, in yeast, and in the invertebrate *Samia cynthia* [4].

[6] *S. Paleus* and *H. Tuppy*, Acta chem. scand. *13*, 641 (1959).

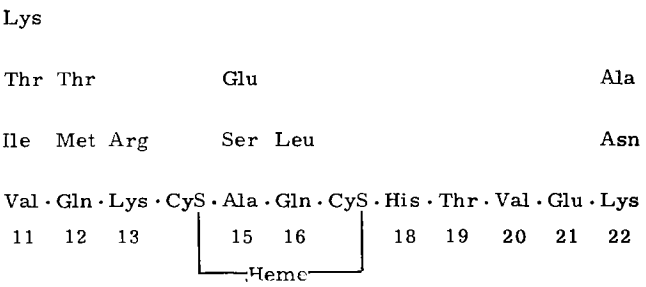


Fig. 3. Substitutions near the heme group in a series of 14 cytochromes c. The base line shows the sequence as found in seven species (after [6] and [4]).

## II. Hemoglobins

Hemoglobin is an abundant protein which can be easily purified and which constitutes almost the entirety of the soluble proteins present in the red cells of the blood. For its isolation the erythrocytes are separated from the plasma by centrifuging, washed with an isotonic solution, and finally lysed with distilled water. Unlike the red cells of mammals, those of lower vertebrates are nucleated, and the purification must then involve the elimination of the nucleic acids. The molecular weights of the hemoglobins of numerous species belonging to different classes of vertebrates were determined by ultracentrifugation. The values found are between 64000 and 68000, except in the case of *Cyclostomata*, the most primitive vertebrates, where it is 17000 [7]. It appears, therefore, that the hemoglobin molecule increased in size at the very beginning of the evolution of the vertebrates.

Study of the primary structure of hemoglobin, *i.e.* of the amino acid sequence, received a new impetus when it was found that the protein is a "tetramer" formed from four peptide chains each having a molecular weight of 17000, and that the molecule can be dissociated simply by lowering the pH. Horse hemoglobin has been separated by electrophoresis and chromatography at pH 2 into two types of peptide chain, $\alpha$ and $\beta$, native hemoglobin containing two of each. This has led biochemists to consider two independent gene-protein systems (corresponding to the $\alpha$ and the $\beta$ proteins) and to postulate the duplication of an ancestral molecule.

### 1. Multiplicity of Chains

The chains of the hemoglobins of mammals have been generally separated by ion-exchange chromatography on Amberlite IRC-50, a carboxylic acid resin, at pH 2.1 with a urea buffer gradient. In the case of the hemoglobins of lower vertebrates, however, it is better to use countercurrent distribution with sec-butanol and dilute dichloroacetic acid as the mobile and the stationary phases, respectively [8]. Two types of chain have been found in the hemoglobins of various species, such as the horse, the rabbit, the pig, the llama, and the cow [8], a great number of primates [10], and the carp [9].

The hemoglobin of adult man contains 90 % of hemoglobin $A_1$, consisting of two $\alpha$ and two $\beta$ chains, and 2–3 % of hemoglobin $A_2$, consisting of two $\alpha$ and two $\delta$ chains. The human fetus has hemoglobin F, consisting of two $\alpha$ and two $\gamma$ chains. The human body thus produces four hemoproteins ($\alpha$, $\beta$, $\delta$, $\gamma$). The amino acid sequence in the $\alpha$, $\beta$, and $\gamma$ chains is now fully known [7–11]. The $\alpha$ chain contains 141 residues, the other three contain 146. Comparison between the $\beta$ and the $\gamma$ chains shows that only 39 out of the 146 sites differ, *i.e.* the degree of homology is 73 %. The 39 substitutions seem to be randomly distributed along the chains without forming blocks. Chains $\beta$ and $\delta$ are likewise similar. As mentioned above, the $\alpha$ chain, which is always present in human hemoglobin, differs from the other three by containing only 141 amino acid units. Although the homology between the $\alpha$ and the $\beta$ chains is only 44 % (64 identical sites), it is still sufficiently great to indicate a common ancestry. In this case the variations are not restricted to substitutions but also involve deletions and insertions.

Detailed investigations on ten apes [10] have revealed the presence of two $\alpha$ and two $\beta$ chains. The simian $\alpha$ chain differs from the human $\alpha$ chain by 0 to 6 substitutions, but the simian $\beta$ chain differs from the human $\beta$ and fetal $\gamma$ chains by 3 to 23 and by 9 to 36 substitutions, respectively.

The two hemoglobins found in the erythrocytes of the horse may be considered to be homologous with the human $A_1$ and $A_2$ types. As in humans, the $\alpha$ chains of both hemoglobins contain 141 residues and are identical. The $\beta$ chains, on the other hand, contain 146 residues and are different. More than one type of hemoglobin has been found in the cow, the sheep, and the mouse [9], and this plurality appears to be the rule.

As in humans, the hemoglobins of all the adult mammals investigated (cow, horse, sheep, rabbit, pig, and llama) consist of two $\alpha$ chains and two $\beta$ chains, and can be represented by the general formula $\alpha_2\beta_2$. As in man, the fetal hemoglobin found additionally in *e.g.* cow, sheep, and goat, consists of $\alpha$ chains, identical to those in the adult hemoglobin, and $\gamma$ chains which differ from the adult $\beta$ chains. The general formula of fetal hemoglobin is therefore $\alpha_2\gamma_2$.

In each group the chain length seems to be the most stable property (see Table 2). On the other hand, the $\alpha$ chain exhibits appreciably fewer substitutions than the

[7] *V. M. Ingram*: The hemoglobins in genetics and evolution. Columbia University Press New York, London 1963.

[8] *G. Braunitzer, K. Hilse, V. Rudloff*, and *H. Hilschmann*, Advances Protein Chem. *19*, 1 (1964).

[9] *G. Braunitzer, V. Braun, K. Hilse, G. Hobom, V. Rudloff*, and *G. v. Wettstein* in *V. Bryson* and *H. J. Vogel*: Evolving genes and proteins. Academic Press, New York, London 1965, p. 183.

[10] *J. Buettner-Janusch* and *R. L. Hill* in *V. Bryson* and *H. J. Vogel*: Evolving genes and proteins. Academic Press, New York, London 1965, p. 167.

[11] *W. A. Schroeder*, Fortschr. Chem. org. Naturstoffe *17*, 322 (1959).

β and γ chains. This is illustrated in Fig. 4 for the amino end of the chains.

Table 2. Number of residues in the α, β, and γ chains of the hemoglobins of some mammals.

| Species | α | β | γ |
|---|---|---|---|
| Man | 141 | 146 | 146 |
| Horse | 141 | 146 | |
| Cow | 141 | 145 | 145 |
| Lemur | | 146 | |
| Camel | | 146 | |

common hemoglobin. The hemoglobin of the lamprey has been isolated in pure form. It contains only one peptide chain consisting of 160 amino acid residues. Its structure is more like that of mammalian myoglobin than that of the α or the β chain of vertebrate hemoglobin [9].

## 2. The Theory of Duplication

Inspection of the number and the sequence of amino acid residues in the hemoglobin chains suggests that

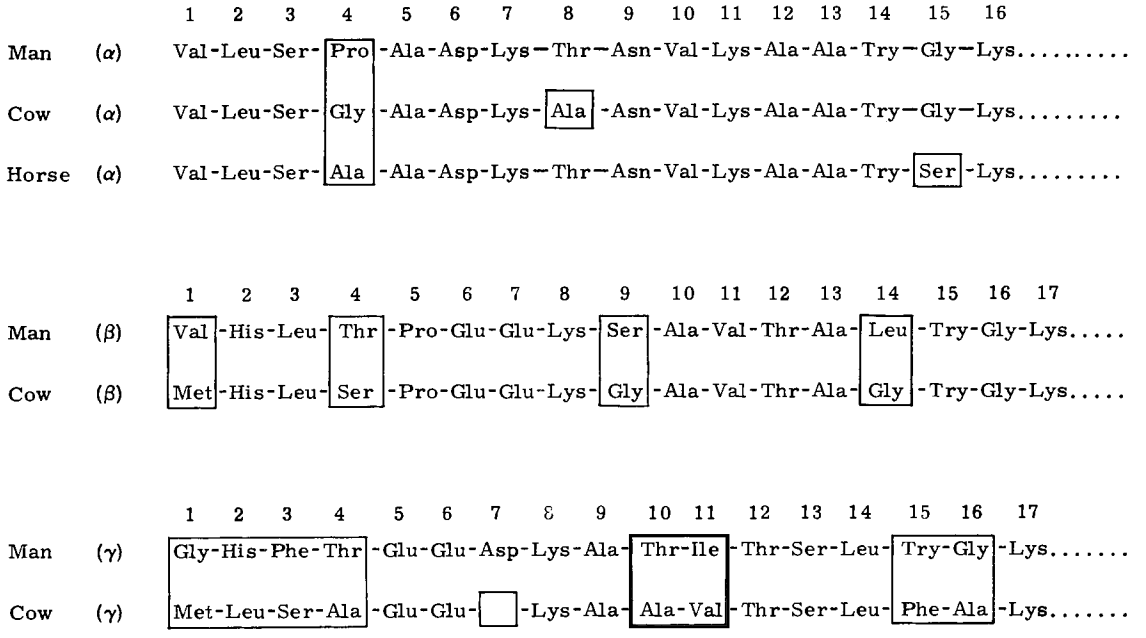


Fig. 4. Comparison of the amino ends of the α, β, and γ chains in human, bovine, and equine hemoglobins. Boxes denote substitutions, empty boxes deletions.

Similar remarks seem to apply to other classes of vertebrates in that the adults frequently contain two or more hemoglobins formed by two types of chain, so that the general formula $\alpha_2\beta_2$ still applies. Thus, in the classes *Aves* and *Pisces*, the hen [12] and the carp [13] have two and three hemoglobins separable by electrophoresis or chromatography. Unlike the β chain, the α chain in the predominant hemoglobin of the carp has an acetylated amino group at one end [13] and, unlike the mammalian α chain (141 residues) contains 142 residues [9]. As with the cytochromes c of the vertebrates, the length of the peptide chains is probably the most constant feature.

Since the *Cyclostomata* constitute the most primitive class of vertebrates, their proteins should be closest to the ancestral type. The lamprey is one of the few remaining representatives of this class. The molecular weight of its hemoglobin is about a quarter of that found in vertebrates [14]. In this respect, it is closer to myoglobin found in the muscles of vertebrates than to they are derived from a single ancestral molecule. Gene duplication is the simplest way to explain the formation of new genes. *Ingram* [8] has advanced this explanation to account for the four types of chain in normal human hemoglobins. As regards their molecular weight, amino acid sequence, *etc.*, these chains resemble the myoglobin of muscles. Accordingly, the gene controlling the biosynthesis of myoglobin should be the oldest and the ancestor of the genes now controlling the biosynthesis of the α, β, γ, and δ chains (Fig. 5).

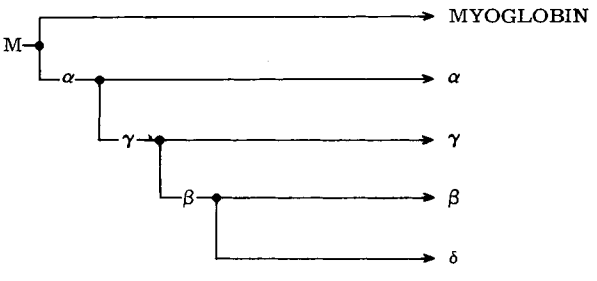


Fig. 5. Evolution of the hemoglobin chains. The dots denote gene duplications (after [8]).

Differentiation of the myoglobin gene M would have given rise to two genes, one of which continues to control the synthesis of myoglobin, the other leading *via* mutations to the formation of the α chain. Duplication of the α gene would give two daughter genes, one

[12] *Cl. Paul, A. G. Schnek*, and *J. Léonis*: Chromatography Symposium II, 1962, p. 133.

[13] *K. Hilse, V. Sorger*, and *G. Braunitzer*, Hoppe-Seylers Z. physiol. Chem. *344*, 166 (1966).

[14] *T. Svedberg* and *I. B. Eriksson-Quensel*, J. Amer. chem. Soc. *56*, 1700 (1934).

form of which continues to control the production of the $\alpha$ chain, the other after modification causing the synthesis of the $\gamma$ chain. The same mechanism would operate in the successive formation of the $\beta$ and $\delta$ chains. This scheme accounts for certain genetic and chemical observations: as implied by the similarity in the amino acid sequences of the corresponding proteins, genes $\gamma$, $\beta$, and $\delta$ are seen to be derived from one another, in that order, while the $\alpha$ gene, which is the most stable, is considered as the oldest of the four. The only reason for placing the $\gamma$ gene before the $\beta$ and $\delta$ genes is that it occurs in the fetus, the other two being found only in the adult.

the amino acid sequence of the corresponding protein. As time proceeds, the two protein structures become more and more dissimilar.

Investigations on the pathological variations of human hemoglobins have revealed a great number of abnormalities. Genetic studies on several generations have shown that these abnormalities result from mutations. The number of the abnormal hemoglobins (B, C, D) has turned out to be so large (about 40) that now a combination of letters (B, C, D) and places of origin is used for denotation. An important feature is that mutation affects almost always only one amino

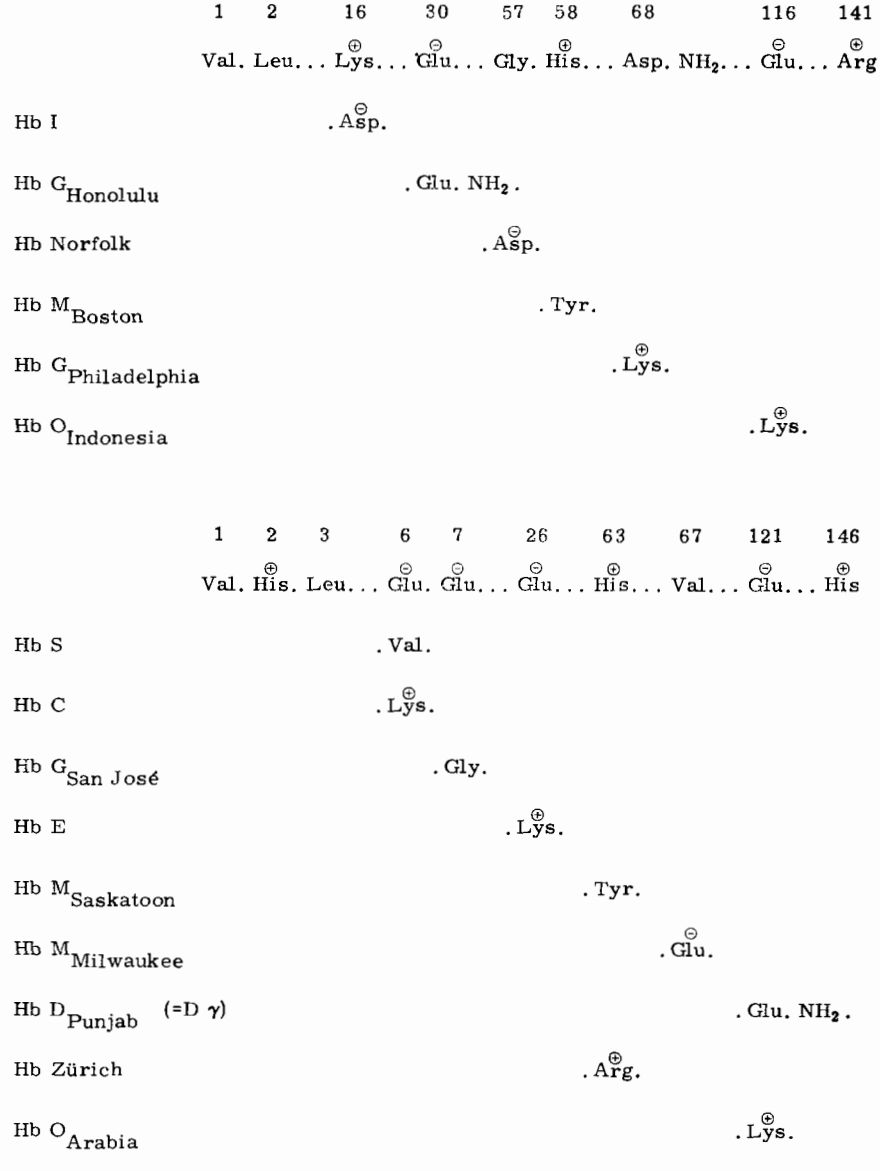


Fig. 6. Substitutions in abnormal human hemoglobins due to the mutations in the genes $\alpha$ (above) and $\beta$ (below) (after [8]).

### 3. Mutations

The hypothesis of duplication explains the formation of two twin genes, each controlling the synthesis of one protein. Initially, the two proteins were also twins. However, each gene suffers some mutations independently of the other. These mutations result in changes in acid residue at a time. Gene $\beta$ is characterized by an appreciably greater number of mutations than gene $\alpha$. The substitutions induced in the protein molecules by mutations are randomly distributed along the chains (see Fig. 6). Furthermore, insertions and deletions must be very rare, since the chain length has been found to be constant.

## III. Neurohypophyseal Hormones

The neurohypophysis produces hormones which have relatively simple structures. For this reason, they were among the first peptide hormones to be characterized. Oxytocin and vasopressin were isolated from cattle [15–17].

### 1. Duality of the Hormones

Tests for oxytocic and pressor activities in the hypophyseal extracts give positive results with all vertebrates, though the levels of activity may differ considerably (Table 3). The neurohypophyseal (NHP) hormones have been isolated from six mammals (man, cow, pig, horse, sheep, and whale), one bird (hen), one amphibian (frog), five bony fishes (bib, pollack, silver hake, cod, and carp), and four cartilaginous fishes (rays). Purification was always carried out by selective adsorption of the hormones onto a protein, neurophysin. The resulting complex was then isolated by fractional precipitation and dialysis. Treatment with trichloroacetic acid precipitated the protein, the hormones remaining in solution. The last step was chromatography on Amberlite CG-50. Some of the chromatographic results are shown in Figures 7a to 7d.

Table 3. Biological activities of posterior pituitary powders from various species of vertebrates.

| Species | | Oxytocic activity [units/mg dry powder] | Vasopressin activity [units/mg dry powder] |
|---|---|---|---|
| Mammals: | Cow | 1.0 | 1.1 |
| | Pig | 1.4 | 1.4 |
| | Horse | 0.9 | 0.8 |
| | Sheep | 0.8 | 0.8 |
| | Whale | 0.5 | 2.5 |
| Birds: | Hen | 0.4 | 0.4 |
| Amphibians: | Frog | 1.2 | 1.0 |
| | Toad | 1.0 | 0.8 |
| Bony fishes [a]: | Bib | 0.6 | 0.5 |
| | Pollack | 0.5 | 0.5 |
| | Hake | 0.5 | 0.3 |
| | Cod | 0.? | 0.2 |
| | Carp | 0.05 | 0.04 |
| Cartilaginous fishes [a]: | Ray | 0.005 | 0.001 |
| | White skate | 0.007 | 0.001 |

Two neurohypophyseal hormones were found in each of the five classes of vertebrates investigated. The purity of the substances was checked by amino acid analysis. In the case of the lower vertebrates, the small size of the hypophysis necessitated the processing of a great number of glands to obtain sufficient material for the determination of the chemical structure. To isolate 1 to 5 mg of hormones, about 5000 to 10000 glands must be extracted. Analysis has shown that mammals contain oxytocin and vasopressin, amphibians mesotocin and vasotocin, bony fishes isotocin and vasotocin, and cartilaginous fishes glumitocin and probably vasotocin. On the various chromatograms, oxytocin, mesotocin, isotocin, and glumitocin occupy the same position. They are the first to be eluted, and are followed by vasotocin or arginine-vasopressin (Fig. 7).

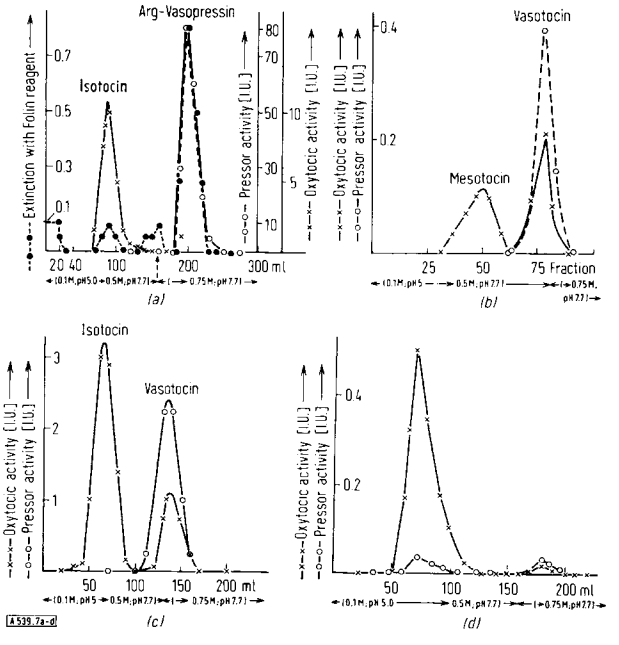


Fig. 7. Chromatograms of the neurohypophyseal hormones of vertebrates (Amberlite CG-50, ammonium acetate gradient) (after [18]). (a) mammals (whale); (b) amphibians (frog); (c) bony fishes (hake); (d) cartilaginous fishes (ray).

### 2. Characterization of the Hormones

All these hormones are peptides having nine amino acid residues (Table 4).

*Mammals*: The NHP hormones of the cow and the pig have been known since 1953, those of the horse, sheep, whale [18], and man [19] having been characterized more recently. All species contain the same oxytocin, five of the six containing the same arginine-vasopressin. Lysine-vasopressin, in which a lysine residue takes the place of an arginine residue, has been found only in the pig.

*Birds and amphibians*: The neurohypophysis of the hen, the only bird investigated, contains oxytocin and vasotocin, that of the edible frog (*Rana esculenta*) containing mesotocin and vasotocin [18].

*Bony fishes*: Isotocin and vasotocin are the two NHP hormones found in four marine species of *Teleostei*: the bib (*Gadus luscus*), the pollack (*Pollachius virens*), the hake (*Merluccius merluccius*), and the cod (*Gadus morhua*), and in one freshwater species of the *Teleostei*, the carp (*Cyprinus carpio*).

*Cartilaginous fishes*: Glumitocin and probably vasotocin are the two NHP hormones found in four species of Elasmobranchs (*Raia clavata*, *Raia batis*, *Raia fullonica*, and *Raia naevus*). The first hormone has been characterized chemically, the second only by pharmacological methods.

[15] *V. DuVigneaud*: A trail of research. Cornell University Press, Ithaca 1952.

[16] *H. Tuppy* and *H. Michl*, Mh. Chem. *84*, 1011 (1953)

[17] *R. Acher* and *C. Fromageot*, Ergebn. Physiol., biol. Chem., exp. Pharmakol. *48*, 286 (1955).

[18] *R. Acher*, *J. Chauvet*, *M.T. Chauvet*, and *D. Crepy*, Bull. Soc. Chim. biol. *47*, 2279 (1965).

Table 4. Neurohypophyseal hormones of some vertebrates.

| | | |
|---|---|---|
| Cartilaginous fishes | 1 2 3 4 5 6 7 8 9<br>Cys.Tyr.Ile.Ser.Asn.CyS.Pro.Gln.Gly($NH_2$)<br>Glumitocin | Vasotocin (?) |
| Bony fishes | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Ile.Ser.Asn.CyS.Pro.Ile.Gly($NH_2$)<br>Isotocin | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Ile.Gln.Asn.CyS.Pro.Arg.Gly($NH_2$)<br>Vasotocin |
| Amphibians | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Ile.Gln.Asn.CyS.Pro.Ile.Gly($NH_2$)<br>Mesotocin | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Ile.Gln.Asn.CyS.Pro.Arg.Gly($NH_2$)<br>Vasotocin |
| Mammals (except pig) | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Ile.Gln.Asn.CyS.Pro.Leu.Gly($NH_2$)<br>Oxytocin | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Phe.Gln.Asn.CyS.Pro.Arg.Gly($NH_2$)<br>Arginine-vasopressin |
| Pig | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Ile.Gln.Asn.CyS.Pro.Leu.Gly($NH_2$)<br>Oxytocin | 1 2 3 4 5 6 7 8 9<br>CyS.Tyr.Phe.Gln.Asn.CyS.Pro.Lys.Gly($NH_2$)<br>Lysine-vasopressin |

## 3. Phylogeny of the Hormones

Although the number of species investigated (about 20) is very small in comparison with the 50000 or so known vertebrates, the following general conclusions may be drawn since almost all the classes of vertebrates were represented:

(i) The neurohypophysis of each species contains two dominant hormones.

(ii) All these hormones have a common structural pattern characterized by nine amino acid residues with a disulfide bridge connecting the amino acids in positions 1 and 6.

(iii) The structure is the same within a given zoological class, and varies by only one or two residues between the classes.

(iv) The changes or mutations seem to affect preferentially "privileged" positions on the chain, in particular positions 4 and 8.

### a) The Ancestral Hormone

The twofold nature of the hormones of the neurohypophysis recalls the chain multiplicity of the hemoglobins and suggests a gene duplication. It must be assumed that this duplication occurred at a very early stage during evolution, since even the *Pisces* contain two hormones. In this connection, the *Cyclostomata*, and especially the lamprey, are of interest. Column-chromatographic and paper-electrophoretic experiments on the pituitary glands of the lamprey revealed only one neurohypophyseal hormone [20], which gave a positive result in pharmacological tests for vasotocin. In addition the lamprey may contain a second hormone, but one which is not detectable by the pharmacological test used. However, this hormone would have to differ greatly from those so far identified, since it is not adsorbed onto neurophysin. Apart from this, it seems

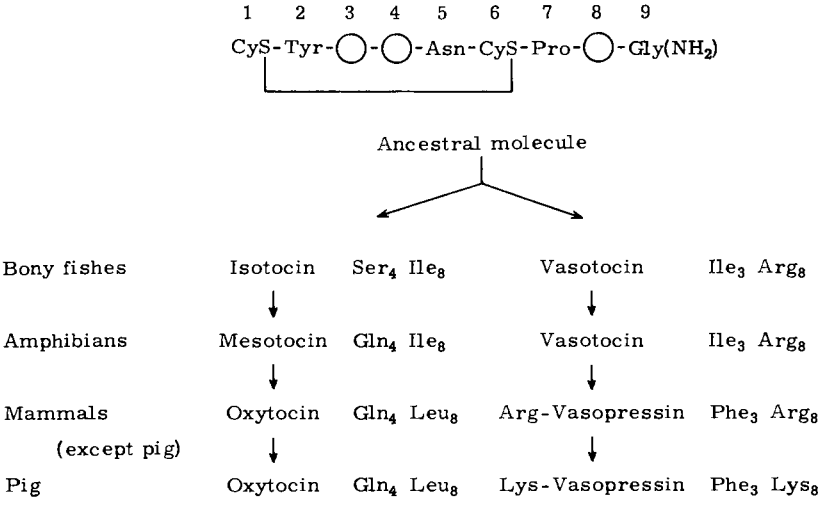


Fig. 8. Hypothetical scheme of the evolution of neurohypophyseal hormones. One gene duplication and a series of subsequent single substitutions in positions 3, 4, or 8 produce two molecular "lines".

feasible to envisage the gene duplication taking place somewhere between the *Cyclostomata* and the fishes. This would mean that two "lines" of molecules are formed, which then undergo diversification independently of each other. One line (isotocin, mesotocin, oxytocin) seems to be specialized in reproduction, the other (vasotocin, vasopressin) being specialized in the regulation of the salt and water balance (see Fig. 8).

b) Molecular Lines

Assuming that the hormones are derived from one another in the same chronological order as the species to which they belong, we can draw up the genealogy of these molecules in juxtaposition to the phylogenealogy proposed by *Simpson*[21]. The cartilaginous fishes and the bony fishes appeared at about the same time some 300 million years ago. However, while the cartilaginous fishes gave rise to no other class of vertebrates, the bony fishes gave rise to the amphibians, these to the reptiles, and these to the birds on the one hand and mammals on the other. It must therefore be examined whether molecular evolution as manifested by the chemical structure of the neurohypophyseal hormones follows the order: bony fish – amphibians – mammals. Considering the NHP hormones involved in the regulation of the water and mineral balance, we note that vasotocin is present in all the vertebrates, with the exception of mammals which contain vasopressin instead. The transformation of vasotocin into vasopressin requires only the substitution of phenylalanine for isoleucine in position 3 (cf. Fig. 8). Although chemically this is merely an interchange between two hydrophobic groups, it precipitates great biological changes: Vasotocin increases the water permeability of the frog bladder, exerts a contracting action on the rat uterus, and stimulates the re-absorption of water at the renal level. When vasotocin is transformed into vasopressin by the substitution $Ile_3 \rightarrow Phe_3$, the first two actions disappear almost entirely, while the third one increases considerably, so that in mammals vasopressin is a powerful antidiuretic.

In addition to the above substitution, porcine vasopressin contains lysine instead of arginine position 8. This second substitution causes practically no chemical change, and only a small biological change. In fact, lysine-vasopressin is the antidiuretic hormone in the pig, just as arginine-vasopressin is in other mammals.

More numerous – and thus more informative – transformations are found in NHP hormones in reproduction. Thus the bony fishes contain isotocin, the amphibians mesotocin, and the mammals oxytocin. The formation of mesotocin from isotocin involves a single substitution in position 4 (glutamine for serine); the formation of oxytocin from mesotocin involves the substitution of leucine in position 8 (see Fig. 8). Mesotocin in amphibians thus represents biochemically an intermediate stage between isotocin and oxytocin: the isoleucine in position 8 is still a piscine feature, but glutamine in position 4 is a mammalian one. From a general point of view, this mixed chemical structure is the molecular equivalent of mixed anatomical structures used by evolutionists to establish the connection between two zoological groups, and mesotocin may therefore be called a "transition molecule", *i.e.* a molecule forming a chemical and, ultimately, a phylogenic link between two genera, orders, and classes.

Although it involves an inference from the above particular case to the general, it seems reasonable to assume that proteins have evolved by a series of single substitutions of amino acids. In fact, this is in agreement with findings on the mutations of various proteins (hemoglobins, tryptophan synthetase, TMV protein), where the changes generally affect only one residue at a time. The transition molecules should provide a clue to the steps of transformation of proteins. It seems logical that the probability of molecular changes increases with time and with increasing chain length. This means that the larger the peptide or protein in question, the more one must restrict the size of the zoological group to be investigated, as otherwise one is confronted with undecipherable complexity.

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[19] *A. Light* and *V. DuVigneaud*, Proc. Soc. exp. Biol. Med. *98*, 692 (1958).

[20] *R. Acher*, *J. Chauvet*, *M.T. Chauvet*, and *D. Crepy*, unpublished.

[21] *G. G. Simpson*: The Meaning of Evolution. Oxford University Press, London 1950.

# The Chemistry and Biochemistry of Insulin

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*The protein hormone insulin occurs widely in the animal kingdom. Although its biological function is always the same, its amino-acid composition varies widely. Insulin consists of two polypeptide chains, which are linked by three cystine residues to form a bicyclic system with a 20-membered and an 85-membered ring. The protein crystallizes in various forms with foreign ions. In solution, insulin normally forms aggregates of 2n molecules. The hormone can be regenerated from the separated polypeptide chains, and its total synthesis has been achieved in a similar manner from synthesized peptide chains. In the biosynthesis of insulin, the two chains are evidently built up separately and subsequently linked together. Insulin promotes the synthesis of glycogen, fat, and protein in the organism; insulin deficiency leads to an increase in the blood-sugar level. At the molecular level, the mechanism of action of the hormone is still unknown. Current hypotheses are discussed. No specific active center has so far been detected in the insulin molecule, which contains several antigenic regions.*

## Introduction

In 1788, the physician *Cowley* [1] observed a connection between disturbance of the pancreas function and diabetes mellitus; *von Mering* and *Minkowski* [2] showed in 1889 that diabetes mellitus could be induced experimentally by extirpation of the pancreas. In 1900, *Schulze* [3] and *Ssobolew* [4] realized that the pancreatic substance responsible for lowering the blood-sugar level was formed in the Langerhans islet cells, and for this reason the unknown substance was named "insulin" in 1909 [5]. The extraction of insulin from the pancreas was achieved as early as 1911 [6], but it was only in 1920 that this extraction was carried out consistently by *Banting* and *Best* [7], with the collaboration of the biochemist *Collip*. Thus began the chemistry of insulin, which has since then progressed through the isolation of pure insulin by *Abel* (1926) [8] to the determination of its constitution by *Sanger* (1955) [9] and its synthesis (1963) [10, 11]; the determination of its steric structure, which was begun 30 years ago [12], will soon be completed.

Little is known as yet about an active center in the insulin molecule, its site of action, and its mechanism of action in the cell. Insulin occurs in organs of higher organisms including fish. Evidence has recently been found of its presence in starfish [13].

## Isolation and Purification

Insulin can be isolated in quantities of up to 5 mg [14] by methods based on the pioneering work of *Collip* [15] and of *Somogyi*, *Doisy*, and *Shaffer* [16]. The hormone is extracted from fresh or deep-frozen glands with 60 to 80 % ethanol at a pH of 1 to 3; this treatment inactivates the exocrine proteases of the pancreas. The extract is evaporated under vacuum and freed from fats; the insulin is then salted out, redissolved and finally precipitated isoelectrically at pH 5.3 to 5.4. It can also be precipitated directly from a more strongly acidic solution by seeding with insulin fibrils [17]. In a more recent

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[2] *J. v. Mering* and *O. Minkowski*, Naunyn-Schmiedebergs Arch. exp. Pathol. Pharmakol. *26*, 371 (1890).

[3] *Schulze*, Arch. f. mikroskop. Anat. u. Entwicklungsmech. *1900*, 56.

[4] *Ssobolew*, Zentralblatt Pathol. *11*, 202 (1900).

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[12] *D. Crowfoot Hodgkin et al.*, Oxford.

[13] *S. Wilson* and *S. Falkmer*, Canad. J. Biochem. *43*, 1615 (1965).

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[15] *J. B. Collip*, J. biol. Chemistry *55*, xl (1923).

[16] *M. Somogyi, E. A. Doisy*, and *P.A. Shaffer*, J. biol. Chemistry *60*, 31 (1924).

[17] *D. F. Waugh*, J. Amer. chem. Soc. *70*, 1850 (1948); *D. F. Waugh, R. E. Thompson*, and *R. J. Weimer*, J. biol. Chemistry *185*, 85 (1950).

process, which avoids the evaporation of the alcohol, the inert proteins are precipitated at pH 8, and residual enzymes are destroyed by brief warming in the acidic solution; the insulin can then be adsorbed on large-mesh ion exchangers (alginic acid [18], DEAE-cellulose, and CM-cellulose [19]) and eluted. This method leads to a 20 to 30 % improvement in yield [18]. From ox pancreas 2000 I.U./kg of gland are obtained, from calf's pancreas up to 10000 I.U. (≈400 mg)/kg, since the exocrine function of the pancreas is not yet developed in the new-born [20], and about 75000 I.U./kg from fish pancreas, since the endocrine part is separate from the exocrine in this case [21].

Methods have been found recently for the isolation of small quantities of insulin, as from single glands of test animals [22]. The pancreas extract can be freed from alcohol under very mild conditions by extraction with ether [23], and the insulin is usually separated by ion-exchange chromatography [19,21] and/or gel filtration [21,24]. Very small quantities of insulin can be isolated by precipitation with antibodies [25].

Crude insulin is most easily purified by repeated crystallization. This procedure gives products with constant biological activity, which were long thought to be absolutely pure. However, more accurate analytical methods showed that even repeatedly recrystallized insulins are not homogeneous [26]. Apart from the insulin antagonist glucagon [27], the most frequent impurity was a deamidoinsulin [28], though insulin-like proteins with little or no biological activity [29] and antigenic substances [30] have also been found.

The preparative final purification of insulin can be achieved by counter-current distribution [26], and chromatographic methods [31] and gel filtration [32] have also been used successfully. Even in highly purified insulins, however, it is generally still possible to detect a few foreign components by electrophoresis [33].

[18] *E. Jorpes, V. Mutt*, and *S. Rastgeldi*, Acta chem. scand. *14*, 1777 (1960).

[19] Cf. *L. F. Smith*, Biochim. biophysica Acta *82*, 231 (1964).

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[21] *R. E. Humbel* and *A. M. Crestfield*, Biochemistry *4*, 1044 (1965).

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[28] *E. J. Harfenist*, J. Amer. chem. Soc. *75*, 5528 (1953).

[29] *K. Nagasawa, S. Nishizaki, T. Hiraoka*, and *S. Fukasawa*, Bull. nat. Inst. hyg. Sci. (Eisei Shikenjo Hôkoku) *75*, 95 (1957).

[30] *T. Deckert*, Dissertation, University of Copenhagen, 1964.

[31] Cf. *A. Chrambach* and *F. H. Carpenter*, J. biol. Chemistry *235*, 3478 (1960).

[32] *C. J. Epstein* and *C. B. Anfinsen*, Biochemistry *2*, 461 (1963).

[33] *F. H. Carpenter* and *S. L. Hayes*, Biochemistry *2*, 1272 (1963).



Pure insulin crystals are difficult to obtain [34,35], but when suitable substances are added the hormone crystallizes fairly readily. Numerous crystalline insulin preparations are known, all of which contain water of crystallization and usually also relatively small quantities (in relation to the size of the molecule) of foreign ions; these are all called "crystalline insulin." The crystals are often externally similar, but they may differ when the insulin components are obtained from different animals [36,37].

Insulin was originally crystallized from buffered solutions in the isoionic range at pH 5.5 to 5.6 without the addition of metal ions [34,38], until *Scott* [39] found zinc in these crystals and showed that bivalent metal ions such as $Zn^{2+}$, $Ni^{2+}$, $Co^{2+}$, or $Cd^{2+}$ are essential to the crystallization of the hormone. $Cu^{2+}$, $Mn^{2+}$, and $Fe^{2+}$ ions [36] fulfil the same purpose, and half of the zinc can be replaced by magnesium or calcium [40]; after extraction with ethylenediaminetetraacetic acid, the zinc can be completely replaced by lead [41].

Since the metal content of the insulin crystals is directly proportional to the atomic weight of the metal [42] (0.52 % Zn, 0.77 % Cd, *etc.*), true compounds must be formed. However, crystals with lower metal contents (0.33 % Zn) are now also known [36], whereas in the other direction the zinc content can be increased to 5 % [43]. These compounds are regarded as double salts of the type 2 $M^{2+}$ insulin$^{4-}$·$n$ $MX_2$ [40,44]. The metal ions can be removed from insulins containing metals without destruction of the crystals [36,45].

In addition to zinc chloride, anions such as acetate, citrate, phosphate, or carbonate must also be present for the crystallization of insulin [46]. Insulin is only slightly associated in acidic solutions (pH 2 to 2.5) of low ionic strength, and it crystallizes from such solutions in the absence of metal [47,48] as the sulfate (2 insulin·12 $H_2SO_4$) in two forms, and as the selenate, phosphate, chloride, formate, acetate, and citrate. Crystalline salts of insulin with organic bases, free from zinc but containing metals, have long been known [49].

[34] *J. J. Abel, E. M. K. Geiling, C. A. Rouiller, F. K. Bell*, and *O. Wintersteiner*, J. Pharmacol. exp. Therapeut. *31*, 65 (1927).

[35] *J. Schlichtkrull*, Dissertation, University of Copenhagen, 1958; Svensk kem. Tidskr. *72*, 166 (1960).

[36] *J. Schlichtkrull*, Acta chem. scand. *10*, 1455, 1459 (1956); *11*, 291, 299, 439, 484, 1248 (1957).

[37] *K. Nagasawa, S. Nishizaki, Y. Takenaka, T. Honma*, and *T. Hiraoka*, Bull. nat. Inst. hyg. Sci. (Eisei Shikenjo Hôkoku) *76*, 217 (1958).

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[39] *D. A. Scott*, Biochem. J. *28*, 1592 (1934).

[40] *K. Marcker*, Acta chem. scand. *13*, 2036 (1959).

[41] *D. Crowfoot-Hodgkin*, personal communication.

[42] *D. A. Scott* and *A. M. Fisher*, Biochem. J. *29*, 1048 (1935); Trans. Roy. Soc. Canada *32 V*, 55 (1938).

[43] Danish Pat. *97*, 363 (1964), Novo Terapeutisk Lab. A./S.; Chem. Abstr. *61*, 9580b (1964).

[44] *E. Jensen, A. T. Jensen*, and *K. Marcker*, Acta chem. scand. *14*, 1919 (1960).

[45] *R. Netter*, Bull. Soc. chim. France *6*, D 1042 (1939).

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[47] *E. Ellenbogen*, Dissertation, Harvard University, Boston, 1949; *J. L. Oncley, E. Ellenbogen*, and *H. H. Dix*, 2e Congr. intern. biochim., Paris, Résumés communs. 61 (1952); *B. W. Low* and *J. E. Berger*, Acta crystallogr. *14*, 82 (1961).

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[49] *D. A. Scott* and *A. M. Fisher*, Trans. Roy. Soc. Canada *36 V*, 45 (1942).

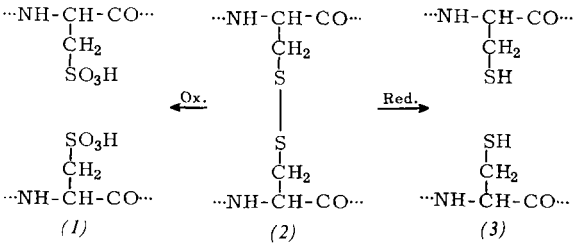
[50] *B. W. Low* and *J. R. Einstein*, Nature (London) *186*, 470 (1960); *J. R. Einstein, A. C. McGavin*, and *B. W. Low*, Proc. nat. Acad. Sci. USA *49*, 74 (1963).

The acidic salts are orthorhombic, and are probably built up from insulin dimers[50]. The cubic metal-free form gives very small rhombododecahedra, in which six insulin dimers[51] appear to form an aggregate. In the monoclinic zinc insulin (from solutions containing phenol) the unsymmetrical unit cell contains aggregates of six insulin molecules and two zinc ions[51]. In the two rhombohedral insulins, the unit cell contains two or four zinc ions in the insulin hexamer, depending on the halide content of the mother liquor[51,52]. The insulin molecules in the dimers are parallel[50,84].

Insulin crystals contain from 30 to 51 % of water of crystallization, depending on the modification[51]. The crystals shrink in air to a water content of 10 %. Part of the water (8 %, *ca.* 30 moles per mole of insulin) is not released even on drastic drying[53]. The zinc can be removed by dialysis or gel filtration[54], and particularly readily when glycine is added.

## Structural Formula

Although *Wintersteiner*, *du Vigneaud*, and *Jensen*[55] recognized insulin as a pure protein as early as 1928, many attempts were made to prepare "protein-free insulin" or to detect a cofactor. However, seventeen different amino acids were repeatedly found in insulin hydrolysates and determined quantitatively[56].




Oxidation of the molecule with performic acid[61] yields two fractions, which can be fractionally precipitated on the basis of the different charges (Acidic and Basic)[62]. The separation can also be carried out by counter-current distribution[63], zone electrophoresis[63] and ion-exchange chromatography[64]. Each of the fractions A and B is homogeneous, insulin therefore consists of the two polypeptide chains A and B.

*Sanger* and his co-workers[65] determined the overall structural formula of bovine insulin (Fig. 1); they first determined the sequences of the 30 and 21 amino acids in the B-[66,67] and A-chains[66,68], respectively, and then the positions of the amide groups[69] and of the three disulfide bridges[9]. The molecular weight was

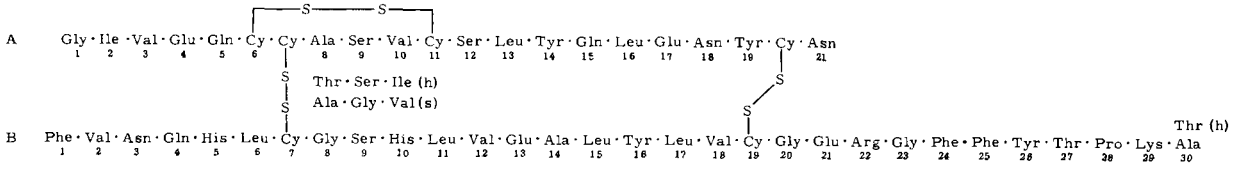



Fig. 1. Primary structure of bovine insulin. Human (h) and sheep (s) insulins differ from this in positions $A_{8-10}$, and human insulin also in position $B_{30}$.

Insulin contains an unusually large amount of sulfur (3.3 %), all of which is present in the form of cystine[57] (methionine has recently also been found in rat and fish insulins). *Freudenberg* and *Wegmann*[58] concluded from this that active (SS) insulin must consist of at least two parallel protein chains held together by SS bridges. This conclusion was confirmed by *Sanger*, who in 1945 found not only phenylalanine[59], but also glycine[60] as an N-terminal amino acid, these two terminal acids being present in the ratio 1:1. Thus it must be possible to break down insulin into polypeptide chains by oxidative or reductive cleavage of the disulfide bridges:

found to be 5734, so that the value of 12000 that had previously been most widely accepted as the lowest molecular weight of insulin must be that of the dimer.

*Sanger* found differences in the amino-acid composition of the A-chains of ox, sheep, and pig insulin, the differences occurring in the $A_{8-10}$ region[70]. The structures of more than 20 insulins have now been elucidated, particularly as a result of the work of *L. F. Smith*[21,71];

[51] *M. M. Harding*, *D. Crowfoot-Hodgkin*, *A. F. Kennedy*, *A. O'Connor*, and *P. D. J. Weitzmann*, J. molecular Biol. *16*, 212 (1966).

[52] *E. Dodson*, *M. M. Harding*, *D. Crowfoot-Hodgkin*, and *M. G. Rossmann*, J. molecular Biol. *16*, 227 (1966).

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[55] *O. Wintersteiner*, *V. du Vigneaud*, and *H. Jensen*, J. Pharmacol. exp. Therapeut. *32*, 397 (1928).

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[61] *F. Sanger*, Nature (London) *160*, 295 (1947).

[62] *F. Sanger*, Biochem. J. *44*, 126 (1949).

[63] Cf. *L. C. Craig*, *H. W. Konigsberg*, and *T. P. King*, Biochem. Preparations *8*, 70 (1961).

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[66] *F. Sanger*, Biochem. J. *45*, 563 (1949).

[67] *F. Sanger* and *H. Tuppy*, Biochem. J. *49*, 463, 481 (1951).

[68] *F. Sanger* and *E. O. P. Thompson*, Biochem. J. *53*, 353, 366 (1953).

[69] *F. Sanger*, *E. O. P. Thompson*, and *R. Kitai*, Biochem. J. *59*, 509 (1955).

[70] *F. Sanger*, Nature (London) *164*, 529 (1949); *H. Brown*, *F. Sanger*, and *R. Kitai*, Biochem. J. *60*, 556 (1955).

[71] *L. F. Smith*, cf. [74]; *L. F. Smith*, quoted by *F. G. Young*, Brit. med. J. *1961* II, 1449; *D. S. H. W. Nicol* and *L. F. Smith*, Nature (London) *187*, 483 (1960); *J. I. Harris*, *F. Sanger*, and *M. A. Naughton*, Arch. Biochem. Biophysics *65*, 427 (1956); *Y. Ishihara*, *T. Saito*, *Y. Ito*, u. *M. Fujino*, Nature (London) *181*, 1468 (1958); *S. Wilson* and *G. H. Dixon*, unpublished; *H. Hama*, *K. Chitani*, *S. Sakaki*, and *K. Narita*, J. Biochem. (Japan) *56*, 285 (1964); *A. Kotaki*, J. Biochem. (Japan) *50*, 256 (1961); *51*, 301 (1962); *53*, 61 (1963).

the hormone occurs in numerous variants, all having the same biological activity. The differences between the insulins increase with the phylogenetic difference between the species. Some fish [72] and rats [73,74] produce insulins with different sequences even in the same pancreas [74]; it is not yet known how widely this phenomenon occurs.

## Steric Structure

The steric structure of the insulin molecule is determined primarily by the positions of the disulfide bridges. From the differences in behavior of insulin films at water/air and water/oil interfaces, it was concluded [75] that the steric structure of insulin depends to a much greater extent on forces of the van der Waals type than that of hemoglobin. Deuterium exchange [76] shows that insulin in solution contains fewer hydrogen bonds than solid insulin. The helical content of the chains is reported to be only 50 % [77], and scarcely exceeds 65 % even in anhydrous media. This must be due to the positions of the disulfide bridges, since under the same conditions the isolated B-chain almost completely forms a right-handed α-helix [78]. *Slobin* and *Carpenter* [79] found that removal of the C-terminal amino acid $B_{30}$ has no effect on the conformation and biological activity of insulin. However, if the terminal group of the A-chain ($A_{21}$) is also removed, the conformation of the molecule changes, and the hormone becomes inactive. A certain steric structure thus appears to be essential to the hormone activity.

Many attempts [50,77,80] have been made to explain experimental results in terms of models. The extent to which these models correspond to the true structure will be shown by three-dimensional X-ray analysis [51,52,81–83] of insulin. Since intramolecular reaction of insulin with 1,5-difluoro-2,4-dinitrobenzene leads to cross-linkage between glycine ($A_1$) and lysine ($B_{29}$) [84] (Fig. 2), it was postulated [85] that the chains are folded back on themselves. This assumption appears to have been confirmed [41].

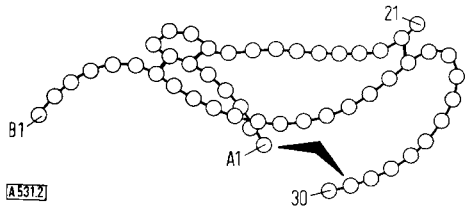


Fig. 2. The intramolecular reaction of insulin with 1,5-difluoro-2,4-dinitrobenzene leads *inter alia* to the formation of a bridge between the α-amino group in $A_1$ and the ε-amino group in $B_{29}$. Consequently the distance between these groups must be about 5 Å.

From the optical rotatory dispersion [86] it was inferred that the conformation of fibrillar (F-insulin) differs greatly from that of dissolved insulin. The reduced iodine uptake [87] of the fibrils and the result that only one of the two histidine units in F-insulin reacts with fluorodinitrobenzene [88], but cf. [89], also suggest a change in the steric structure, but cannot be taken as concrete evidence since these phenomena could be due to diffusion and surface effects. X-ray diagrams [90] show no essential difference between the monomers in F-insulin and in acidic insulin crystals.

## Aggregation and Complex Formation

The particle weight of insulin in solution depends on the pH, temperature, ionic strength, concentration, and foreign ions (Fig. 3). Taking hydration into account, it should be about 6000. This value is found in acidic solutions (pH ≤ 2) at low insulin concentrations [91,92]. As the concentration and alkalinity are increased, the molecule dimerizes. Above pH 4, complexes are formed in the presence of suitable metal ions ($Zn^{2+}$), and between pH 4 and pH 7 these complexes precipitate as

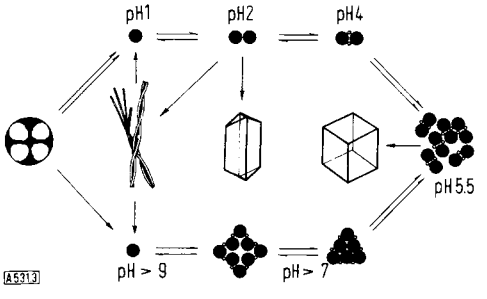


Fig. 3. Behavior of zinc insulin in solutions (greatly simplified). In the middle row from left to right: spheres, fibrils, insulin chloride, zinc insulin, isoelectric precipitation. The large black circles represent insulin molecules and the small white circles $Zn^{2+}$ ions.

[72] *K. Nagasawa* and *S. Nishizaki*, Bull. nat. Inst. hyg. Sci. (Eisei Shikenjo Hôkoku) *77*, 197, 203 (1959); *S. Nishizaki, ibid. 81*, 30, 34 (1963); *M. Yamamoto, A. Kotaki, T. Okuyama*, and *K. Satake*, J. Biochem. (Japan) *48*, 84 (1960).

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[76] *A. Hvidt* and *K. Linderstrøm-Lang*, C. R. Trav. Lab. Carlsberg, Sér. chim. *29*, 385 (1955).

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[79] *L. I. Slobin* and *F. H. Carpenter*, Biochemistry *5*, 499 (1966).

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[81] Insulin was the first protein of which an X-ray crystal diagram was published: *D. Crowfoot*, Nature (London) *135*, 591 (1935).

[82] *D. Crowfoot*, Proc. Roy. Soc. (London) Ser. A *164*, 580 (1938).

[83] *B. W. Low* and *C. C. H. Chen*, Acta crystallogr. *19*, 686 (1965) and preceding papers.

[84] *H. Zahn* and *J. Meienhofer*, Makromolekulare Chem. *26*, 153 (1958).

[85] *H. Zahn*, Sixth Intern. Congr. of Biochem., New York, August 1964.

[86] *J. A. Schellman*, C. R. Trav. Lab. Carlsberg, Sér. chim. *30*, 415 (1958).

[87] *P. H. Springell*, Biochem. J. *83*, 7 P (1962); Biochim. biophysica Acta *63*, 136 (1962).

[88] *R. R. Porter*, Biochem. J. *46*, 304 (1950).

[89] *K. Wallenfels* and *A. Arens*, Biochem. Z. *333*, 395 (1960).

[90] *W. L. Koltun, D. F. Waugh*, and *R. S. Bear*, J. Amer. chem. Soc. *76*, 413 (1954).

[91] *E. Fredericq* and *H. Neurath*, J. Amer. chem. Soc. *72*, 2684 (1950).

[92] *P. D. Jeffrey* and *J. H. Coates*, Nature (London) *197*, 1104 (1963); Biochim. biophysica Acta *109*, 551 (1965).

amorphous, highly aggregated products (Fig. 4). In solutions with high zinc contents, the hormone takes up increasingly large amounts of metal as the pH is increased (*e.g.* 2.2 % at pH 7.2), and the solubility in the neutral range (pH 6 to 8) decreases sharply [93]. The amorphous precipitate slowly crystallizes at pH 5.6 to 6.0 [94].

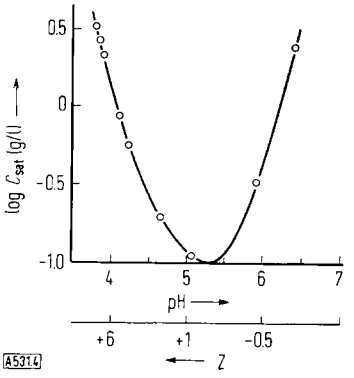


Fig. 4. Solubility of insulin in 0.1 N NaCl; the values of the charge $Z$ relate to the dimer (after *Fredericq* and *Neurath* [91]).
Ordinate: Logarithm of the saturation concentration in g/l.
Upper abscissa: pH; Lower abscissa: Charge $Z$.

Despite numerous investigations [95], the nature of the binding of zinc by insulin has not yet been elucidated. One of the two imidazole groups of the hormone is certainly involved [96]; the participation of the amino groups is not impossible [97], and that of the carboxyl groups has been stated to be necessary on theoretical grounds [80]. X-ray diagrams of crystalline zinc insulin, in contrast to those of lead insulin, can be interpreted in several ways. Possibly the zinc ion can occupy different positions in the insulin aggregates [41].

Zinc insulin in solution at pH > 7 has a particle weight of 36000 [98] to 48000 [99], *i.e.* it is present as a hexamer or octamer, in contrast to the metal-free hormone, which dissociates into the monomer to various extents under these conditions, depending on concentration [100]. Zinc insulin dissociates only at pH > 9 [101], and this process appears to be associated with a change in the conformation of the monomer [102]. At the same time, the hormone is inactivated [103]. Guanidinium chloride [104], urea [105], some salts [91], organic solvents [106], and detergents [107] deaggregate insulin.

Whereas the dimer predominates in acidic solutions (pH 2) at 20 °C, a thixotropic gel is formed at 80 to 100 °C, the micelles of which consist of fibrillar insulin [108]. The fibrils are up to 20000 Å long and about 80 Å in diameter [109, 110], and appear to be composed of four filaments having a diameter of 25 to 30 Å and a period of 1200 Å [110]. The width of 25 to 30 Å corresponds roughly to the diameter of the insulin dimer.

At pH 1, the fibrils form spherical aggregates [111], from which the "heat precipitate" is formed on continuous heating [112]. Fibrillar insulin is biologically inactive, but can be largely converted into crystallizable, active hormone by treatment with alkali at 0 °C and pH 11 to 11.5 [113, 114] or by dissolution in cold 20 % hydrochloric acid [115], or in phenol [116] or urea solutions [117]. The basic fish insulins cannot be precipitated [118], whereas the bis-S-sulfonate of the B chain of bovine insulin readily forms fibrils [119].

Since fibrils are also formed from acetylated and esterified insulin [90], and since no disulfide exchange occurs [120], the association must be due to non-polar forces [121].

Insulin forms compounds with many substances; for example, the well-defined mixed complexes with zinc and protamine [122].

## Stability

Pure insulin is remarkably stable, and remains active for years in a sterile solution at pH 4 and 2 °C. The activity of a crystalline sample was found to be unchanged after storage for two years at 0 °C, whereas a 20 % loss of activity occurred after one year at 20 to 25 °C [124].


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Insulin is rapidly decomposed in alkaline solutions, as a result of hydrolysis of the amide linkages and degradation reactions on cystine. Dilute acids cleave the hormone into several components [48], hydrolysis occurring preferentially at the asparagine and glutamine residues [125]. In non-aqueous media, an N → O peptidyl shift also occurs in serine and threonine residues [126]. On acidic and basic ion exchangers, bonds at the carboxyl end of the B-chains appear to be preferentially hydrolysed [127], while concentrated urea cause carbamylation [117, 128] without reduction of activity. Reducing agents such as hydrogen sulfide and cysteine rapidly inactivate the hormone.

Insulin is very sensitive to high-energy radiation. Thus sterilization with $^{60}Co$ $\gamma$-rays leads to rapid inactivation [130] as a result of changes in the polar and the aromatic groups [129]. X-rays and deuterons have a similar effect [131]. Ultraviolet light breaks down the cystine groups; the tyrosine units are also decomposed, though more slowly [132]. Photooxidation, on the other hand, leads to preferential breakdown of the imidazole group of histidine [133]. Ultrasonic degradation is less specific [134]. Insulin can form monomolecular layers at interfaces [135]; unlike other globular proteins, it is not denatured in the process.

## Analysis

A gravimetric method for the determination of insulin makes use of fibril formation [17]; physico-chemical and chromatographic analyses [136–138] have been reported, but these are suitable only for concentrated insulin. Biological methods are preferred for crude products, body fluids, *etc.*, since these, and particularly the immunological methods, permit the determination of insulin at concentrations down to 0.1 ng/ml.

The biological activity of insulin is expressed in international units (I.U.). Crystalline bovine insulin has an activity of 25 to 27 I.U./mg. Insulins from different animal species appear to have the same activity in spite of their different amino acid sequences. For example, insulin from the fish *Lophius piscatorius* has an activity of 26 to 27 I.U. determined on rat adipose tissue [21]. An exception appears to be guinea-pig insulin, which differs from bovine insulin in 17 amino acids, and has a higher activity in guinea pigs than in mice [74].

The activity of pure insulin is determined by the mouse convulsion test [139] or by the rabbit blood-sugar method [140]. Several biological and immunological methods have recently been described. Owing to their greater sensitivity these can also be used to determine very small quantities of insulin in plasma. The biological *in vitro* method now most commonly used is that described by *Renold et al.* [141], in which the stimulation of the conversion of [1-$^{14}C$]glucose into $^{14}CO_2$ in epididymal rat adipose tissue is measured. The most commonly used immunological method is that described by *Yalow* and *Berson* [142]. A useful combination of biological and immunological methods has been described by *Froesch et al.* [143]; the precipitation in the two-antibody system [144] proceeds rapidly and easily, but does not appear to be absolutely specific (cf. the review by *Renold et al.* [145]). Biological *in vitro* methods for plasma insulin generally give higher results than immunological methods; it is not yet known whether the biological methods determine insulin *and* insulin-like factors, or whether the immunological method covers only part of the plasma insulin, the so-called "unbound" [146] or "typical" [147] insulin or "antibody-nonsuppressible insulin-like activity" [143]. Recent results on nonsuppresible insulin [148] cast doubt on its physiological importance. The insulin content of human plasma probably varies between about 20 $\mu$U/ml (immunological method) to 100 $\mu$U/ml (biological method with adipose tissue from the rat), *i.e.* 1 l of plasma contains about 1 $\mu$g of insulin.

## Substitution Reactions

In 1927, *Freudenberg* began a systematic study of the action of various reagents on insulin and the resulting changes in activity. More recently this work has been

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continued particularly by *Fraenkel-Conrat* [149]. In this way it was hoped to gain an insight into the relationship between chemical structure and biological activity. If it is assumed that a functional group is not essential to the action of the hormone if chemical modification of this group has no influence on the activity, the three amino groups, the aliphatic hydroxyl groups, and the guanidine residue are unnecessary, whereas the amide, phenolic hydroxyl, imidazole, and carboxyl groups are essential to the activity [133, 149–151].

No consideration is given the fact that substitutions also cause a marked change in the pK and solubility of a protein. Thus with increasing degree of esterification, the isoionic point of insulin is diplaced from 5.6 to 13.0. Changes in solubility should be accompanied by parallel changes in activity [152]. On sulfation, a progressive loss of activity is observed as the sulfate content increases, *i.e.* as the isoionic point decreases [151]. The fundamental error possible in estimating the "value" of a group from substituent effects is shown by *du Vigneaud's* work on oxytocin (activity of oxytocin: 546 I.U./mg, that of acetyloxytocin: 1.7 I.U./mg, but that of deaminooxytocin: 803 I.U./mg.).

Two substitution reactions of insulin are of practical importance: iodination and sulfation. Insulin is sulfated on amino, tyrosine, and histidine groups by the pyridine-sulfur trioxide complex [151], and by chlorosulfonic acid in pyridine [153]. Concentrated sulfuric acid at low temperatures causes preferential esterification of the aliphatic hydroxyl groups, with less attack on the aromatic hydroxyl groups [154]. Slightly esterified insulins are hypoglychemically active and not very strongly antigenic, and are scarcely bound by antibodies already present [155]; they are now produced for the treatment of insulin-resistant diabetics.

The iodination of insulin occurs *ortho* to the hydroxyl groups in the four tyrosine residues. Thus it is possible to obtain $3^4-1 = 80$ different iodoinsulins, and more by additional reaction with the histidine residues [157]. The iodinating agents normally used are $I_3^-$,$I^-$/Chloramine T, and ICl. No conditions leading exclusively to mono- or diiodoinsulins (more highly iodinated insulins are biologically inactive [158]) are known as yet, though the ease of reaction should differ for the four tyrosine residues [87, 159] ($A_{19} > A_{14} > B_{16} > B_{26}$ [160]). The mixture of iodoinsulins can be fractionated by density-gradient electrophoresis [156].

Insulins labeled with $^{131}I$ and $^{125}I$ [138, 161] are the most important indicators for small quantities of insulin. Strongly radiating samples (>10 mCi/mg) undergo rapid self-decomposition [142, 162], but the rate of this decomposition is reduced by dilution with foreign protein, *e.g.* human serum albumin [157]. Despite its wide use it is not yet known whether iodinated insulin behaves in the organism in the same manner as the native hormone.

Insulin labeled with $^{82}Br$ [163] is too short-lived, and the hormone sulfated with $^{35}S$-labeled $H_2SO_4$ is probably more interesting [164]. Insulins containing $^{35}S$, $^{14}C$, and $^{3}H$ are obtained by biosynthesis with labeled amino acids, and are significant for biochemical studies of insulin. Their isolation is tedious, and the specific activities, even of the directly tritiated hormone, are low [165]. Several authors have acylated the amino groups of insulin with $^{14}C$-labeled amino acids, but there is no evidence that these products behave like the native hormone. It is preferable to synthesize insulin with labeled amino acids [166].

## Enzymatic Degradation

The native hormone is very highly resistant towards hydrolysing enzymes *in vitro*, the zinc content appearing to be particularly important in this respect (*e.g.* leucine aminopeptidase digests only metal-free insulin [168]). Native insulin is cleaved only slowly by trypsin and chymotrypsin [169]; however, as soon as one bond has been broken, the remainder of the hydrolysis proceeds rapidly [170]. Insulin is most strongly attacked by subtilisin [171].

Careful degradation with carboxypeptidase [79] is interesting in that fully active dealanine-insulin can be

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obtained by removal of only the C-terminal amino acid from the B-chain [172]. On further digestion with carboxypeptidase, the amide linkage in the C-terminal asparagine $A_{21}$ is broken. The activity of the resulting dealanine-deamido-insulin is about two-thirds that of insulin [173–175]; however, if the aspartic acid unit is also removed, the product (dealanine-deasparagine insulin) in inactive [175, 176].

Trypsin cleaves only the B-chain, slowly between $B_{22}$ and $B_{23}$, and rapidly between $B_{29}$ and $B_{30}$ [174]. "Deoctapeptide-insulin" is inactive [175, 177].

Leucine aminopeptidase rapidly breaks down the B-chain from the hydrophobic N-terminal end. The first six amino-acid residues are supposed to be unnecessary for the hypoglycemic action of insulin [168].

Enzymatic reduction of the disulfide bridges is insignificant *in vitro* [178], but is apparently the first step in the *in vivo* degradation of insulin.

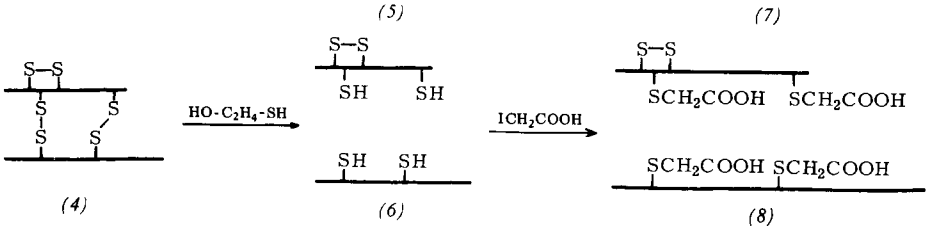
## Non-Enzymatic Degradation Reactions

The primary β-amide group in the C-terminal asparagine residue ($A_{21}$) is particularly sensitive to hydrolysis [173]. Therefore, during the acidic extraction of the pancreas, insulin is already partially degraded to deamidoinsulin, which is still almost fully active [26], and which can be isolated by countercurrent distribution [26] and by ion-exchange chromatography [179].

Peroxyacids break all three disulfide bridges in insulin, each cystine residue giving two cysteic acid residues. The so-called "oxidized chains" are stable, hypoglycemically inactive compounds, which cannot be selectively reduced, but which are degraded by proteases [167].

The chemistry of the reductive and sulfitolytic cleavage of insulin is much more interesting. When the protein is treated with hydrogen sulfide or thioglycollic acid [180] in acidic media, the reduction occurs slowly, whereas rapid reduction takes place in alkaline media. The reduction with mercaptoethanol shows practically no pH-dependence. The hormone becomes inactive as soon as one of the three cystine bonds is broken [181]. Alcohols and heavy-metal ions accelerate the reduction [182], which proceeds only incompletely in the absence of denaturing agents [180]. To ensure cleavage of all three disulfide bonds, therefore, the reaction is generally carried out in 6 to 8 M urea solution [183] or with a many-hundredfold excess of mercaptoethanol [184]. Since thiol groups in the reduced chains are oxidized even in air, they are usually irreversibly blocked in preparative work by carboxymethylation ($RS-CH_2COOH$) with iodoacetic acid [21, 184, 185], amidomethylation ($RS-CH_2CONH_2$) with iodoacetamide [180, 186], or aminoethylation ($RS-CH_2CH_2NH_2$) with 2-bromoethylamine [123], or reversibly blocked by conversion into the *S*-sulfonates (Bunte salts, thiosulfates, $RS-SO_3^-$).

Electrochemical measurements show that the two disulfide bridges linking the chains are easier to reduce than the intrachain bridge [187]; however, owing to the disulfide exchange reaction, it is difficult to use this effect for the preparation of a 7,20-dithiol-6,11-disulfide A-chain *(5)*. On the other hand, if insulin is treated for only a short time with eight equivalents of mercaptoethanol, followed by blockage of the SH groups with




iodoacetic acid, the compound *(7)* can be isolated in a yield of about 65 % [188], *i.e.* the $A_{6-11}$ disulfide bridge is more difficult to attack than the other two S–S bridges.

This is also confirmed in the oxidative sulfitolysis in accordance with

$$RS-SR' + 2\,SO_3^{2-} \rightleftharpoons RS-SO_3^- + R'S-SO_3^- + 2\,e^-,$$

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[181] *O. Wintersteiner*, J. biol. Chemistry *102*, 473 (1933); in conjunction with the discovery that the molecular weight per cystine unit is 2000 [*V. du Vigneaud, ibid. 75*, 393 (1927)], it should have been possible to deduce a minimum molecular weight of 6000 as early as 1933.

[182] *J. Lens* and *J. Neutelings*, Biochim. biophysica Acta *4*, 501 (1950).

[183] *Y.-c. Du* and *C.-l. Tsou*, Acta biochim. biophys. sinica *3*, 89 (1963).

[184] *E. O. P. Thompson* and *I. J. O'Donnel*, Biochim. biophysica Acta *53*, 447 (1961).

[185] *A. M. Crestfield, S. Moore*, and *W. H. Stein*, J. biol. Chemistry *238*, 622 (1963).

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[187] *R. Cecil* and *P. D. J. Weitzmann*, Biochem. J. *93*, 1 (1964); *G. Markus*, J. biol. Chemistry *239*, 4163 (1964); *P. D. J. Weitzmann*, Biochim. biophysica Acta *107*, 146 (1965).

[188] *H. Zahn* and *H. G. Gattner*, unpublished.

in which air, $Cu^{2+}$ [189], air with traces of $Cu^{2+}$, 1,2-diiodoethane [190], *o*-iodosobenzoate, or sodium tetrathionate [191] can be used as oxidizing agent.

The reaction goes to completion in the presence of urea and guanidine [192, 193, 206, 207], but in their absence it leads to a complex mixture, which has recently been resolved and characterized [194]. The compounds isolated from the mixture included several that were not expected to exist under the conditions of the reaction, *e.g.* disulfides of the A-chain of the type $[A(SS)_2]_n$ where $n$ = 1,2(3,4?). The most interesting product, the 7,20-bis-*S*-sulfonate with the 6,11-disulfide ring intact, is formed in a yield of up to 30 % [192, 195]. This substance, like the A-chain disulfides, was stated to have a low insulin activity [196], but these findings have not been confirmed [193, 197]. It is relevant in this connection that sulfur dioxide poisoning in animal experiments leads to inactivation of the insulin [198].

The two *S*-sulfonates are the most important derivatives of the insulin chains from the preparative point of view. On the one hand they are sufficiently stable for easy isolation [190–192, 199, 207, 209], and on the other they can be readily converted into the reactive thiol chains by excess of thiol [205–207, 210], and can also be useful for the synthesis of disulfides:

$$RS{-}SO_3^{\ominus} + H{-}SR' \rightleftharpoons RS{-}SR' + HSO_3^{\ominus}$$

$$RS{-}SR' + H{-}SR' \rightleftharpoons RS{-}H + R'S{-}SR'$$

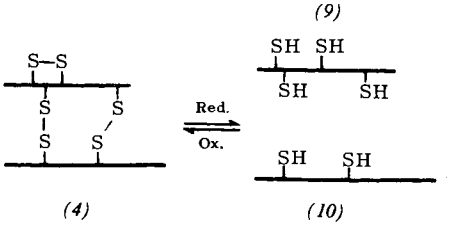
$$R'S{-}SR' + HSO_3^{\ominus} \rightleftharpoons R'SH + R'S{-}SO_3^{\ominus}$$

The thiosulfate chains play an important part in synthetic studies on insulin.

## Regeneration and Resynthesis

Of the many attempts to regenerate native hormone from chemically modified insulin, only a few have been successful. *Freudenberg* and *Dirscherl* [200] recovered part fo the biological activity from acetylated insulin by treatment with alkali. Insulin denatured with hot acids can be reactivated [113–117]. However, the product could be deamido-insulin, since elimination of ammonia is to be expected during precipitation [201].

The oxidative regeneration of insulin from reduced samples is difficult and has been successfully carried out only with partially reduced products [58, 202]; however, the results of these studies have been questioned [203]. One argument against the possibility of resynthesis is the fact that the linkage of the insulin chains during the oxidation can lead to a very large number of products. If the SH chains *(9)* and *(10)* are oxidized in very dilute solutions, intramolecular reactions should, in accordance




with the Ruggli-Ziegler principle, lead to three monomeric bisdisulfides of the A-chain *(11)*, *(12)*, *(13)* and the disulfide *(14)* of the B-chain. These conditions are ideal for the $A_{6-11}$ ring closure, but extremely unfavorable for the formation of the $A_7{-}B_7$ and $A_{20}{-}B_{19}$ bridge, which should occur only at higher protein concentrations. In this case, however, eleven isomers *(15)* to *(25)* of the hormone, as well as an infinite number of oligomers and polymers of the individual chains and of both chains, are to be expected in addition to insulin *(4)* itself. Thus the probability of the formation of insulin by the simultaneous oxidation of the SH chains is small [204, 205].

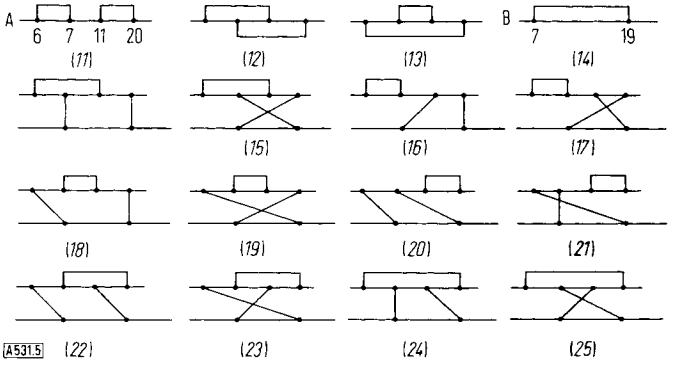



Fig. 5. Schematic representation of the A- and B-chains of insulin with intrachain disulfide bridges (top line) and the isomers of insulin that can result from the formation of different interchain disulfide bridges. Native insulin is shown at the beginning of the second line.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[195] Contradictory data [*J. Meienhofer* and *O. Brinkhoff*, Nature (London) *199*, 1095 (1963)] could not be reproduced; under the conditions given in this paper, the substance was formed in a yield of less than 5 % [194].

[196] *P. Volfin, A.-M. Chambaut, D. Eboué-Bonis, H. Clauser, O. Brinkhoff, H. Bremer, J. Meienhofer*, and *H. Zahn*, Nature (London) *203*, 408 (1964).

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[202] *R. S. Allen* and *J. R. Murlin*, Proc. Soc. exp. Biol. Med. *22*, 492 (1925); *K. Freudenberg* and *A. Münch*, Hoppe-Seylers Z. physiol. Chem. *263*, 1 (1940).

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[204] *W. Kauzmann* in: Sulfur in Proteins, Proc. Symposium, Falmouth, Mass. 1958. Academic Press, New York, 1959, p. 93.

[205] *K. M. Pruitt, B. S. Robison*, and *J. H. Gibbs*, Biopolymers *4*, 351 (1966).

It was therefore even more surprising that *Dixon* and *Wardlaw* [206] and *Tsou et al.* [207] in 1960 were able to resynthesize insulin from polypeptide chains that had previously been completely separated. The chains were separated as S-sulfonates and purified. The inactive chains were reduced with an excess of thiol and precipitated as the SH chains *(9)* and *(10)*. When the precipitates were mixed and oxidized with air at pH 8.5 to 9.0, they gave products having an insulin content of 1 to 2 %.

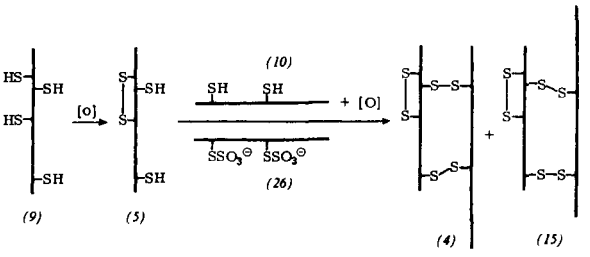
The fact that the activity of the oxidation products is due to insulin was shown by the reaction with insulin antiserum [206] and by the isolation of crystallizable insulin from the resynthesis products by extraction with acidified butanol [207].

By variation of the reaction conditions, the yield was increased initially to 5 to 10 % [205, 208, 209], and then by *Tsou et al.* [210] to 50 %. However, the authors of a recent paper [211] still report yields of only 10 to 20 % (cf. [205]); on repeating this work, *Zahn et al.* obtained a maximum yield of 25 %.

In the method used by *Tsou et al.*, the A-chain is used in a 50 % excess, and the reaction is carried out at the unusual pH of 10.6. Under these conditions insulin [101], and probably also the individual B-chains, does not aggregate. On resolution of the insulin resynthesis mixtures by gel filtration, electrophoresis, or countercurrent distribution [212], a substance having the amino-acid composition $[AB_2]_n$ was isolated as the main product, together with $[AB]_n$ (insulin) and $[A]_n$, but very little $[B]_n$. $[AB_2]_n$ may be formed by two routes: by reaction of the poly-B-chain and by the recently discovered [194] reaction of the thiol-B-chain with insulin.

The simultaneous oxidation of the chains, therefore, does not necessarily lead to a statistical mixture. *Zahn et al.* [213, 214] also obtained maximum insulin yields of 50 % when they first oxidized the A chains alone in the thiol form *(9)* until 50 % of the SH groups had been converted into disulfide groups, then added the equivalent quantity of thiol-B-chain *(10)* and completed the oxidation (pH 8.9).

In this procedure, the more stable [187, 192] $A_{6-11}$ disulfide ring *(5)* may be formed first. On subsequent combination with the B-chain, practically the only product, apart from native insulin, should be the isomer with the antiparallel chain arrangement *(15)*. The insulin yields could be further increased (maximum 70 %) [214, 215] by reaction of the B-chain in the form of its *S*-sulfonate *(26)* with preoxidized A-chain *(5)*; in this case the formation of $[B]_n$ and $[AB_2]_n$ is probably prevented.




Insulin resyntheses using oxidizing agents other than air, *e.g.* diiodoethane and dimethyl sulfoxide [216], or the glutathione disulfide/triphosphopyridine nucleotide [216] and glutathione disulfide/glutathione insulin transhydrogenase systems [217], gave a maximum insulin yield of 11 %.

The resynthesis of insulin from natural chains has also been used for the preparation of "hybrid insulins" of immunochemical interest, in which the A- and B-chains are obtained from different species [209, 218].

## Synthesis

The general progress in peptide chemistry encouraged several research groups to synthesize peptide sequences of insulin after the publication of its formula. The main obstacle to a total synthesis appeared to be the linking of the chains. As soon as it was found possible to solve this problem, albeit only in low yields [206, 207], the way was open for a synthesis of insulin: it should be possible to synthesize the two polypeptide chains separately on the basis of *du Vigneaud*'s work [219], using *S*-benzylated cysteine residues and with permanent blocking of functional groups in the side chains, then to remove all the protective groups with sodium in liquid ammonia and link the resulting SH chains by oxidation. Though this total synthesis would not provide proof of the structure (for which the three disulfide bridges would have to be formed individually and in simple reactions), it would be the simplest route to synthetic insulin.

The plan of synthesis was correct; at the end of 1963 *Zahn* and his co-workers [10], and at about the same time *Katsoyannis* in collaboration with *Dixon* [11], succeeded in preparing sheep insulin. In 1965, research groups working in China under Professors *Niu*, *Wang*, *Hsing*, *Tsou*, and *Tsao* synthesized bovine insulin [220] which differs from sheep insulin in the amino acid (serine

[206] *G. H. Dixon* and *A. C. Wardlaw*, Nature (London) *188*, 721 (1960).

[207] *Y.-c. Du*, *Y.-s. Zhang*, *Z.-x. Lu*, and *C.-l. Tsou*, Scientia sinica *10*, 84 (1961).

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[209] *S. Wilson*, *G. H. Dixon*, and *A. C. Wardlaw*, Biochim. biophysica Acta *62*, 483 (1962).

[210] *Y.-c. Du.*, *R.-q. Jiang*, and *C.-l. Tsou*, Scientia sinica *14*, 229 (1965).

[211] *C.-i. Niu*, *Y.-t. Kung*, *W.-t. Huang*, *L.-t. Ke*, *C.-c. Chen*, *Y.-c. Chen*, *Y.-c. Du*, *R.-q. Jiang*, *C.-l. Tsou*, *S.-c. Hu*, *S.-q. Chu*, and *K.-z. Wang*, Scientia sinica *15*, 231 (1966).

[212] *H. Zahn*, *O. Brinkhoff*, *E. Drechsel*, and *H. Klostermeyer*, unpublished.

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[217] *H. M. Katzen*, *F. Tietze*, and *d. W. Stetten, Jr.*, J. biol. Chemistry *238*, 1006 (1963).

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[220] *Y.-t. Kung*, *Y.-c. Du*, *W.-t. Huang*, *C.-c. Chen*, *L.-t. Ke*, *S.-c. Hu*, *R.-q. Jiang*, *S.-q. Chu*, *C.-i. Niu*, *J.-z. Hsu*, *W.-c. Chang*, *L.-l. Cheng*, *H.-s. Li*, *Y. Wang*, *T.-p. Loh*, *A.-h. Chi*, *C.-h. Li*, *P.-t. Shi*, *Y.-h. Yie*, *K.-l. Tang*, and *C.-y. Hsing*, Scientia sinica *14*, 1710 (1965); *15*, 544 (1966); Kexue Tongbao *17*, 241 (1966).

instead of glycine) in position $A_9$ (Fig. 1). This hormone was also synthesized with a $^{14}C$-labeled glycine residue in position $A_1$ [166].

Human insulin (Fig. 1) differs from bovine insulin in having threonine instead of alanine in positions $A_5$ and $B_{30}$, and isoleucine instead of valine in position $A_{10}$. Whereas the synthesis of the chains [221–223] and of the peptide sequences that differ from those of sheep insulin [224, 225] proceeds normally, removal of the *S*-benzyl protective groups from the B-chain of human insulin has so far always led to destruction of the C-terminal threonine unit [222, 223]. As the amino-acid analysis shows, this also appears to apply to the product [221] described in 1966 as "synthetic human insulin". However, the $B_{30}$ unit is not essential to the hormone action [175].

The insulin syntheses published so far differ only in details of the method, and a scheme of the synthesis of *Zahn et al.* is shown in Fig. 6. The synthesis of the A-chain required 89 reaction steps, that of the B-chain 132 steps, while a further 3 steps were required to link the two chains. All reaction sequences were so chosen that changes in the 48 asymmetric centers were practically impossible [226].

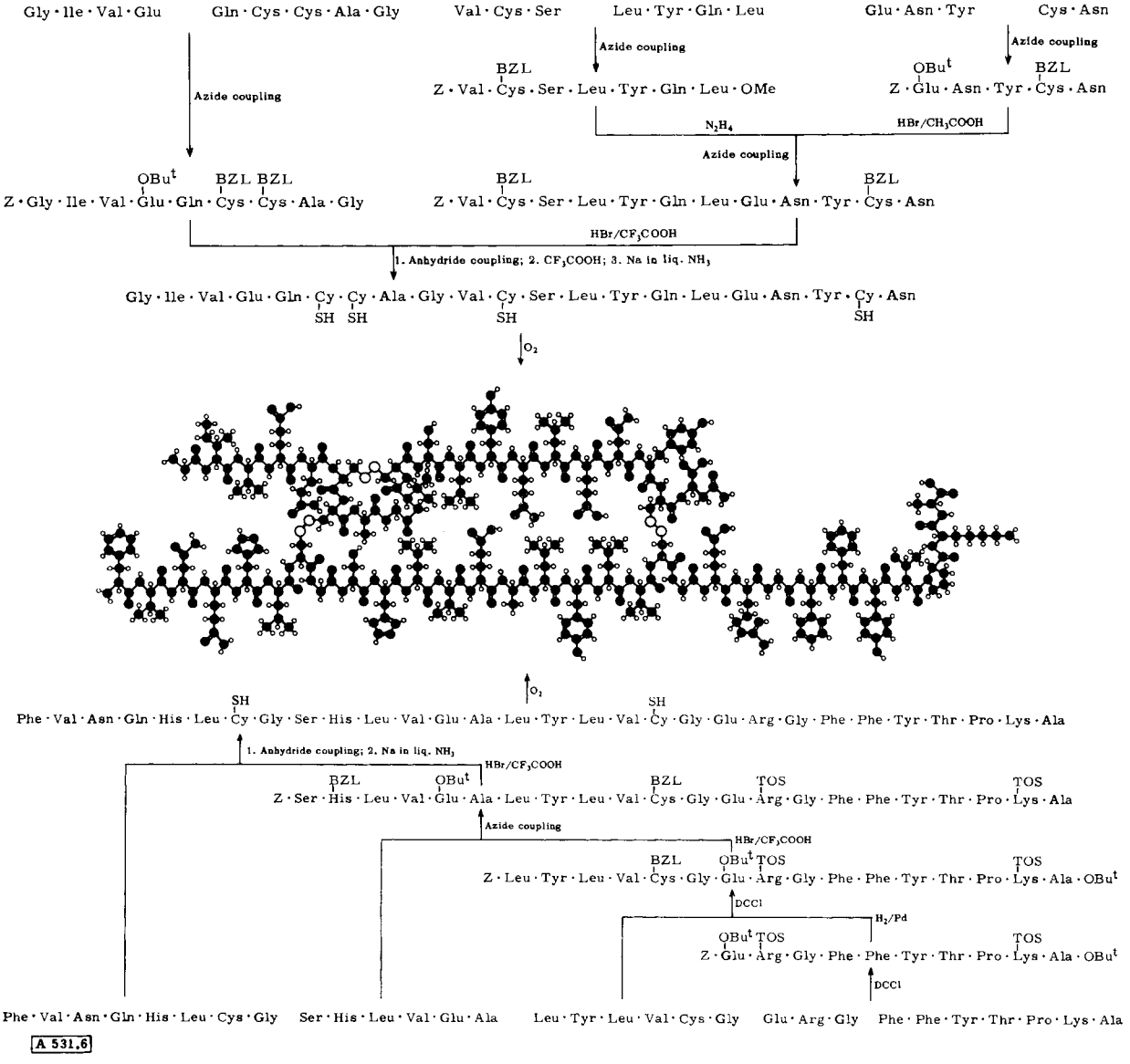


Fig. 6. Projection formula of sheep insulin (middle) and synthetic route, after *Zahn et al.* [10]. The chain fragments were synthesized by stepwise elongation by one amino-acid residue.
Abbreviations: BZL = benzyl, DCCI = dicyclohexylcarbodiimide, OBut = tert-butyl ester, OMe = methyl ester, TOS = *p*-toluenesulfonyl, Z = benzyloxycarbonyl.

Linkage of the chains was surprisingly easy. A stoichiometric mixture of the protected polypeptide chains was dissolved in liquid ammonia and treated with sodium; after evaporation of the solvent, the residue was dissolved in a buffer (pH 9.0), dialysed against water that had not been deaerated, and freeze-dried. The insulin content of the product was found by various methods to be 0.2 to 1.0 % (0.05 to 0.25 I.U./mg), and its activity could be completely neutralized with insulin

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[222] *H. Zahn*, Konf. Spez. Probleme Proteinstrukt., Oestrich, Oct. 1965, Ges. f. Physiol. Chemie, Abstracts p. 6; Excerpta Medica Int. Congr. Ser. No. *112*, 336 (1965).

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[227] *H. Zahn, O. Brinkhoff, J. Meienhofer, E. F. Pfeiffer, H. Ditschuneit*, and *Ch. Gloxhuber*, Z. Naturforsch. *20b*, 666 (1965).

antiserum[227]. The yield obtained in the linking of the chains was of the same order as that obtained in the recombination of natural chains by the usual method at that time (no intermediate purification of the chains).

The combination of synthetic chains to native chains of the other type to give "semi-synthetic insulins" showed that the synthetic A-chains[11,228] give more insulin than the synthetic B-chains[11,229]. Since the discovery in 1961[208] that natural insulin chains that have been treated with sodium in liquid ammonia give less insulin than untreated chains, it is known that on removal of the final protective groups, the B-chain in particular is degraded very rapidly, mainly between positions 27 and 28 (–Thr-Pro–)[230]. For this reason, repetition and attempted improvement[222,231,232] of *Zahn*'s synthesis have not led to an increase in yield, but simply demonstrate the reproducibility of the synthesis.

After removal of the protective groups the synthetic chains can be freed from cleavage products and other impurities *via* the *S*-sulfonates[211]. Material purified in this way must be equivalent to the Bunte salt chains obtained from natural insulin and should, on purification, give products containing at least 0.25 I.U. of insulin/mg (Table 1). The isolation of pure crystalline insulin from synthetic material[220,222,232] is simpler if the insulin chains are purified before being combined, but the overall yield is then lower.

The yields (based on the C-terminal amino acids) in one synthesis of *Zahn et al.* were 2.9 % for the protected A-chain, 7.0 % for the protected B-chain, and 0.25 to 0.55 % for the insulin content of the final product. Similar yields were probably obtained in the Chinese and American work. An economical synthesis of insulin is probably impossible by this route.

Table 1. Biological activities of synthetic insulin preparations

| Product | Activity (I.U./mg) | Authors |
|---|---|---|
| Sheep insulin | 0.05–0.25 [a] | 1963 *Zahn et al.* [10] |
| Sheep insulin | 0.005–0.017 [b] | 1964 *Dixon* [11] |
| Bovine insulin | 0.30–0.60 [b, c] | 1965 *Niu, Wang, Hsing, et al.*[220] |
| Human insulin | *ca.* 0.48 [b] | 1966 *Katsoyannis et al.* [221] |

[a] Not corrected for water and salt contents.

[b] Chains purified *via* the *S*-sulfonates before being linked.

[c] The insulin was isolated in the crystalline form (>20 I.U./mg) from this material.

A solution to this problem may be offered by the peptide synthesis on solid supports[233] developed by *Merrifield*. The A- and B-chains of human, bovine and sheep insulins were synthesized in a few weeks by this method[223,234]. The yields of purified protected B-chains, for example, were 45 to 60 %. Since *S*-benzylated cysteines were also used in these recent studies, so that the protective groups had to be removed by treatment with sodium, the activity of the insulin obtained was only of the usual order of magnitude.

*Zervas et al.*[235] have started development of selectively cleavable protective groups for sulfur, and the progress made in the next few years will probably allow removal of the protective groups under mild conditions.

## Biosynthesis

Insulin is synthesized and stored in the β-cells of the Langerhans islets. The islets are scattered over the entire pancreas, of which they amount to only about 1 %. Investigations on the biosynthesis of insulin in the pancreas of mammals with labeled amino acids are therefore difficult. Insulins biosynthetically labeled with $^{3}H$ and with $^{14}C$ have been isolated from ox, calf, and rat pancreases[236–241]. Investigations are easier on the isolated islet tissue of some types of fish, the exocrine pancreas of which is physically separate from the endocrine pancreas. The metabolism of isolated islet tissue was first studied in fish islets[242,243]. Owing to the absence of exocrine tissue, it was also possible, after incubation with labeled amino acids, to isolate insulin of high specific activity[244,245].

The biosynthesis of insulin appears to follow the general pattern of protein biosynthesis. Thus it has been shown[246] that insulin is synthesized in the endoplasmatic reticulum (by the ribosomes). Puromycin, an inhibitor of protein biosynthesis, also inhibits the biosynthesis of insulin[247,248]. Results on labeled insulin from fish islets[248] indicate that the synthesis of the insulin B-chain begins at the N-terminal end, in agreement with results obtained for other proteins such as hemoglobin, lysozyme, or ribonuclease.

A special problem in the biosynthesis of insulin is the linking of the two chains *via* disulfide bridges. There are two fundamental possibilities. A single-chain precursor of insulin containing all the amino acid residues of

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[232] *H. Zahn, W. Danho*, and *B. Gutte*, Z. Naturforsch. *21b*, 763 (1966).

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[246] *A. Lazarow, G. E. Bauer*, and *A. W. Lindall* in: The Structure and Metabolism of Pancreatic Islets. Pergamon Press, Oxford 1964, p. 203.

[247] *K. W. Taylor* and *D. G. Parry*, Biochem. J. *89*, 94P (1963).

[248] *R. E. Humbel*, Proc. nat. Acad. Sci. USA *53*, 953 (1965).

the molecule and possibly also a hypothetical link may be formed first. The disulfide bridges could be formed in this precursor, as in ribonuclease or in lysozyme, as intrachain bridges, whereupon hydrolytic cleavage at one or more points would lead to the two-chain insulin molecule. This is the route followed in the synthesis of chymotrypsin, in which the single-chain chymotrypsinogen is formed first, and this is then split into the three chains of chymotrypsin. The second possibility for the biosynthesis of insulin involves the separate synthesis of the two chains followed by the formation of the correct interchain disulfide bridges.

*Wang* and *Carpenter* [249] sought a single-chain precursor of insulin in fractions of pancreas extracts, but found none. *Givol et al.* [250] incubated insulin with a microsomal enzyme from liver that catalyses the exchange of sulfhydryl and disulfide groups in ribonuclease. From the fact that this enzyme could inactivate insulin, *Givol et al.* concluded that the correct disulfide bonds are not favored thermodynamically, and that the synthesis of insulin *in vivo* from the two chains is therefore unlikely. However, the high yields obtained in the *in vitro* recombination of isolated A- and B-chains (see above) now suggest that the combination of separately synthesized chains *in vivo* would be possible. The separate biosynthesis of the A- and B-chains has been demonstrated in doubly-labeled insulin from fish islets [248], so that a single-chain precursor of insulin can very probably be ruled out.

If *Humbel*'s results [248] can be confirmed, a further question is whether linkage of the two chains *in vivo* occurs spontaneously, or whether the process is catalysed by an enzyme ("insulin zipase" [246]). A glutathione insulin transhydrogenase [252] that can split insulin into the A- and B-chains by reduction of the disulfide bridges [253, 254] has been isolated from liver. The reverse process, *i.e.* the synthesis of insulin from the two reduced chains, could also be catalysed by the enzyme, but the extent of the resynthesis was low [217]. *Kotoulas*, *Morrison*, and *Recant* [255] detected glutathione insulin transhydrogenase activity in isolated islets from rat pancreas, and *Varandani* and *Tomizawa* [256] isolated the enzyme from ox pancreas. Thus an enzyme capable of reductive cleavage of insulin appears to be present not only in the liver, but also in the pancreas; it is not yet known whether the function of this enzyme is the catalysis of the combination of the separately synthesized insulin chains or the cleavage of insulin.

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Little is known about the regulation of the biosynthesis of insulin. *Smith, Taylor*, and *Parry* [239] discovered that the synthesis of insulin in ox pancreas is slightly stimulated by glucose, whereas glucose has no effect in fish islets [243, 244]. It can be calculated from the rate of *in vivo* incorporation of leucine into insulin in fish islets [242, 245] that about 12 days are required for the synthesis of the amount of insulin normally present in the pancreas. The human pancreas contains about 250 I.U. of insulin (10 mg), *i.e.* five to ten times the daily consumption of insulin.

## Secretion

After its biosynthesis in the endoplasmatic reticulum, insulin is stored in the secretory granules, which can be selectively stained with insulin antibodies coupled with fluorescein [257]. β-Granules have been isolated from fish islets by centrifugation in a density gradient [258]. Insulin forms about 10% of the granule protein [258]. Thus insulin may be stored in the form of a complex with other proteins. *Lindner* [122] first described such a complex ("native insulin") of insulin with a basic protein of low molecular weight. *Antoniades et al.* [259] postulated a similar complex, since pancreatic insulin is bound by a cation exchanger at pH 6.6, whereas the isoelectric point of crystalline insulin is 5.3. On the basis of the difference in solubility of crystalline and pancreatic insulins, *Meade et al.* [260] also support a special form for pancreatic insulin, though they were unable to confirm the findings of *Antoniades et al.* [259].

The islet cells contain large quantities of zinc [261, 262], which could be important in the storage of insulin. Recent investigations on the behavior of zinc, β-granules, and extractable insulin after glucose infusion [263] indicate that the role ascribed to zinc in the secretion of insulin is open to question [262].

The transport of insulin from the synthesis site in the ribosomes to the granules and the actual secretion process, *i.e.* the fusion of the granule membrane with the cell membrane, with simultaneous liberation of insulin into the blood capillaries, has been studied [264] electron-microscopically, and appears to be similar to the secretion process in the exocrine pancreas [265].

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The secretion of insulin is regulated mainly by the glucose and insulin levels in the blood [266]. Recent work on pancreas tissue *in vitro* shows a direct dependence of the rate of secretion on the sugar concentration [267, 268]. Simultaneous inhibition of the insulin synthesis by dinitrophenol has no effect on the secretion [269]. The secretion is inhibited by addition of insulin to the pancreas preparation [270]. On the basis of experiments with substances that inhibit the degradation of glucose [271, 272], it is thought that the secretion is stimulated, not by glucose itself, but by a degradation product. Preliminary results indicate that intestinal glucose resorption increases the glucagon level, which in turn stimulates insulin secretion [251].

## Mode of Action

Insulin is an anabolic hormone in the intact organism, *i.e.* it promotes the synthesis of glycogen, fat, and protein. An elegant method by which all the symptoms of insulin deficiency can be produced is the injection of guinea-pig bovine-insulin antiserum [273] into rats or mice. In addition to an increase in blood sugar concentration, other symptoms of acute diabetes such as increased plasma fatty acid concentration, elimination of glucose and ketones in the urine, negative nitrogen balance, and increasing blood acidosis are observed [274].

The action of insulin has been studied *in vitro* mainly on isolated muscle and adipose tissue. Insulin effects in cell-free systems have been described, but it appears that only its effect on the swelling of the mitochondria is reproducible [275], and this seems to be a general property of disulfides.

There are a number of theories in which most of the effects of insulin are attributed to one primary effect. The best known of these is the permeability theory proposed by *Levine* and *Goldstein* [276], which is still used, though not in its original form [277]. *Levine* and *Goldstein* postulated that the primary effect of insulin is to promote the entry of glucose into the cell. The increased synthesis of glycogen and fat, the increased oxidation of glucose, the decreased degradation of protein and fat, and the prevention of ketone formation can be easily explained on this basis. This theory is supported by numerous results obtained *in vivo* and *in vitro* (cf. [277]).

However, an increasing number of insulin effects observed recently can no longer be explained by increased glucose transport. For example, insulin also promotes the transport of some amino acids [278, 279] and of $K^+$ [280], even in the absence of glucose. Insulin also inhibits the liberation of free fatty acids and of glycerol from adipose tissue, again in the absence of glucose [281, 282]. *Rodbell* [283] also showed in work on isolated fat cells that all the effects of insulin on adipose tissue can be imitated by phospholipase C. He postulated that the action of insulin on the plasma membrane is due to modification of the membrane lipids. This would expand the original glucose permeability theory into a general membrane permeability theory, but some of the effects of insulin cannot be explained even with the aid of this extended theory. These include the stimulation of protein synthesis [284], which is clearly distinguished from the influence on the amino-acid transport [279], the stimulation of RNA synthesis [285, 286], the stimulation of glycogen synthetase [287], and the induction or repression of a number of enzymes [288, 289].

In order to preserve the unitary concept of the mode of action of insulin, *Krahl* [290] and *Hechter* [291] suggested that the change occurring during the primary reaction of the hormone with the cell membrane could propagate itself into the cell. The experiments carried out by *Cadenas et al.* [292] and by *Carlin* and *Hechter* [293] suggested a disulfide-sulfhydryl exchange between insulin and the cell membrane. A similar process had previously

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been postulated for the action of adiuretin [294], but this theory had to be abandoned [295] when it was shown that analogues of adiuretin that do not contain disulfide bridges are also active, though to a smaller extent.

Hormones are now often regarded as allosteric effectors, which can either suppress or induce the transcription of genetic information [296]. This theory is so general and flexible that it is difficult to refute. An important objection in the case of insulin is probably the fact that even when the synthesis of RNA is strongly inhibited, the effect of insulin on transport processes through membranes remains unchanged [297].

We are still a long way from finding a satisfactory explanation of the mode of action of insulin. A promising means of clarifying this question appears to be the investigation of the active center of insulin. Once the active group in the insulin molecule is known, it will be possible to make a more systematic search for a suitable receptor at the cell membrane.

## Biological Inactivation

From the pancreatic vein, insulin first passes into the liver, where approximately half of it is degraded and removed from circulation [298,299]. The half-life of insulin is about 30 minutes in man [300]. The two principal breakdown sites are the liver and the kidneys. The insulinase described by *Mirsky* [301] is probably identical with insulin glutathione transhydrogenase [217,252–254,256,302], which catalyses the reductive cleavage of the interchain disulfide bridges of insulin, the chains then being hydrolysed to smaller fragments [303,304]. The enzyme has no absolute substrate specificity, and vasopressin and oxytocin are also degraded, though more slowly [217].

*Ensinck et al.* [305] concluded from studies on $^{131}$I-insulin, which was incubated with partially purified glutathione insulin transhydrogenase, that the reduced insulin B-chain is bound to albumin and circulates in the plasma, where it competitively inhibits the action of insulin on muscles [306]. These results have not yet been confirmed (cf. [307]), nor has the inhibition of the glutathione-insulin transhydrogenase by the reduced B-chain reported by *Langdon* [308]. It is unlikely [193,197] that the partially reduced A-chain [196,215,309] or the reduced B-chain [308] have any residual biological activity.

Not only the liver, but also the pancreas [255,256,310,311], muscle tissue [312], and adipose tissue [312,313] appear to have the ability to cleave insulin reductively [255,256] or proteolytically [310–313].

## Immunochemistry

The antigenic nature of insulin was established by *Banting et al.* [314], who detected insulin-neutralizing antibodies in the serum of a schizophrenic patient who had been treated with insulin. *Moloney* and *Coval* [315] showed that guinea-pigs form antibodies that neutralize pig, bovine, sheep, mouse, and rabbit insulins. The electrophoretic behavior of $^{131}$I-insulin in normal serum is similar to that of albumin, whereas $^{131}$I-insulin in the serum of diabetics that have been treated with insulin is bound to the γ-globulins [300]. Fortunately for all diabetics, who rely on insulin from another species, insulin is a weak antigen, but the existence of specific insulin antibodies has now been established by these and other investigations (cf. [316]).

Insulin-binding and insulin-neutralizing antibodies exhibit no pronounced species specificity. Thus bovine and pig insulin antibodies react not only with bovine and pig insulins, but also with mouse [315], whale, dog, rabbit [317], sheep, horse, monkey [318], and human insulins [300,319]. However, quantitative differences do exist [320], these differences increasing with the differences in the primary structures of the insulins. Thus the reaction of cod insulin [321] or bonito insulin [317] with anti-bovine-insulin serum is weaker than that of bovine insulin.

When bovine insulin is injected into guinea-pigs, antibodies can be detected in the serum after a time, but the guinea-pigs do not become diabetic. On the other hand, their serum neutralizes mouse insulin, and mice become diabetic when such a guinea-pig serum is injected into them [274,315,316,318]. In general, insulin antibodies do not appear to react with circulating insulin of the test animal that produces the antibody [322]. *Moloney* [318] therefore postulated a special form of endogenous insulin, which differs from extracted insulin (from the pancreas or from serum) used for immunization.

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This appears to be supported by the results obtained by *Renold et al.*[323], who detected antibodies for extracted bovine insulin in cattle after injection with bovine insulin. Other authors[324, 325] have reported antibodies for extracted pig insulin in a pig.

*Berson* and *Yalow*[326] observed antisera that could distinguish between sperm whale and pig insulins, even though the amino-acid sequences of these two insulins are thought to be identical. *Berson* and *Yalow* concluded that the tertiary structure of proteins can differ even when the amino-acid sequences are the same. However, this result should be viewed with caution until absolute proof of the purity and of the identical amino-acid sequences of the two insulins is available.

The groups in the insulin molecule that are involved in the binding of antibodies are probably neither the N-terminal amino acids[327] nor the C-terminal sequence $B_{23-30}$[328]. *Arquilla*[327] has discussed the possibility that $^{131}$I-insulin differs immunologically from uniodinated insulin, since iodination of insulin occurs mainly in the tyrosine residues of the A-chain[329], which are probably important to the antigenic action. By hybridization of the chains of bovine and cod insulins, *Wilson, Dixon,* and *Wardlaw*[209] showed that the immunologic specificity of insulin is determined primarily by the A-chain. The immunologic behavior of bovine-A-cod-B insulin towards anti-bovine insulin is similar to that of bovine insulin, whereas cod-A-bovine-B insulin behaves like cod insulin. *Yagi, Maier,* and *Pressman*[330] prepared antibodies against *S*-sulfonated ($S-SO_3^-$) A- and B-chains. Antibodies against such A-chains reacted only with A-chains, whereas antibodies against such B-chains reacted with B-chains and with insulin. Insulin antibodies reacted with insulin, weakly with the B-chain, and not at all with the A-chain. It was concluded that the insulin molecule contains several (three?) antigenic regions. This conclusion was recently confirmed by investigations[327] on insulin antibodies from pure guinea-pig strains, by cross tests with numerous insulins and their antisera, as well as with *S*-amidomethylated insulin chains and their enzymatic hydrolysates[186]. Surprisingly, even a relatively small synthetic cystine peptide of the insulin B-chain reacts as a complete antigen[331].

Insulin binding antibodies frequently occur in the serum of diabetics who have been treated with large doses of insulin, but there is no strict correlation between insulin-binding capacity and insulin requirement. The antibodies in the serum of diabetics appear, above, all to retard the degradation of insulin[332].

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# Methods and Applications of Quantum Chemistry

## Part I: Physical and Mathematical Basis

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*After an introduction to the fundamental concepts of quantum mechanics it is shown how to describe a chemical system in the language of theoretical physics. The equations which one obtains can not, in general, be solved in closed form. Approximate numerical methods that furnish sufficiently accurate solutions for many problems of interest are, however, available. The most important of these are presented briefly, and are given physically visualizable interpretations as far as this is possible. Special attention is devoted to more modern methods of quantum chemistry, to the basic assumptions underlying them, their scope, and their limitations. Treatment of the theory of the chemical bond is reserved for Part II.*

### 1.1. Introduction

Although chemists nowadays use many concepts derived from quantum theory, they often do not know their real meaning and the conditions under which they can be identified with quantities and ideas derived from chemical experience.

The first part of the present article is concerned with the principles on which current quantum-chemical methods are based. Its aim is to aid chemists towards a more critical appreciation of particular applications of quantum chemistry.

In principle, quantum chemistry enables us to calculate bond energies, dissociation energies, ionization potentials, electron affinities, frequencies and intensities of spectral transitions, electron densities, spin densities, dipole moments, polarizabilities, equilibrium internuclear distances, force constants, potential barriers for internal rotations, basicity constants, and many other properties of molecules, ions, and atoms without knowledge of empirical data of these systems. It is further possible to treat intermolecular forces and chemical reactions.

Different applications require a different amount of effort. For example, electron density distributions may be accounted for accurately enough with approximate methods that are much too crude for the calculation of electronic spectra. Bond lengths are obtained to an accuracy of a few percent by methods that would lead to errors of more than 100% for bond energies. Certain expectation values, on the other hand, require much more accurate wave functions than those that are good enough if one wants to calculate energies. The question of which simplifications may be introduced, and hence often of whether the computational effort can be reduced to a reasonable level, depends to a very large extent on the type of problem.

It should, in principle, be possible to calculate the properties of any known or unknown, stable or unstable compound or to predict theoretically the result of any chemical experiment, irrespective of whether this experiment can actually be carried out. That numerical *ab initio* quantum chemistry is still concerned with comparatively modest problems is due to the extreme complexity of the quantum-mechanical equations. A few molecular species, like $H_3$ and $H_2^+$, are, however, better known from theory than from experiment. The best value available for the electron affinity of the H atom is that obtained from theoretical calculations [1]. The existence of the stable cation of cycloheptatriene and of the stable anion of cyclopentadiene was deduced from theory [2] and was later confirmed experimentally.

There have been many other examples of theoretical predictions that were later confirmed by experiment. Collaboration of theory and experiment has proved very successful in many fields of research, including ultraviolet spectroscopy, nuclear magnetic and electron-spin resonance spectroscopy, and the study of metal complexes of aromatic compounds, and will undoubtedly play an even greater role in the coming decades.

The methods used in theoretical chemistry include, besides quantum theory, also statistical mechanics, which bridges the gap between molecular processes and macroscopic properties of matter. There is also some overlap between quantum chemistry and theoretical solid-state physics. The present paper will be confined to quantum chemistry in the restricted sense, *i.e.* to the theory of molecules and their interactions. As far as is possible within the framework of an elementary review, special attention will be given to such problems and results that are topics of current research and still outside the scope of textbooks.

Quantum chemistry is not limited to numerical solutions, with the aid of computers, of highly complicated equations referring to very particular systems. Its scope is rather to help us to understand and to systematize in terms of very general theorems the diversity of chemical facts.

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## 1.2. Physical Formulation of a Chemical System

A chemically interesting system may be an atom, an ion, a molecule, a complex, or a whole crystal, or it may consist of several like or unlike atoms, molecules, *etc.* in stationary interaction with one another, moving relative to each other, or taking part in a chemical reaction. From the physical point of view, each of these systems consists of a number of atomic nuclei and electrons, which exert electrostatic (coulombic) forces on one another, and the movements of which are described by the laws of quantum mechanics.

If the laws of classical mechanics were valid on the atomic level, it would be necessary to set up and solve the equations of motion for such a system, and certain initial conditions would have to be known in order to establish the solutions [3]. These solutions would then give the position and momentum of each individual particle (nuclei, electrons) as a function of time, *i.e.* its trajectory. In closed systems, certain physical quantities, such as energy, momentum, and angular momentum, would remain invariant with time; they are called *constants of motion.*

Whereas in the equations of classical mechanics the physically measurable quantities, *i.e.* the *observables*, such as position, momentum, and energy, are directly related to one another, the equations of quantum mechanics do not contain the observables themselves but rather "operators" assigned to them. To each solution of the classical equations of motion, there corresponds in quantum mechanics a *state* of the system; this state is described by a wave function $\psi$, which is a function of the coordinates of all the particles (*i.e.* for a system of $n$ particles, a function of $3n$ position coordinates and $n$ spin coordinates, though the latter may be ignored for the moment). The square of the wave function (or when $\psi$ is complex, the product of $\psi$ with its complex conjugate $\psi^*$) can be regarded as the *probability density* that the first electron will be found at the point $x_1$, $y_1$, $z_1$, the second at the point $x_2$, $y_2$, $z_2$, *etc.* Since the total probability is unity, $\psi$ is *normalized* to unity, *i.e.*

$$\int_{-\infty}^{+\infty}\int_{-\infty}^{+\infty}\cdots\int_{-\infty}^{+\infty}\psi^*(x_1,y_1,z_1,x_2,y_2,z_2\ldots)\,\psi(x_1,y_1,z_1,x_2,y_2,z_2\ldots)\,dx_1dy_1dz_1dx_2dy_2dz_2\ldots = 1, \quad (1)$$

or in an abbreviated notation:

$$\int\psi^*(1,2,\ldots n)\,\psi(1,2,\ldots n)\,d\tau_1\,d\tau_2\ldots d\tau_n \equiv \int\psi^*\psi\,d\tau = 1 \quad (2)$$

where the subscript 1 denotes the coordinates of the first particle and

$$d\tau_1 = dx_1dy_1dz_1$$

denotes the volume element of the first particle, *etc.* and the integration is carried out over the entire space for each particle. This is a $3n$-fold (or $4n$-fold with spin) integral, but it is usual to write just one integral sign.

The two basic concepts of quantum mechanics are the *wave function* and the *operator.* An operator has an explicit meaning only if it precedes a wave function. It then indicates that a certain mathematical operation is to be applied to the wave function. Operators may be multiplicative or differential operators [4].

The operator $\mathbf{x}_1$ of the position coordinate $x_1$ is a multiplicative operator, and it simply means: "$\psi$ is to be multiplied by the coordinate $x_1$", *i.e.*

$$\mathbf{x}_1\psi = x_1\psi \quad (3)$$

On the other hand the operator $\mathbf{p}_{x_1}$ of the $x$-component of the momentum of the first electron is a differential operator, and signifies: "$\psi$ is first to be differentiated with respect to $x_1$, and the derivative is then to be multiplied by the constant $h/\mathrm{i}$" ($h = h/2\pi$, where $h$ is Planck's constant and $\mathrm{i} = \sqrt{-1}$), *i.e.*

$$\mathbf{p}_{x_1}\psi = \frac{h}{\mathrm{i}}\frac{\partial\psi}{\partial x_1} \quad \text{or} \quad \mathbf{p}_{x_1} = \frac{h}{\mathrm{i}}\frac{\partial}{\partial x_1} \quad (4)$$

If in the equations of classical physics one replaces coordinates and momenta by the corresponding operators, one obtains the quantum-mechanical counterparts. Just as in classical physics the kinetic energy $T_i$ of a particle is equal to the square of the momentum divided by twice the mass, the same is true in quantum mechanics. Thus the operator of the overall kinetic energy is

$$\mathbf{T} = \sum_i \mathbf{T}_i = \sum_{i=1}^{n}\frac{\mathbf{p}_{x_i}\mathbf{p}_{x_i} + \mathbf{p}_{y_i}\mathbf{p}_{y_i} + \mathbf{p}_{z_i}\mathbf{p}_{z_i}}{2m_i}$$

$$= -h^2\sum_{i=1}^{n}\frac{1}{2m_i}\left[\frac{\partial^2}{\partial x_i^2} + \frac{\partial^2}{\partial y_i^2} + \frac{\partial^2}{\partial z_i^2}\right], \quad (5)$$

*i.e.* a differential operator. The potential energy is a function of the position coordinates, and therefore a multiplicative operator, as are those of the position coordinates themselves.

$$\mathbf{V} = \frac{1}{2}\sum_{ij=1}^{n}{}' \frac{Z_iZ_je^2}{r_{ij}} \quad (6)$$

Equation (6) is the well-known expression for the Coulomb energy of a system of point charges. The prime by the summation sign means that the term for $i = j$ is to be omitted. $Z_i$ is the charge, including sign, on the $i$-th particle in units of electronic charge, and $r_{ij}$ is the distance between the $i$-th and $j$-th particles.

$$r_{ij} = \left[(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2\right]^{1/2} \quad (7)$$

The total energy operator, *i.e.* the sum of the kinetic and potential energy operators, is called the Hamiltonian operator or simply the Hamiltonian, $\mathbf{H}$.

$$\mathbf{H} = \mathbf{T} + \mathbf{V} \quad (8)$$

[3] A discussion of classical mechanics as a basis for quantum mechanics can be found, *e.g.*, in *L. Pauling* and *E. B. Wilson*: Introduction to Quantum Mechanics, with Applications to Chemistry. McGraw-Hill, New York 1935; now available as a paperback. Another good introduction to quantum mechanics for chemists is *M. W. Hanna*: Quantum Mechanics in Chemistry. Benjamin, New York 1965.

[4] Integral operators also play a certain role. For example, the "effective potential" of the Hartree-Fock theory (see Section 1.6) is an integral operator. An operator of this type is defined by an integral kernel $A(x,x')$: $\mathbf{A}\varphi(x) = \int A(x,x')\varphi(x')\,d\tau'$.

The link between the abstract operators and the observables is established through the concept of *expectation values*[5]. The expectation value $< \mathbf{A} >$ of the operator **A** for a system in a state described by the wave function $\psi$ is the mean value to be found in a measurement of the quantity $A$. Various notations (9) are used for the expectation value:

$$\overline{A} \equiv < \mathbf{A} > \equiv (\psi, \mathbf{A}\psi) \equiv < \psi | \mathbf{A} | \psi > = \int \psi^* \, \mathbf{A} \, \psi \, d\tau \qquad (9)$$

Any of these expressions means that **A** is to be applied to $\psi$, and the result is to be multiplied by $\psi^*$ and integrated over the entire space occupied by all the particles.

Suppose we know the wave function of a system in a certain state and we want to know the dipole moment $\mathfrak{M}$ of the system; the dipole moment operator $\hat{\mathfrak{M}}$ is

$$\hat{\mathfrak{M}} = e \sum_{i=1}^{n} Z_i \, \mathfrak{r}_i$$

($e$ = unit charge)

and its expectation value $< \hat{\mathfrak{M}} > = (\psi, \hat{\mathfrak{M}} \, \psi)$[6] or the $x$, $y$, and $z$ components of $\hat{\mathfrak{M}}$:

$$< \hat{\mathfrak{M}}_x > = e \sum_{i=1}^{n} Z_i \int \psi^* \, x_i \, \psi \, d\tau$$

*etc.* are then obtained simply by integration.

The concepts presented in this section and their relations are summarized in the following table.

| | Related by equations | Measurable | Relation |
|---|---|---|---|
| Classical | Observables *e.g.* $A$ | Observable, *e.g.* $A$ | Identical |
| Quantum-mechanical | Operators, *e.g.* **A** | Expectation value, *e.g.* $< \mathbf{A} >$ | *via* the wave function |

The properties of a state are evidently known if its wave function is known. This can be obtained as a solution of the *Schrödinger equation*, namely of the time independent one (10) for "stationary" systems, and the time-dependent Schrödinger equation (11) for substantially time-dependent ones. In a stationary state all expectation values of operators that do not explicitly depend on time are constant with time.

$$\mathbf{H}\psi = E\psi \qquad (10)$$

$$\mathbf{H}\psi = -\frac{\hbar}{i}\frac{\partial \psi}{\partial t} \qquad (11)$$

Equation (10) is simply the quantum-mechanical formulation of the statement that the total energy $H$ of a closed system (not interacting with its surroundings) is a constant $E$. While the constant $E$ in classical mechanics can have any value, equation (10) has solutions $\psi$ that can be normalized in the sense of equation (1) only for certain values of $E$. The allowed values of $E_i$ are known as the *eigenvalues* of the equation (or as those of the Hamiltonian **H**), and the corresponding functions $\psi_i$ are called the *eigenfunctions*.

It is very important that a system in a stationary state can assume only certain discrete energy values. The lowest energy eigenvalue is always finite, and the corresponding state of the system is called the *ground state*, while the other discrete energy levels refer to *excited states*. At higher energies generally a *continuum* follows, which corresponds to continously distributed instead of discrete eigenvalues. Physically this means ionized or dissociated states. Zero energy is – by definition – that of a state in which all the nuclei and electrons are at rest at an infinite distance from one another. The total energy of an atom or molecule in the ground state is therefore the energy necessary to ionize and dissociate it completely, which for heavy atoms or large molecules amounts to many thousands of electron volts. Bond energies, on the other hand, are of the order of a few electron volts or even less. This indicates how extremly accurate quantum-chemical calculations must be in order to reproduce chemically interesting quantities correctly[7].

If the energy eigenvalues of a system are known the frequencies $\nu_{ij}$ of the spectral transitions are given by *Bohr*'s relation:

$$h\nu_{ij} = E_i - E_j. \qquad (12)$$

The intensity of the transition is determined by the transition moment $\mathfrak{M}_{ij} = (\psi_i, \hat{\mathfrak{M}}\psi_j) = \int \psi_i^* \hat{\mathfrak{M}} \psi_j d\tau$ where $\hat{\mathfrak{M}}$ is the dipole moment operator already defined, and $\psi_i$ and $\psi_j$ are the wave functions of the two states between which the transition occurs. If $\mathfrak{M}_{ij}$ vanishes, the transition is "forbidden". Certain $\mathfrak{M}_{ij}$ vanish for symmetry reasons. This gives rise to the so-called *selection rules*. $\mathfrak{M}_{ij}$ is a vector, and often only one component, *e.g.* $(\mathfrak{M}_x)_{ij}$, is different from zero. In this case the transition is polarized in the $x$-direction.

### 1.3. Variation Principle and Perturbation Theory

It is generally very simple to formulate the Schrödinger equation for a given system. A closed solution can be given only for the hydrogen atom and a few other one-electron systems. Thus in all practical applications of quantum chemistry one has to rely on numerical (and

[5] In addition to the expectation value, its "mean deviation" is defined: $< \Delta \mathbf{A} >^2 \equiv \int | \mathbf{A} - < \mathbf{A} > |^2 \, d\tau = | < \mathbf{A}^2 > - < \mathbf{A} >^2 |$. For operators that correspond to constants of motion, this deviation is equal to zero, *i.e.* the expectation value is "sharp". In quantum mechanics, a physical quantity $\Omega$ is a constant of motion if the operator $\hat{\Omega}$ assigned to it "commutes" with the Hamiltonian, *i.e.* if $\mathbf{H}\hat{\Omega} = \hat{\Omega}\mathbf{H}$ or $\mathbf{H}(\hat{\Omega}\psi) = \hat{\Omega}\,(\mathbf{H}\psi)$ for any $\psi$. Operators do not in general commute, *i.e.* $\mathbf{x}\mathbf{p}_x \neq \mathbf{p}_x\mathbf{x}$. For atoms the angular momentum is a constant of motion.

[6] $\mathfrak{r}_i$ denotes a vector, *i.e.* it denotes three coordinates $(x_i, y_i, z_i)$. Accordingly, $\hat{\mathfrak{M}}$ and its expectation value $< \hat{\mathfrak{M}} >$ are vectors.

[7] If the bond energy of a large molecule is determined by calculation of the total energy of the molecule and subtraction of the total energies of the isolated atoms (and this is generally the procedure that must be used), the resulting problem, according to *C. A. Coulson* [Rev. mod. Physics *32*, 170 (1960)] is equivalent to finding the weight of the captain of a ship by weighing the ship first with, and then without the captain.

necessarily approximate) methods of solution. The most important ones are those based on the variation principle.

Let the Hamiltonian $\mathbf{H}$ of a system be given and let $\psi_\tau$ be an arbitrary (normalized) function of all the coordinates of the system. It can then be shown [8] that

$$< \mathbf{H} >_\tau = (\psi_\tau, \mathbf{H}\psi_\tau) \geq E_o, \qquad (13)$$

*i.e.* the energy expectation value $< \mathbf{H} >_\tau$ calculated with $\psi_\tau$ is greater than or equal to the energy $E_0$ of the ground state of the system. Moreover the difference $< \mathbf{H} >_\tau - E_0$ is a measure [9] of the goodness of the approximate wave function $\psi_\tau$. In general, the closer the energy $< \mathbf{H} >\tau$ calculated from an approximate function $\psi_\tau$ to the true energy $E_0$, or in accordance with equation (13), the lower $< \mathbf{H} >_\tau$, the better is the approximation. When the variation principle is used, the true energy can only be approached "from above" [10].

In order to apply the variation principle, one formulates the *variation function* $\psi_\tau$ so that it contains certain variable parameters $\lambda_i$ [11]. The expectation value $< \mathbf{H} >_\tau$ will then be a function of these parameters. $<\mathbf{H}>_\tau$ is differentiated with respect to the parameters $\lambda_i$ in order to find its minimum as a function of the $\lambda_i$ and so to obtain the "best" function (in the sense of the variation principle) within the family of (normalized) $\psi_\tau$. In this $\psi_\tau$ the parameters $\lambda_i$ then have their optimum values. If the function is sufficiently flexible, we may come quite close [12] to the true eigenvalue $E_0$ and the true eigenfunction $\psi_0$.

The most important special form of the variation method is the Ritz procedure, in which one starts from a given set of functions $\varphi_1, \varphi_2, \ldots \varphi_n$ of the coordinates of the system and one approximates the variation function as a linear combination of the $\varphi_i$:

$$\psi_\tau = c_1 \varphi_1 + c_2 \varphi_2 + \ldots c_n \varphi_n. \qquad (14)$$

The coefficients $c_j$ are now the variation parameters with respect to which the expectation value $< \mathbf{H} >$ has to be differentiated. If this differentiation is carried out (subject to $\psi_\tau$ being normalized to unity), we obtain a system of linear equations for the determination of the "best" $c_j$:

$$\sum_j [H_{ij} - WS_{ij}]\, c_j = 0 \qquad i = 1, 2 \ldots n \qquad (15)$$

In this equation, the $H_{ij}$ are the *matrix elements* [13] of the Hamiltonian in the chosen basis $(\varphi_1, \varphi_2 \ \ldots \ \varphi_n)$, and the $S_{ij}$ are the *overlap integrals*.

$$H_{ij} = (\varphi_i, \mathbf{H}\varphi_j) = \int \varphi_i^* \mathbf{H}\, \varphi_j \, d\tau$$
$$S_{ij} = (\varphi_i, \varphi_j) = \int \varphi_i^* \varphi_j \, d\tau \qquad (16)$$

It is convenient to use a so-called orthogonal basis, for which the overlap integrals between different functions vanish, *i.e.* $S_{ij} = 0$ for $i \neq j$. If the $\varphi_i$ are also normalized, *i.e.* if $S_{ij} = 1$, the basis is said to be orthonormal. In this case the system of equations (15) reduces to

$$\sum_j H_{ij} c_j = W c_i. \qquad (17)$$

Such systems of equations occur in other fields of physics; they are called secular equations. The system of equations (17) has non-trivial solutions [14] only if

$$| H_{ij} - W\delta_{ij} | = 0 \qquad (18)$$

The vertical lines on both sides indicate that the determinant [15] of the matrix whose elements are $H_{ij} - W\delta_{ij}$ has to be taken ($\delta_{ij} = 1$ when $i = j$ and 0 when $i \neq$ j). This determinant, known as the *secular determinant*, vanishes only for certain values of $W$, the *eigenvalues* of

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[8] This can be seen as follows: The eigenfunctions $\psi_i$ (with the eigenvalues $E_i$) of the operator $\mathbf{H}$, as for Hermitian operators in general, form a complete orthonormal set, in the sense that any $\psi_\tau$ can be written as a linear combination of the $\psi_i$: $\psi_\tau = \sum_i c_i^\tau \psi_i$.

If we now form the expectation value $< \mathbf{H} >_\tau$ and bear in mind that the $\psi_i$ are eigenfunctions, *i.e.* that $\mathbf{H}\psi_i = E_i \psi_i$, and that the $\psi_i$ are orthogonal, insertion and rearrangement gives:

$$< \mathbf{H} >_\tau = \sum_{ij} c_i^{\tau *} c_j^\tau (\psi_i, \mathbf{H}\psi_j)$$

$$= \sum_i | c_i^\tau |^2 E_i = E_o + \sum_i | c_i^\tau |^2 (E_i - E_o)$$

However, the sum on the right is greater than or equal to zero, since $E_i \geq E_0$ when $E_0$ is the lowest eigenvalue. (Owing to the normalization of $\psi_\tau$ and $\psi_i$, $\sum_i | c_i^\tau |^2 = 1$).

[9] The difference between the calculated energy $(\psi, \mathbf{H}\psi)$ and the true energy $E_0$ is related to the goodness of the approximate solution $\psi$ by the Eckart inequality (*C. Eckart*, Physic. Rev. *36*, 878 (1930), note added in proof):

$$\int | \psi - \psi_0 |^2 \, d\tau \leq \frac{(\psi, \mathbf{H}\psi) - E_0}{E_1 - E_0},$$

where $E_1$ is the energy of the first excited state.

[10] Methods are also possible by which an eigenvalue is approximated *from below*. The distance between upper and lower bounds is then a measure of the accuracy of the calculation – a purely theoretical one, independent of comparison with experiment. The lower limits of *G. Temple* [Proc. Roy. Soc., Ser. A *119*, 276 (1928)] and *D. H. Weinstein* [Proc. nat. Acad. Sci. USA *20*, 529 (1934)], are too far from the true eigenvalues to be of practical use. However, significant progress has been made in recent years, owing mainly to the work of *N. Bazley* and *D. W. Fox* [J. Math. Physics *4*, 1147 (1963); Rev. mod. Physics *35*, 712 (1963)]. It should be mentioned that variation methods to give good approximations for expectation values other than the energy have been suggested [*e.g.*, *H. Preuss*, Z. Naturforsch. *13a*, 439 (1938); *16a*, 598 (1961); *L. M. Delves*, Nuclear Physics *41*, 497 (1963); *45*, 2 (1963)]. The "double perturbation theory" (see [18]) should be mentioned in this context.

[11] The variation parameters, to which optimum values are assigned purely theoretically *via* the variation principle, should not be confused with "semi-empirical" parameters, to which explicit values are given to force agreement with certain empirical data.

[12] "Arbitrarily close" means that the integral $\int | \psi - \psi_0 |^2 \, d\tau$ becomes arbitrarily small ("mean square convergence").

[13] The matrix elements of any operator are generally integrals of the form (16) when $\mathbf{H}$ is replaced by this operator. An overlap integral may be regarded as the matrix element of the "identity operator" (which leaves the function on which it acts unchanged). Diagonal matrix elements, in which the function on the right and on the left of the operator is the same, may of course be regarded as expectation values calculated with this function. The notation using brackets is easier to visualize than the integral notation. Note that the asterisk denoting the complex conjugate is omitted in the former notation.

[14] Let all $c_i = 0$. Obviously this is a solution, but it has no physical significance since it corresponds to zero probability everywhere; such a solution is a *trivial* one.

the matrix ($H_{ij}$). If equation (18) is multiplied out [15], a polynomial of degree $n$ in $W$ is obtained, which in general has $n$ roots which are the $n$ eigenvalues of the matrix. Like most quantum-mechanical operators, $\mathbf{H}$ is *Hermitian, i.e.* $H_{ij} = H_{ji}^*$, and therefore it has only real eigenvalues; some of the $W_i$ may coincide, in which case we say that the corresponding eigenvalue is *degenerate*. The lowest eigenvalue $W_0$ is an approximation to the lowest eigenvalue $E_0$ of the Schrödinger equation, each matrix eigenvalue $W_i$ being an upper bound to one of the true energies $E_i$ of the corresponding state.

Thus the Ritz method reduces the eigenvalue problem of a differential equation, a difficult task, to a matrix eigenvalue problem, which can be solved by routine methods with the aid of electronic computers. Most quantum-chemical problems can be formulated in the language of matrix algebra [16].

More difficult than the solution of the system (17) or (15) is the calculation of the matrix elements $H_{ik}$ (see Section 1.6). The accuracy of the solutions obtained by the Ritz procedure increases in general with the size of the basis set. There exist so-called complete sets of functions. Any wave function referring to a given number of particles can be strictly [17] represented as a linear combination of the functions of this set. If one applies the Ritz procedure with an increasing number of basis functions of this set, then the solution converges to the true solution. For practical purposes the convergence is often so good (consider the analogy to convergent power series, where it often suffices to consider only the first few terms) that even a relatively small basis set may lead to sufficiently accurate solutions.

An alternative to the variation method is *perturbation theory* [18]. It can be applied if the Hamiltonian of the problem can be written as the sum of an operator $\mathbf{H}^{(0)}$ whose eigenfunctions $\varphi_i$ and eigenvalues $\varepsilon_i$ are known, and a perturbation operator $\mathbf{H}'$, which should be small compared to $\mathbf{H}^{(0)}$.

$$\mathbf{H} = \mathbf{H}^{(0)} + \mathbf{H}' \qquad \mathbf{H}\,\psi_i = E_i\,\psi_i$$
$$\mathbf{H}^{(0)}\,\varphi_i = \varepsilon_i\,\varphi_i \tag{19}$$

There are essentially two variants of perturbation theory, that of *Rayleigh* and *Schrödinger* and that of *Brillouin* and *Wigner*; we shall confine ourselves to the former. The eigenfunction $\psi_0$ and the eigenvalue $E_0$ (we are considering the ground state, which is supposed to be nondegenerate [19], *i.e.* there should be only one $\varphi_0$ for $\varepsilon_0$ and only one $\psi_0$ for $E_0$) of the perturbed problem are then expressed in terms of those of the unperturbed problem *plus* a perturbation correction, which is expanded as power series in the perturbation operator. If $\mathbf{H}'$ is very small, the expansion may be confined to first-order and possibly second-order terms, *i.e.* to terms that are linear and quadratic in $\mathbf{H}'$, respectively. The first-order perturbation of the energy is

$$\Delta E^{(1)} = (\varphi_o, \mathbf{H}'\,\varphi_o);$$
$$E^{(1)} = \varepsilon_o + \Delta E^{(1)} = (\varphi_o, \mathbf{H}^{(0)}\,\varphi_o) + (\varphi_o, \mathbf{H}'\,\varphi_o) = (\varphi_o, \mathbf{H}\,\varphi_o) \geqslant E \tag{20}$$

$E^{(1)}$ is the unperturbed energy plus the first-order perturbation energy. In order to calculate the energy to first order, one need only know the *unperturbed* function $\varphi_0$. The calculation of $E^{(1)}$ requires just the calculation of an integral, and does not require the solution of an equation. As can be seen from equation (20), since $E^{(1)}$ is an expectation value of the operator $\mathbf{H}$, it obeys the variation principle, *i.e.* it represents an upper limit for the energy. This is not true of $E^{(2)}$, the energy to second order, which may lie *below* the true energy. The difference between $E^{(2)}$ and the true energy $E$ is therefore not a measure of the goodness of the wave function.

The first-order perturbation correction $\Delta\psi^{(1)}$ of the wave function is conventionally expanded as a linear combination of the eigenfunctions of the unperturbed system. These form a complete set only when the so-called continuum functions are also taken into account. The following expressions are obtained for $\psi^{(1)}$ and $E^{(2)}$:

$$\psi^{(1)} = \varphi_o + \Delta\psi^{(1)} = \varphi_o + \sum_{i>0} c_i\,\varphi_i \tag{21}$$

$$c_i = \frac{(\varphi_o, \mathbf{H}'\,\varphi_i)}{\varepsilon_o - \varepsilon_i} \qquad E^{(2)} = E^{(1)} + \sum_{i>0} \frac{(\varphi_o, \mathbf{H}'\,\varphi_i)\,(\varphi_i, \mathbf{H}'\,\varphi_o)}{\varepsilon_o - \varepsilon_i}$$

The summations over an infinite number of terms containing continuum contributions are extremely inconvenient. One therefore prefers expressions that are equivalent to (21), but easier to evaluate [18].

The second-order perturbation correction to the energy is of interest mainly in those cases where the first-order perturbation vanishes.

A simple example is the Stark effect for the ground state of the hydrogen atom, in which the perturbation operator is simply

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[15] A (square) matrix $\mathbf{A}$ of dimension $n$ is a square array of $n^2$ numbers $A_{ik}$ arranged in $n$ rows and $n$ columns, *e.g.*, for $n = 2$: $\mathbf{A} = \begin{pmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{pmatrix}$. To each matrix is assigned a determinant $|\mathbf{A}| = \det \mathbf{A}$, which is a single number or a single algebraic expression, and which is calculated from the elements $A_{ij}$ of the matrix as follows:

$$|\mathbf{A}| = \sum_{\mathrm{p}} \varepsilon_{\mathrm{p}}\, A_{1i_1} A_{2i_2} \cdots A_{ni_n}$$

where $i_1, i_2 \ldots i_n$ is any permutation of the numbers $1,2 \ldots n$, the sum being taken over all possible permutations, and $\varepsilon_{\mathrm{p}}$ is the so-called parity of the permutation, *i.e.* $\varepsilon_{\mathrm{p}} = 1$ when $i_1, i_2 \ldots i_n$ can be obtained by an even number of transpositions, and $\varepsilon_{\mathrm{p}} = -1$ when an odd number is required.

Examples: $n = 2; |\mathbf{A}| = \begin{vmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{vmatrix} = A_{11}A_{22} - A_{12}A_{21}$

$$n = 3; |\mathbf{A}| = \begin{vmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{vmatrix} = A_{11}A_{22}A_{33} + A_{12}A_{23}A_{31} + A_{13}A_{21}A_{32} - A_{11}A_{23}A_{32} - A_{12}A_{21}A_{33} - A_{13}A_{22}A_{31}$$

[16] Matrix algebra probably is the most important mathematical tool of the theoretical chemist. A suitable introduction to the subject is given in, *e.g.*[22], Appendix V, as well as in the chapters on matrices in *H. Margenau* and *G. M. Murphy*: The Mathematics of Physics and Chemistry. Van Nostrand, Princeton 1943, or in *E. Wigner*: Gruppentheorie. Vieweg, Braunschweig 1931. More detailed treatments are given in *R. Zurmühl*: Matrizen. Springer, Berlin 1958, and *G. G. Hall*: Matrices and Tensors. Pergamon, London 1963.

[17] In the sense that the mean square deviation vanishes (cf. [12]). Complete sets are infinite.

[18] An excellent survey of the present state of perturbation theory in quantum chemistry is given by *J. Hirschfelder, W. Byers-Brown*, and *S. Epstein* in Adv. Quantum Chem. *1*, 256 (1965).

[19] The formalism is somewhat more complicated for degenerate states. Here one has first to find the zeroth-order function adapted to the perturbation, as a linear combination of the eigenfunctions belonging to the same eigenvalue $E_0$.

the potential energy of the electron in the applied external field. $(\varphi_0, \mathbf{H}\varphi_0) = \Delta E^{(1)}$ vanishes in this case, and $\Delta E^{(2)}$ gives approximately the change of the ground state energy due to the field. The interaction energy between two neutral atoms a large distance apart vanishes to first order as well, and the London (or van der Waals) attraction is obtained in the second order. Perturbation corrections of higher than second order are rarely evaluated in practice.

Perturbation theory is based on the assumption that an expansion in powers of the perturbation operator converges. This assumption is not necessarily justified [20]. It is a rule of thumb that perturbation theory fails whenever the difference $E - \varepsilon$ is of the same order as the energy difference between $E_0$ and the first excited state $E_1$.

In time-dependent problems, a stationary system may be regarded as the unperturbed one and the time dependence as the perturbation. "Time-dependent" perturbation theory is used, *e.g.*, in treatment of light absorption.

## 1.4. Energy (or Potential) Hypersurfaces

In the Schrödinger equation (10) with the Hamiltonian operator **H** given by equations (8), (5), and (6), electrons and nuclei are treated in the same way. However, the mass of a proton is about 1800 times that of an electron, and other nuclei are heavier still. If we idealize the nuclei as having infinite mass, then only the electrons move, and only the coordinates of the electrons need to be regarded as variables in the Schrödinger equation. The nuclei are not really infinitely heavy, and they move slightly, but their movement is slow enough for them to be regarded as fixed for a time that is long for the movement of the electrons.

These considerations justify the so-called *adiabatic* or *Born-Oppenheimer approximation* [21], according to which the wave function $\psi$ of a system may be expressed (approximately) as the product of a function $R$ of the nuclei alone and a function $\Phi$ of the electrons (which contains the coordinates of the nuclei as parameters). If within the family of wave functions having the form of such a product $\psi = R\Phi$, we look for the best one in the sense of the variation principle, we obtain a Schrödinger equation $\mathbf{H}_{el}\Phi = E_{el}\Phi$ for the electronic wave function $\Phi$ and a second one, $\mathbf{H}_K R = E_K R$ for the movement of the nuclei, the Hamiltonian operators $\mathbf{H}_{el}$ and $\mathbf{H}_K$ being given approximately by (22) and (23).

$$\mathbf{H}_{el} = \sum_i \mathbf{T}_i - e^2 \sum_i \sum_I \frac{Z_I}{r_{Ii}} + e^2 \sum_{i<j} \frac{1}{r_{ij}} + e^2 \sum_{I<J} \frac{Z_I Z_J}{r_{IJ}} \qquad (22)$$

$\mathbf{H}_{el}$ is the operator of the (kinetic plus potential) energy of the electrons in the field of the "fixed" nuclei.

The summation over $i,j$ refers to the electrons, and that over $I,J$ to the nuclei. $\mathbf{T}_i$ is the kinetic energy operator of the $i$-th electron. The second sum represents the potential energy of the electrons in the field of the nuclei, and the third term the mutual repulsion of the electrons; the last term, representing the repulsion of the nuclei, is constant for fixed nuclei. The Schrödinger equation involving this Hamiltonian operator (22) is now solved to obtain the electronic eigenfunction $\Phi$ and the energy $E_{el}$, both of which depend on the arrangement of the nuclei.

Solution of the equation for all possible nuclear configurations gives $E_{el}$ as a function of nuclear positions. The nuclear configuration is in general characterized by $3N - 6$ *internal coordinates* [22], where $N$ is the number of nuclei. A plot of the electronic energy $E_{el}$ as a function of the internal coordinates gives an *energy hypersurface* [23]. For diatomic molecules, the only internal coordinate is the distance $r$ between the atoms, and the energy hypersurface is a plane curve $E_{el}(r)$ (Fig. 1). In the Born-Oppenheimer approximation, the energy

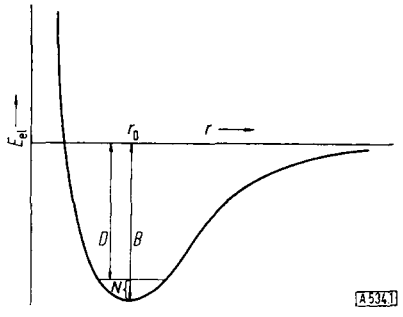


Fig. 1. Potential curve of a diatomic molecule.
$r$: interatomic distance
$r_0$: equilibrium distance
$B$: bond energy
$D$: dissociation energy
$N$: energy of the zero-point vibration

hypersurface plays the part of the potential energy for the movement of the nuclei, and is therefore often called the *potential hypersurface*. The Hamiltonian for the movement of the nuclei is

$$\mathbf{H} = \sum_I \mathbf{T}_I + E_{el}(1,2 \ldots I \ldots). \qquad (23)$$

The potential energy for the movement of the nuclei in a diatomic molecule is represented by the potential curve of Figure 1. For motion with a small total energy, only small displacements from the equilibrium configuration are likely. The potential for small movements near the minimum may be approximated by a parabola:

$$E_{el}(r) = \text{const.} + a(r - r_0)^2 + \ldots \qquad (24)$$

$$a = \frac{1}{2}\left(\frac{\partial^2 E_{el}}{\partial r^2}\right)_{r=r_0}$$

The Schrödinger equation for such a harmonic oscillator can be solved rigorously [22]. If higher powers of $r$ are included in the expansion (24) of the potential, one can account for the anharmonicity of the nuclear vibrations.

[20] The question of the convergence of the perturbation expansion has been studied particularly by *F. Rellich* [Math.-Ann. *173*, 600, 677 (1936); *117*, 336 (1940)] and by *T. Kato* [J. Fac. Sci., Imp. Univ. Tokyo, Sect. I, *6*, 145 (1951); Progr. theoret. Physics (Kyoto) 5, 95 (1950)].

[21] *M. Born* and *R. Oppenheimer*, Ann. Physik *84*, 457 (1927).

[22] The potential energy is invariant with respect to rotation or translation of the molecule, *i.e.* it is independent of the three coordinates corresponding to translation and of the three (or two) coordinates corresponding to rotation. A detailed treatment of the *internal coordinates* and of the quantum theory of molecular vibrations is given in *E. B. Wilson, J. C. Decius,* and *P. C. Cross:* Molecular Vibrations. McGraw-Hill, New York 1955.

[23] A function of $M$ coordinates can be regarded as an $M$-dimensional entity called a *hypersurface* in an $(M+1)$-dimensional space. A hypersurface in two-dimensional space is a curve, and in three-dimensional space a surface. An easily understandable treatment of potential hypersurfaces is given in *H. Preuss*: Quantentheoretische Chemie I. Bibliographisches Institut, Mannheim 1964.

Knowledge of the potential hypersurface for a molecule provides us with some important information.

If the potential hypersurface (or the potential curve) passes through a minimum (at least of the depth of the zero-point vibration) for a finite distance of all nuclei from one another, the molecule is physically stable. If the potential trough is sufficiently deep (larger than $kT$), the molecule can be regarded also as chemically stable [24]. If several minima are present, there are several stable arrangements (*e.g.*, tautomeric forms). If $E_{el}$ is independent of a coordinate corresponding to rotation about a bond, there is free rotation, *etc.* The minimum of the hypersurface gives the equilibrium configuration, *i.e.* the equilibrium distances and angles. The curvature at the potential minimum is a measure of the force constants. The difference between the potential minimum and the energy corresponding to an infinite distance between the atoms is equal to the binding energy (which differs from the experimental dissociation energy by the zero-point energy of the molecular vibrations).

Potential hypersurfaces are also defined for (electronically) excited states. The potential curve for the $He_2$ "molecule" has no minimum in the ground state, but in the first excited state it has. Potential surfaces for different states can intersect (when they belong to different symmetry species or to different spin multiplicities), so that for different nuclear configurations, the electronic ground state may belong to different hypersurfaces. Expectation values of operators can not, of course, be calculated from the hypersurfaces; one needs the wave functions. One should not forget that a potential hypersurface is rigorously defined only when the Born-Oppenheimer approximation is valid. In certain cases this term may have no meaning at all.

Potential hypersurfaces are useful for the discussion of chemical reactions. The nuclei and electrons of the atoms and molecules involved in the reaction are regarded as forming one "super-molecule", and the potential hypersurface of this super-molecule is determined as a function of the arrangement of all the particles. For the reaction A + B = C + D, the potential hypersurface must have at least two minima, one of which corresponds to the isolated (*i.e.* widely separated) molecules A and B, and the other to C and D. Between these two minima there may be peaks, maxima, saddle points, or other minima.

The time-dependent Schrödinger equation should be solved for the movement of the nuclei in this potential. Since it is at present not possible to solve this type of equation, one contents oneself often with a "semiclassical" theory [25] in which the potential hypersurface is calculated quantum-mechanically, while for the movement of the nuclei one uses classical mechanics. This is probably not too rough a simplification, though effects such as the *zero-point vibrations* and the *tunnel effect* [26] (which is presumably non-neglegible only in special cases) are neglected.

In this scheme, the question of whether a chemical reaction takes place depends essentially on the inital conditions, *i.e.* on the relative positions of the molecules A and B at a given instant, and on their kinetic energy, particularly the distribution of the vibrational energy over the vibrational degrees of freedom.

In order to describe a chemical reaction, it is obviously necessary to calculate the movement of the super-molecule for various initial conditions and to take into account their statistical distribution.

Somewhat dubious is the adiabatic postulate, which means that during the reaction the nuclei move on an adiabatic potential hypersurface that belongs to one and the same electronic state. This postulate is probably not justified when potential hypersurfaces intersect or come close to one another. It is better, though more difficult, to treat chemical reactions non-adiabatically. First attempts to do so based on quantum-mechanical scattering theory have not yet attained practical importance.

Since the calculation of the potential hypersurface of a molecule is very laborious, one confines oneself often to calculating some isolated points on this hypersurface, *e.g.*, one that corresponds to the non-interacting starting materials, one to the end-products of the reaction, and another to represent a hypothetical "activated complex" which, however, often has no physical reality.

There are still many unsolved questions in the quantum theory of chemical reactions [27].

For calculations involving a single molecule it is often not necessary to know the whole hypersurface; the equilibrium geometry known from experiment may be used in the calculation when one just wants to know the properties of the molecule in the equilibrium configuration. Most current quantum-chemical studies aim at calculating electronic states of molecules in fixed nuclear configuration.

### 1.5. Treatment of a Separable Many-Body Problem

Let us now confine ourselves to the problem of solving the electronic Schrödinger equation for a fixed arrangement of the nuclei. The number of electrons, and hence the number of coordinates involved in the wave function, is generally so large that in addition to the Born-Oppenheimer approximation other simplifications must be introduced to keep the amount of calculation required within reasonable limits.

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[24] The stability referred to here is with respect to dissociation or to internal rearrangements. It does not tell us whether the compound is stable in the sense that it can be poured into a bottle and stored (in air or *in vacuo*, at or below room temperature). In order to get information about this kind of stability, one has to consider all possible reactions of the molecule with other molecules of the same kind or with foreign molecules on the basis of the potential hypersurfaces of super-molecules, and to examine both kinetic and thermodynamic aspects.

[25] See, *e.g.*, *H. Eyring*, J. chem. Physics *3*, 107 (1935).

[26] The tunnel effect (passage through a potential barrier that is higher than the kinetic energy of the particle) appears to be of some significance for the movement of a proton in a potential field with two minima, such as occur in hydrogen bonds. No final conclusion appears to have been reached as yet. Cf., *e.g.*, *H. Zimmermann*, Angew. Chem. *76*, 1 (1964); *P. O. Lowdin*, Rev. mod. Physics *35*, 724 (1963).
Somewhat superior to the purely classical treatment of the nuclear motion is the so-called phase-integral or WKB (*Wentzel, Kramers, Brillouin*) method (see textbooks on quantum mechanics), which can be justified on the basis of quantum theory, and by means of which it is possible, *e.g.*, to study the tunnel effect.

[27] An easily understandable, but in many respects outdated, introduction to the theory of chemical reactions is given by *H. Eyring*: Modern Chemical Kinetics. Reinhold, New York 1963. The present state of the (largely classical-mechanical) theory of unimolecular dissociations is described by *N. B. Slater*: Theory of Unimolecular Reactions. Cornell University Press, Ithaca 1959. An example of a quantum-mechanical paper on theoretical reaction kinetics is *L. Hofacker*, Z. Naturforsch. *18a*, 607 (1963). In contrast to the fundamental theory of chemical reactions, the semi-empirical theories of the reactivity of organic molecules have been quite successful; cf. *M. J. S. Dewar*, Adv. chem. Physics *7*, 65 (1965).

If we examine the electronic Hamiltonian operator in equation (22) more closely, we find that it consists of the following terms:

1. [Fourth term in eq. (22)] a constant (*i.e.* independent of the coordinates of the electrons) term for the repulsion of the nuclei, abbreviated to $V_K$.

2. [First and second terms in eq. (22)] a sum of terms, each of which depends only on the coordinates of one electron, and each of which consists of the kinetic energy $\mathbf{T}_i$ and the potential energy of the $i$-th electron in the field of all the nuclei, $e\sum_I Z_I/r_{Ii}$. The two energies are combined to give $\mathbf{h}(i)$:

$$\mathbf{h}(i) = \mathbf{T}_i + e\sum_I Z_I/r_{Ii}$$

3. [Third term in eq. (22)] expressions of the form $e^2/r_{ij}$, each of which are denoted by $\mathbf{g}(i,j)$.

$$\mathbf{g}(i,j) = e^2/r_{ij}$$

Using these abbreviations, the electronic Hamiltonian operator can be written:

$$\mathbf{H}(1,2,\ldots n) = V_K + \sum_{i=1}^{n} \mathbf{h}(i) + \sum_{i<j=1}^{n} \mathbf{g}(i,j) \qquad (25)$$

If the term for the repulsion of the electrons were absent, the Schrödinger equation would be *separable*, *i.e.* the $n$-electron $\psi$-function could be written as a product of functions, each of which depends only on the coordinates of one electron:

$$\psi(1,2,\ldots n) = \varphi_1(1)\,\varphi_2(2)\ldots\varphi_n(n) \qquad (26)$$

The one-electron functions $\varphi_i(i)$ would then be determined as solutions of the single-particle Schrödinger equation

$$\mathbf{h}(i)\,\varphi_i(i) = \varepsilon_i\,\varphi_i(i) \qquad (27)$$

which is a relatively simple numerical problem. The total energy in this case is found to be $E = V_K + \sum_{i=1}^{n}\varepsilon_i$. This can be seen by insertion of (26) and (27) in (25) without the last term.

We must now keep in mind that a wave function must not only be a solution of the Schrödinger equation and satisfy the boundary conditions (to vanish at infinity and to be normalizable), but also be *antisymmetric*[28] with respect to permutation of the coordinates (including spin coordinates) of all the particles. (This is the rigorous formulation of the *Pauli principle*).

The wave function for a (separable) two-electron problem, therefore, must not be of the form $\psi(1,2) = \varphi_1(1)\varphi_2(2)$, but rather

$$\psi = \frac{1}{\sqrt{2}}[\varphi_1(1)\varphi_2(2) - \varphi_2(1)\varphi_1(2)] = \frac{1}{\sqrt{2}}\begin{vmatrix}\varphi_1(1) & \varphi_1(2)\\ \varphi_2(1) & \varphi_2(2)\end{vmatrix} \qquad (28)$$

It is assumed here that $\varphi_1$ and $\varphi_2$ are mutually orthogonal [this is true if they are different solutions of the same differential equation (27)] and are normalized; the factor $1/\sqrt{2}$ guarantees then that $\psi$ is normalized as well.

An antisymmetric $\psi$-function for a separable Hamiltonian can be most conveniently written as a determinant[15], the *Slater determinant*.

$$\psi(1,2,\ldots n) = \frac{1}{\sqrt{n!}}\begin{vmatrix}\varphi_1(1) & \varphi_2(1) & \ldots & \varphi_n(1)\\ \varphi_1(2) & \varphi_2(2) & \ldots & \varphi_n(2)\\ \vdots & & & \\ \varphi_1(n) & \varphi_2(n) & \ldots & \varphi_n(n)\end{vmatrix} \qquad (29)$$

The determinant, when expanded[15], is a sum of $n!$ product functions.

A direct consequence of the antisymmetry principle is that no two electronic functions in the Slater determinant may be identical, since a determinant with two identical columns is equal to zero. For *separable problems*, therefore, the Pauli principle may be simply formulated as the *exclusion principle*: Each one-electron function can be occupied by at most one electron.

Bearing in mind that there are only two single-particle spin functions, denoted by $\alpha$ and $\beta$, and that each single-particle function can be written as the product of a pure position function, a so-called orbital, and a spin function (such a product is called a *spin orbital*), it follows that each orbital can accommodate at most two particles. For a separable problem, the state with minimum energy, *i.e.* the ground state, is obviously obtained when the orbitals having the lowest one-electron energies $\varepsilon$ in accordance with equation (27) are doubly occupied (and in the case of odd numbers of electrons, when the last orbital is singly occupied).

Here, like in many other examples of quantum chemistry, the spin plays a very indirect role and only affects the permutation properties of the wave function, since the Hamiltonian (when spin-orbital interactions *etc.* are ignored) does not involve the spin coordinates. Many attempts have therefore been made to eliminate the (difficult to visualize) spin as far as possible from quantum chemistry and to find some other means of allowing for its role in connection with the antisymmetry principle. However, none of the approaches towards a "spin-free" quantum mechanics[29] is simpler than the conventional formulation. On the other hand, it is always possible to eliminate the spin, whenever it is not directly involved, by using the formalism of reduced "density matrices"[30]. Density matrices play an important role in other domains of present-day quantum chemistry as well. To say more about them would, however, go beyond the scope of the present paper.

For one- and two-electron systems (but not for many-electron systems), the wave function can be expressed as the product of a position function and a spin function. In the two-electron case there are three symmetrical spin functions:

$$^t\Theta_1(1,2) \equiv \alpha(1)\,\alpha(2)$$

$$^t\Theta_{-1}(1,2) \equiv \beta(1)\,\beta(2)$$

$$^t\Theta_0(1,2) \equiv \frac{1}{\sqrt{2}}\{\alpha(1)\,\beta(2) + \beta(1)\,\alpha(2)\}$$

and an antisymmetric spin function:

$$^s\Theta(1,2) \equiv \frac{1}{\sqrt{2}}\{\alpha(1)\,\beta(2) - \alpha(1)\,\beta(2)\}$$

[28] A function is said to be antisymmetric if the transposition of the coordinates of two particles give the same function multiplied by $-1$.

[29] *F. A. Matsen*, Adv. Quantum Chem. *1*, 60 (1965).

[30] See the review by *R. McWeeny*, Rev. mod. Physics *32*, 335 (1960).

The corresponding position functions must be antisymmetric (triply spin-degenerate, triplet state) and symmetric (singlet state), respectively. In spin-free two-electron problems, the spin functions may often be ignored; it is then sufficient to take a symmetric function of the space coordinates for a singlet state and an antisymmetric one for a triplet state.

### 1.6. The Independent Particle Model

The Schrödinger equation for a many-electron problem is not separable, since the Hamiltonian operator contains the electronic interaction $\sum_{i<j}\mathbf{g}(i,j)$.

The (separable) Hamiltonian operator without electronic interaction may be regarded as the "unperturbed" Hamiltonian $\mathbf{H}_0$ and the electronic interaction as the perturbation $\mathbf{H}'$, and the formalism of the perturbation theory may then be used [31]. This procedure has been rather successful for atoms, since the unperturbed problem in this case can be solved in closed form. The solution of the unperturbed system is a Slater determinant built up from "hydrogen-like" functions. This kind of perturbation treatment is less suitable for molecules.

The best-known and most important model used to describe many-electron systems approximately is the independent particle model (IPM) [32], on which nearly all quantitative and qualitative chemical applications are based.

In this model one assumes that the approximate wave function can be written as a single Slater determinant. This can be a rigorous solution only if the electronic interaction vanishes, however, even if there is electron interaction, we can look for the best possible wave function that can be expressed as a single Slater determinant. There are several criteria for defining the best IPM function. Usually one defines it as the best function in the sense of the variation principle, *i.e.* in the family of all functions of the form (29) the one that minimizes the energy expectation value. The condition for this energy minimum leads to a system of *single-electron equations*, which determine the best orbitals.

$$\mathbf{h}_{\text{eff}}\,\varphi_i = \varepsilon_i\,\varphi_i \tag{30}$$

$\mathbf{h}_{\text{eff}}$ is known as the effective one-electron operator, and the system of equations the (unrestricted) *Hartree-Fock equations*. $\mathbf{h}_{\text{eff}}$ consists of the true one-electron operator $\mathbf{h}(i)$ and an effective potential $\mathbf{J}(i)$, which can be interpreted as the potential of the average field produced by the other electrons [33]. Thus the effective potential $\mathbf{J}(i)$, and hence $\mathbf{h}_{\text{eff}}(i)$, depends on the distribution of the electrons, *i.e.* in order to construct it, the solutions $\varphi_i$ should already be known.

In practice, one assumes a starting electron distribution, from which one constructs the initial Hartree-Fock operator; new $\varphi_i$ are obtained as solutions of equation (30), and are used to calculate a new effective potential. This procedure is repeated until the field is *self-consistent*, which is generally the case after a few iterations. The method is therefore known as the self-consistent field (SCF) method.

The solution of the effective one-electron equation, *i.e.* the calculation of the Hartree-Fock orbitals or SCF orbitals, is generally carried out by the Ritz method, *i.e.* the SCF orbitals are approximated as a linear combination of a given set of one-electron functions. The basis in case of atoms may be so-called *Slater functions* of the form

$$\psi_{nlm}(r,\vartheta,\varphi) = N\,r^{n-1}\,\mathrm{e}^{-2\eta r}\,\mathrm{Y}_l^m(\vartheta,\varphi). \tag{31}$$

where $N$ is a normalization factor, $\eta$ is a variable parameter, $n$, $l$, and $m$ are integers satisfying the inequality $m \leqslant l < n$, and $\mathrm{Y}_l^m$ are normalized spherical harmonics [34].

The integrals required for calculating the matrix elements can be evaluated in closed form for atomic calculations, and expansions of *atomic orbitals* in terms of Slater functions converge rather well, so that very accurate analytical SCF orbitals of the atoms are now available. As *Slater* has shown in 1930, one may approximate any orbital by a single Slater function and the optimum values of $\eta$ and $n$ can then be given approximately by very simple rules [35]. Thus according to the *Slater rules*, the approximate atomic orbitals of the carbon atom are

$$\begin{aligned}
&1\mathrm{s}\ :\ \psi_{100} = N\,\mathrm{e}^{-5.7r}\\
&2\mathrm{s}\ :\ \psi_{200} = N'\,r\,\mathrm{e}^{-1.625r}\\
&2\mathrm{p}\sigma\ :\ \psi_{210} = N''\,r\,\mathrm{e}^{-1.625r}\cos\vartheta = N''\,z\,\mathrm{e}^{-1.625r}\\
&2\mathrm{p}\pi\ :\ \psi_{211} = N'''\,r\,\mathrm{e}^{-1.625r}\sin\vartheta\,\mathrm{e}^{\mathrm{i}\varphi} = N'''\,(x+\mathrm{i}y)\mathrm{e}^{-1.625r}\\
&2\mathrm{p}\bar{\pi}\ :\ \psi_{21\bar{1}} = N'''\,r\,\mathrm{e}^{-1.625r}\sin\vartheta\,\mathrm{e}^{-\mathrm{i}\varphi} = N'''\,(x-\mathrm{i}y)\mathrm{e}^{-1.625r}.
\end{aligned}$$

$2\mathrm{p}\pi$ and $2\mathrm{p}\bar{\pi}$ may be replaced by the real functions

$$2\mathrm{p}_x = N''\,x\,\mathrm{e}^{-1.625r} = \frac{1}{\sqrt{2}}\,(2\mathrm{p}\pi + 2\mathrm{p}\bar{\pi})$$

and

$$2\mathrm{p}_y = N''\,y\,\mathrm{e}^{-1.625r} = \frac{-\mathrm{i}}{\sqrt{2}}\,(2\mathrm{p}\pi - 2\mathrm{p}\bar{\pi})$$

The Slater functions resemble somewhat the eigenfunctions of hydrogen-like ions, with one important dif-

[31] The method is due to *Hylleraas* [Z. Physik *65*, 209 (1930)]. An up-to-date survey is given by *D. Layzer et al.*, Ann. Physics *29*, 101 (1964)

[32] The independent particle model is discussed in detail by *W. Kutzelnigg* and *V. H. Smith* (Preprint 130 and 138, Quantum Chemistry Group, Uppsala 1964).

[33] $\mathbf{h}_{\text{eff}}$ also contains the so-called exchange operator, which is difficult to interpret pictorially, and which ensures that electrons having the same spin do not approach one another too closely. A number of good reviews of the Hartree-Fock method have been published, *e.g. D. R. Hartree*: Calculation of Atomic Structures. J. Wiley, New York 1957; *R. K. Nesbet*, Rev. mod. Physics *33*, 28 (1961); *C. C. J. Roothaan*, Rev. mod. Physics *23*, 69 (1951); *32*, 179 (1960).

[34] If the effective field is a central field, *i.e.* if the potential is only a function of the distance from the nucleus, then an atomic orbital can be written as the product of a function $R(r)$ and a spherical harmonic $\mathrm{Y}_l^m$ that depends only on the polar coordinates $\vartheta$ and $\varphi$ (which are similar to geographical latitude and longitude). The possible spherical harmonics are indicated by two indices $l$ and $m$, where $|m| \leqslant l$. The simplest spherical harmonic, $\mathrm{Y}_0^0$, is independent of $\vartheta$ and $\varphi$; $\mathrm{Y}_0^0 \propto \cos\vartheta$; $\mathrm{Y}_1^{-1} \propto \sin\vartheta\mathrm{e}^{-\mathrm{i}\varphi}$; $\mathrm{Y}_1^1 \propto \sin\vartheta\mathrm{e}^{\mathrm{i}\varphi}$ belong to $l=1$. For details see *e.g.* [3]; for the symmetry behavior of the orbitals in general see [32].

[35] *C. Zener*, Physic. Rev. *36*, 51 (1930); *J. C. Slater*, *ibid. 36*, 57 (1930). The best orbitals of this form calculated recently by *E. Clementi* [J. chem. Physics *38*, 2686 (1963); *40*, 1944 (1964)] *via* the variation principle do not differ appreciably from those given by *Slater*'s rules.

ference that the "effective nuclear charge" differs for different orbitals of the same atom. (In the hydrogen-like functions $\eta = Z/n$, where $Z$ is the nuclear charge and $n$ is the principal quantum number.) In this approximation, the influence of the other electrons is taken into account by partial screening of the nuclear charge. It is necessary to distinguish between the Slater functions in the sense of the Slater rules, where each atomic orbital is approximated by a single function of the type (31), and the use of Slater functions as the basis for calculations by the Ritz method. The abbreviation STO (Slater-type orbitals) is commonly used in the second case.

For a single electron in the field of a point charge, the possible orbitals can be characterized by three *quantum numbers* $n$, $l$, and $m$, known respectively as the principal, the angular, and the magnetic quantum number, the orbital energy depending only on the principal quantum number $n$. The inequalities $l < n$; $|m| \leqslant l$ hold; orbitals with $l = 0, 1, 2, 3$, *etc.*, are called s, p, d, f, *etc.*, orbitals, respectively.

For an electron in a central field that is not the field of a point charge, $n$, $l$, and $m$ are still so-called "good quantum numbers", but the energy now depends on $l$ as well as on $n$. This is the case, to a good approximation, for the orbitals in most atoms.

The order of the orbital energies is shown schematically in Figure 2. The structure of the periodic system of

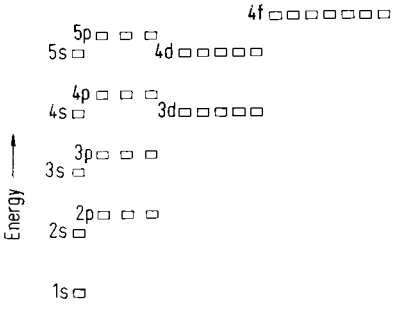


Fig. 2. Energies of the possible orbitals in an atom. Each box can accommodate at most two electrons.

elements is due to the fact that the electrons always occupy the orbitals with the lowest energies. It is easy to see that the K shell ($n = 1$) will be occupied first, then the L shell ($n = 2$), in which the two s electrons ($l = 0$) are followed by the six p electrons ($l = 1$). The lowest 3d level in the potassium atom is slightly higher than 4s, so that the 3d sub-shell is filled (Sc to Zn) only after the 4s shell. The existence of the rare earths can also be explained by this "Aufbau principle" within the framework of the independent particle model. In order to understand the details of the structure of the periodic table and of the spectral terms of the atoms, one must, of course, go beyond this simple model. Even within the IPM the total energy is not the sum of the orbital energies.

In the framework of the independent particle method, electronic transitions, observable in the ultraviolet spectra, are usually described qualitatively as the promotion of an electron from the highest occupied orbital in the ground state to the lowest, or one of the lowest, unoccupied orbitals (Fig. 3).

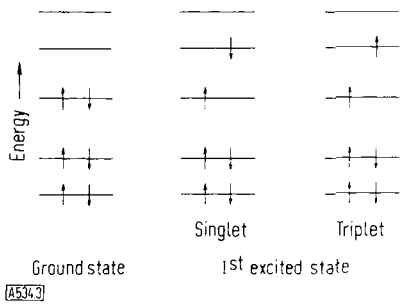


Fig. 3. Schematic representation of an electronic transition in the one-electron scheme. In order to understand the difference between the energies of the singlet and triplet states, it is necessary to take the electronic interaction into account.

More difficult than for atoms is the solution of the Hartree-Fock equations for *molecules, i.e.* the calculation of the best "molecular orbitals" (MO's)[36]. Only for the hydrogen molecule has an accuracy comparable with that of atomic calculations been achieved[37]. However, it has been possible in recent years to come close to the solutions of the Hartree-Fock equations for many diatomic and other small molecules. For this reason, we are now becoming aware of the limitations of the independent particle model (see Section 1.7).

It is sufficient in simple applications to approximate a molecular orbital as a linear combination of the atomic orbitals (or alternatively – what one does in practice – a single Slater orbital for any atomic orbital) of the atoms involved, the optimum values of the expansion coefficients $c_i$ being determined by the variation principle in accordance with equation (14). This is known as the LCAO (linear combination of atomic orbitals) approximation. Better molecular orbitals can in principle be obtained if one uses a basis set of Slater type orbitals the size of which is larger than the number of AO's. Since these STO's are defined for different centers, one has to evaluate many-center integrals, which require very laborious calculations, so that extended LCAO calculations do not at present appear very promising (except for diatomic molecules). In fact, for decades even "minimum basis set" MO-LCAO calculations failed to pass the bottleneck of calculating the necessary matrix elements[38]. The MO-LCAO method

[36] The molecular orbital method ("Methode der Molekülzustände" in the earlier German literature) is the standard scheme of valence theory. It goes back to *F. Hund* [Z. Physik *40*, 741 (1927); *51*, 759 (1928); *52*, 601 (1928); *73*, 1, 565 (1932)] and *R. S. Mulliken* [Physic. Rev. *32*, 186 (1928); *41*, 49 (1932)]. See also *F. Bloch*, Z. Physik *52*, 555 (1928); *G. Herzberg*, Z. Physik *57*, 601 (1929); *J. Lennard-Jones*, Trans. Faraday Soc. *25*, 668 (1929); *E. Hückel*, Z. Physik *70*, 204 (1931); *72*, 310 (1931); *76*, 628 (1932); *83*, 632 (1933).

[37] *C. A. Coulson*, Proc. Cambridge philos. Soc. *34*, 204 (1938); *G. Berthier* and *M. Mayot*, J. Chim. Phys. *1959*, 504; *E. R. Davidson*, J. chem. Physics *37*, 1918 (1962).

[38] When Slater type functions are used as the basis, closed mathematical expressions can be obtained only for one-center integrals and for certain two-center integrals. Complicated auxiliary functions defined *e.g.* by infinite power series occur in the calculation of the other integrals. Up to the end of the 1950's, the problem of calculating these integrals was the main obstacle to further development of numerical quantum chemistry. Between 1955 and 1960, several tables of integrals were published,

for molecules is often referred to as the "Roothaan SCF method" [39], whereas the "Pople SCF method" [40] involves further approximations and semi-empirical corrections.

There is a tendency nowadays, rather than use the extended LCAO approximation which involves Slater type functions defined for different centers, to prefer such types of basis functions that are liable to give poorer convergence, but for which the integrals involved are soluble in closed form. These include the one-center expansion method in which the molecular orbitals are expanded as linear combinations of Slater functions all of which are defined for the same center, *e.g.* the centroid of the molecule. This method is well suited for molecules such as $CH_4$. Gaussian functions [41] have also enjoyed great popularity for a number of years. Let $\mathfrak{r}_i = (x_i, y_i, z_i)$ be the center around which $\varphi_i$ is defined. If $\mathfrak{r} = (x, y, z)$ is any point in space, then the Gaussian function $\varphi_i$ (this is a "pure" Gaussian function [42]) is given by

$$\varphi_i(\mathfrak{r}) = N\,\mathrm{e}^{-\alpha|\mathfrak{r}-\mathfrak{r}_i|^2};$$
$$|\mathfrak{r}-\mathfrak{r}_i|^2 = (x-x_i)^2 + (y-y_i)^2 + (z-z_i)^2. \qquad (32)$$

where $\alpha$ is a variable parameter. The origins of the Gaussian functions can be chosen freely, and need not coincide with the positions of the nuclei. A p-function can be very roughly represented by two such Gaussian functions arranged in the form of a dumb-bell about the nucleus in question [42].

from which the desired integrals could be interpolated with some difficulty. Nowadays such tables are rarely used, and one prefers to have the integrals calculated by subroutines within automatic computer programs. A few research groups have excellent integral programs that are not accessible to the general public, so that the same programming work has often been repeated independently. The situation is probably going to improve. The quantum-chemical program exchange (QCPE) (Indiana University, Bloomington, USA) revealed itself as a promising idea.

[39] *C. C. J. Roothaan*, Rev. mod. Physics *23*, 69 (1951); *G. G. Hall*, Proc. Roy. Soc. (London) *205*, 541 (1951).

[40] *J. A. Pople*, Trans. Faraday Soc. *49*, 1375 (1953); *R. Pariser* and *R. G. Parr*, J. chem. Physics *21*, 466, 767 (1953).

[41] The recent literature on the use of Gaussian functions is very extensive. Gaussian functions do not compare too unfavorably with Slater type functions. About three to four times as many functions are needed in a Gaussian basis (compared with an STO basis) to obtain a comparable accuracy, *i.e.* one has to calculate $3^4$ to $4^4$ times as many two-electron integrals, but any of these integrals can be calculated about 100 times as fast, so that the computer time needed is more or less the same. Integrals for Gaussian functions are, however, much easier to program than those for Slater type functions. A general SCF program for molecules using Gaussian functions is now available to anyone through the QCPE (see [38]) under the name POLYATOM. It seems that meanwhile much faster (probably 10 times as fast) programs exist that are not yet publicly available.

Gaussian functions necessarily give a poor approximation to the true wave function close to and at a long distance from the nucleus, but may give rather good approximation at intermediate distances. This shortcoming seems to be unimportant for many applications. Progress has been achieved also in rational programming of Slater type integrals, so that the Slater functions are liable to recover the ground lost to the Gaussian functions. See, *e.g.*, *F. E. Harris* and *H. H. Michels*, J. chem. Physics (1966), in press. It should be mentioned that other sets of functions like Laguerre functions have been used for special atomic probiems, and two-center functions defined in elliptic coordinates for diatomic molecules.

[42] *H. Preuss*, Z. Naturforsch. *11a*, 823 (1956).



The independent particle model is easily visualized; the number of electrons is equal to the number of orbitals (AO's in atoms, MO's in molecules), so that one may regard one electron as being in one orbital. Calculations based on this model usually are not too difficult.

The solutions of the SCF equations are satisfactory only for certain problems; for others the scheme fails completely. The electron density $\varrho$ as a function of position, which is defined by

$$\varrho(1) = n \int \psi^*(1,2,\ldots n)\,\psi\,(1,2,\ldots n)\mathrm{d}\tau_2\mathrm{d}\tau_3\ldots\mathrm{d}\tau_n \qquad (33)$$

is generally obtained with reasonable accuracy. Good results are often also obtained for the expectation values of one-electron operators, *i.e.* operators of the form $\mathbf{A}(1,2,\ldots n) = \mathbf{a}(1) + \mathbf{a}(2) + \ldots \mathbf{a}(n)$. The error in the total energy is about 1% in atomic SCF calculations (and generally somewhat higher for molecules); this would be satisfactory if the total energy were the final purpose of the calculation.

In fact are we interested in *energy differences* (*e.g.*, bond energies or the energies of spectral transitions), which are small compared with total energies. The effects that are ignored when the independent particle model in the form of the Hartree-Fock approximation is used are usually referred to as *electron correlation* [43]. In particular, the difference between the Hartree-Fock energy and the true (non-relativistic) energy is called the *correlation energy*. If the correlation energy for different states of the same atom or molecule were approximately the same (which is not the case) it would cancel in the calculation of the spectral transition energies. Similarly, the change of correlation energy on going from isolated atoms to a molecule is of the same order of magnitude as the change in the SCF energy. Electron correlation must not be ignored in the calculation of bond energies and spectra.

The standard method to take electron correlation at least partly into account is the *configuration interaction* (CI) method. The name originated in atomic spectroscopy, where it referred to states that could not be described by a single electronic configuration even in first approximation. CI is now understood to mean the approximation of the wave function as a linear combination [44] of Slater determinants (rather than as a single Slater determinant like in the SCF method), the optimum coefficients in this linear combination being determined by means of the variation principle. If there is a complete set of spin orbitals $\varphi_i$, then all possible Slater determinants (configurations) that can be constructed from $n$ such $\varphi_i$ are a complete set of $n$-electron functions.

[43] A good survey of the correlation problem is given by *P. O. Löwdin*: The Correlation Problem in Many-electron Quantum Mechanics. Adv. chem. Physics *2*, 207 (1959); see also Physic. Rev. *97*, 1474 (1955).

[44] In some cases, for symmetry reasons, a sum of Slater determinants is used instead of a single Slater determinant; however, the coefficients are then fixed from the outset. It is not customary to call this "configuration interaction".

If we start from a sufficiently large basis of one-electron functions, say $m$ such functions, we can in principle represent the true wave functions as accurately as desired [12] by a CI expansion. One difficulty is that the method does not in general converge very rapidly, and that as the number $n$ of electrons increases, the number of possible configurations increases with $\binom{m}{n}$, so that secular equations (15) occur that are beyond the capacity of even the largest computers.

Any set of one-electron functions may be used as basis set in the CI method, but one usually starts with an SCF calculation and chooses then the SCF orbitals plus some more functions as the basis set. The CI wave function is then a linear combination of the SCF Slater determinant and other Slater determinants. In most CI calculations, only a few additional determinants are taken into account, and normally these are selected on the basis of heuristic considerations, since a systematic CI calculation would be too laborious. The term "complete CI calculation" is generally a euphemism, since it means that one chooses an LCAO basis (for benzene *e.g.* the six $p_z$ orbitals of the 6 C-atoms), constructs all possible $n$-electron Slater determinants from them (benzene has 6 atomic $p_z$ orbitals, *i.e.* 12 spin orbitals, and $\binom{12}{6}$ determinants are possible, neglecting all $\sigma$ electrons), and approximates the desired wave function as a linear combination of these determinants. Often (especially for the calculation of spectra) one chooses the SCF Slater determinant plus some "singly excited configurations", *i.e.* determinants in which one spin orbital of the SCF determinant is replaced by another (so-called virtual) spin orbital. This procedure generally gives better approximations for the excited states than are obtained by simple SCF calculations, but the correlation of the ground state is not accounted for.

There are methods that take the electron correlation into account more successfully than the configuration interaction method, but generally these are applicable only in special cases, such as the Hylleraas expansion [45] for the He atom, which is limited to two-electron systems. A number of recent methods permit the inclusion of electron correlation without becoming unwieldy, *e.g.* the methods of generalized product functions [30], or cluster expansions [46], the direct calculation of "natural" orbitals [47], *etc.*

Figure 4 shows the main types of quantum-mechanical methods, an additional approximation being introduced from one line to the next lower one. The methods given in the first three lines have so far been successfully applied only to one- and two-electron systems. The first non-adiabatic calculation of the $H_2$ molecule (with relativistic corrections) was carried out only in 1963 [48].

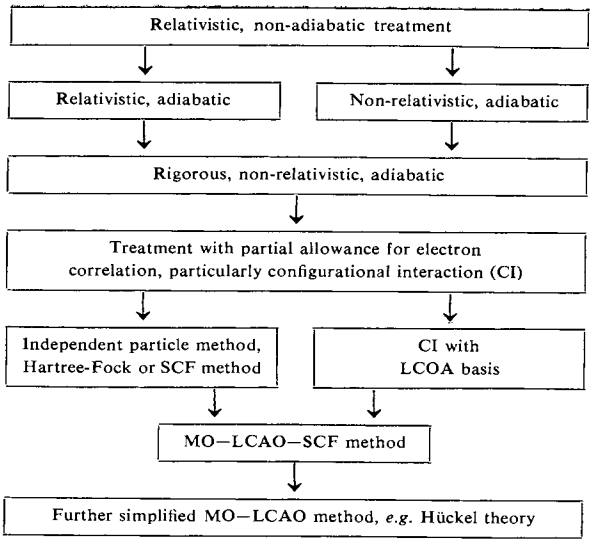


Fig. 4

## 1.8. Conclusion

In quantum-mechanical calculations one generally makes two tacit assumptions. One of them is that all relativistic effects may be neglected, and the second that the Born-Oppenheimer approximation is justified. These two approximations are not critical for most applications. In recent years, however, special interest has been shown in such cases for which at least one of the two approximations is not valid. Nuclear magnetic and electron spin resonance spectra cannot really be explained without recourse to a relativistic theory. On the other hand "vibronic interactions", *i.e.* the interaction between vibrational and electronic states, and the lowering of the symmetry of molecules in the degenerate ground state (Jahn-Teller-theorem) [49] play an important part in the current theory of the electronic spectra of molecules, and in order to explain these phenomena it is necessary to abandon the Born-Oppenheimer approximation.

More critical are approximations such as the independent particle model, the SCF scheme, and the LCAO approximation. Neglect of electron correlation may lead to quantitatively or even qualitatively erroneous results. For example, in the SCF approximation, the $H^-$ ion has a higher energy (−0.485 atomic units [50]) than an H atom plus an isolated electron (−0.500 atomic units); thus the $H^-$ ion should not be stable. However, a more accurate calculation (including correlation) of the energy of $H^-$ gives a value of −0.528 atomic units that shows, in agreement with experiment, that the H atom has a positive electron affinity.

[45] *E. A. Hylleraas*, Z. Physik *48*, 469 (1928); *54*, 347 (1929); *T. Kinoshita*, Phys. Rev. *105*, 1490 (1957); *C. L. Pekeris*, *ibid. 112*, 1649 (1958).

[46] *L. Szasz*, Z. Naturforsch. *15a*, 909 (1960); Physic. Rev. *132*, 936 (1963); *O. Sinanoğlu*, Adv. chem. Physics *6*, 315 (1964).

[47] *W. Kutzelnigg*, J. chem. Physics *40*, 3640 (1964); *D. D. Ebbing* and *R. C. Henderson*, J. chem. Physics *42*, 2232 (1965).

[48] *W. Kolos* and *L. Wolniewicz*, Rev. mod. Physics *35*, 473 (1963); J. chem. Physics *41*, 3674 (1964).

[49] *H. A. Jahn* and *E. Teller*, Proc. Roy. Soc. (London), Ser. A *161*, 220 (1937); *164*, 117 (1938).

[50] The atomic unit of energy is defined as twice the ionization energy of the H atom, and is equal to 27.2 eV or 628 kcal/mole. The atomic units of mass, electric charge, and length are the mass of the electron, the charge of the electron, and the Bohr radius of the hydrogen atom in the ground state (0.529 Å). In these units $\hbar$, $e$, and $m$ have the numerical value 1, and the quantum-mechanical equations assume a particularly simple form. For this reason, quantum-mechanical calculations are nearly always carried out in atomic units.

The larger a molecule, the more approximations have to be introduced in order to obtain a solution in a finite time. Since the accuracy attainable is rarely satisfactory even for small molecules, calculations on large molecules would be completely in vain unless one tried to compensate the crudeness of the approximations by semi-empirical adjustments. One deals then no longer with quantum-mechanical approximations but rather with *interpolation schemes.*

In this Part I, we looked at the methods of quantum chemistry from the physico-mathematical side. Our next task is to correlate the purely quantum-mechanical ideas with concepts known from experiment, such as valence, valence angle, bond length, electronegativity, inductive effect, *etc.* This brief (and rather simplified) survey of "mathematical" quantum chemistry will be followed by one of "interpretative" quantum chemistry. Neither aspect is independent of the other.

In this article an important tool in quantum chemistry is ignored, namely *group theory*, which allows us to take advantage of the symmetry properties of atoms and molecules [51]. The great value of group theory is that it yields information about the solutions of the Schrödinger equations irrespective of whether they can be calculated. Particularly in the early days of quantum theory, when numerical calculations were much more difficult than they are now, the importance of group-theoretical considerations could hardly be overestimated, *e.g.* for the interpretation of atomic spectra. The ligand field theory of metal complexes is still essentially applied group theory.

The scope of quantum-chemical research is very wide. It extends from the formal theory of the solutions of the Schrödinger equation and other abstract mathematical disciplines to the theory of the magnetic properties of matter, intermolecular interactions, and chemical reactivity, and from rigorous *ab initio* calculations on atoms and small molecules to the semi-empirical theory of biologically interesting macromolecules.

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Translated by Express Translation Service, London

[51] A large number of textbooks on group theory is available. Works particularly suitable for chemists are *R. McWeeny*: Symmetry. Pergamon, London 1963; *F. A. Cotton*: Chemical Applications of Group Theory. Wiley, New York 1963; *V. Heine*: Group Theory in Quantum Mechanics. Pergamon, London 1960.

# COMMUNICATIONS

## A New Benzimidazole Cleavage with Subsequent Ring Closure [1]

By Prof. W. Ried and H. Lohwasser

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der Universität Frankfurt/Main (Germany)

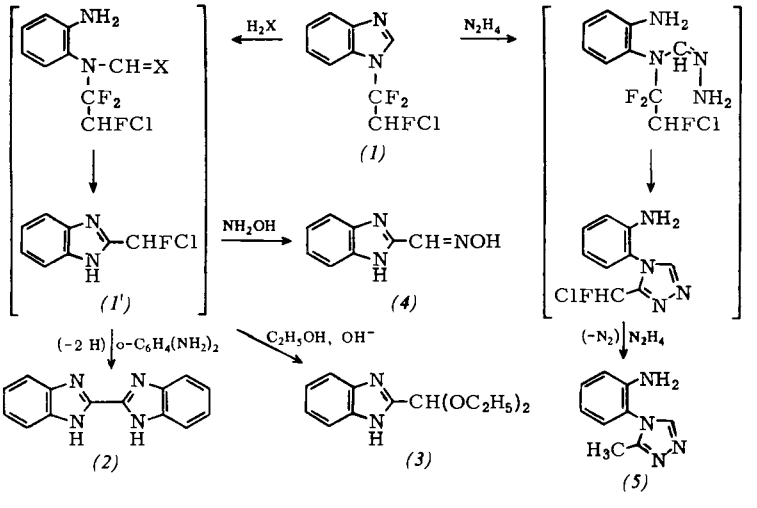
Benzimidazole is alkylated by trifluorochloroethylene in position 1 to give a liquid adduct *(1)*. The halogenoalkyl group is stable to alkaline or acid hydrolysis. Because of the strong electron attraction by the halogenoalkyl group the imidazole ring is attacked at position 2 by nucleophilic reagents $H_2X$ ($o$-$NH_2C_6H_4NH_2$, $C_2H_5OH/OH^-$, $NH_2OH$, or $N_2H_4$), with intermediate formation of *N,N*-disubstituted $o$-phenylenediamines. The active difluoromethylene group of these causes ring closure with the unsubstituted phenyl amino group [yielding a new benzimidazole *(1')*] or, if hydrazine hydrate is used, with the hydrazone amino group (yielding a triazole). Further reaction of the intermediate *(1')* with $o$-phenylenediamine and loss of hydrogen affords compound *(2)*.

Of the reactions with $o$-phenylenediamine to compound *(2)*, with alkoxide to *(3)*, with hydroxylamine to *(4)*, and with hydrazine to *(5)*, only the second and last are preparatively useful. Some analogous reactions have been observed for *N*-trifluorochloroethyl derivatives of 2-methylbenzimidazole, 2,3-naphthimidazole, and perimidine [1].

*N-(1,1,2-Trifluoro-2-chloroethyl)benzimidazole (1)*: 35 g of benzimidazole and 53 g of trifluorochloroethylene in 200 ml of anhydrous THF, when heated for 5 hr in an autoclave at 130–140 °C and distilled, give 61 g (88 %) of compound *(1)* as a colorless oil, b.p. 138 °C/12 mm.

*2,2'-Bibenzimidazolyl (2)*: 5 g of compound *(1)*, 10 g of $o$-phenylenediamine, and 15 g of ethanolamine in 50 ml of ethylene glycol, when boiled for 5 hr and then diluted with water, give 200 mg of compound *(2)* as pale yellow crystals, m.p. > 400 °C (from dilute acetic acid) [3].

*Benzimidazole-2-carbaldehyde diethyl acetal (3)*: 5 g of compound *(1)*, 10 g of potassium hydroxide, and 100 ml of ethanol, when boiled for 3 hr, freed from alcohol, and extracted with ether, afford 1.5 g (32 %) of compound *(3)* as colorless leaflets, m.p. 172 °C (173 °C [2]) (from water).




*Benzimidazole-2-carbaldehyde oxime (4)*: 6 g of compound *(1)* and 8 g of hydroxylamine hydrochloride in 30 ml of pyridine are boiled for 3 hr, then made alkaline with sodium carbonate; unchanged *(1)* is removed in steam, whereafter neutralization gives a small amount of compound *(4)* as colorless crystals, m.p. 302 °C (287 °C [2]) (from methanol/benzene).

*4-(o-Aminophenyl)-3-methyl-1,2,4-triazole (5)*: 30 g of compound *(1)* and 200 ml of 100 % hydrazine hydrate in 200 ml of ethylene glycol, when boiled for 15 hr and then extracted with methylene chloride, afford 15.6 g (73 %) of compound *(5)* (colorless leaflets, m.p. 164 °C, from benzene).

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Publication delayed at the authors' request

[1] From the Dissertation of *H. Lohwasser*, Universität Frankfurt/Main, 1966.

[2] *H. R. Hensel*, Chem. Ber. *98*, 1330, 1331 (1965).

[3] *E. S. Lane*, J. chem. Soc. (London) *1955*, 538.

## Hydridopentakis(trifluorophosphine)rhenium [1]

By Prof. Th. Kruck and A. Engelmann

Anorganisch-Chemisches Laboratorium, Technische Hochschule München and Anorganisch-Chemisches Institut, Universität Köln (Germany)

Reduction of an ethereal solution of chloropentakis(trifluorophosphine)rhenium [2] (0.12 mole/l) with an excess of about 1 % potassium amalgam at 20 °C affords potassium pentakis(trifluorophosphine)rhenate, which on treatment with 88 % phosphoric acid forms $HRe(PF_3)_5$, the first hydrido-trifluorophosphine complex of a group VIIA metal. Use of $D_3PO_4$ affords the analogous deuterido compound.

$$ClRe(PF_3)_5 \xrightarrow[(C_2H_5)_2O]{K(Hg)} K[Re(PF_3)_5] \xrightarrow{H^{\oplus}} HRe(PF_3)_5$$

$HRe(PF_3)_5$ is, however, also directly accessible, in 40 % yield, by reduction of $ReCl_5$ with Cu powder (molar ratio *ca.* 1:40) at 300 °C with a $PF_3$ pressure of 250 atm and a $H_2$ pressure of 100 atm. It is purified by sublimation.

Hydridopentakis(trifluorophosphine)rhenium resembles the monohydrido compounds $HM(PF_3)_4$ of cobalt and iridium [3] in its high thermal and chemical stability. The colorless, centimeter-long needles of this hydrophobic compound (m.p. 42 °C, decomp. from 160 °C) sublime at 20 °C/10 mm and are stable for several days in dry air. The covalent nature of the Re–H bond is confirmed by an intense Re–H stretching vibration at 1882 (m) $cm^{-1}$ [4] [$\tilde{\nu}_{Re\text{-}D}$ = 1346 (m) $cm^{-1}$] and the strong chemical shift to high field of its broad $^1H$–NMR signal (no fine structure) [5] ($\delta$ = 8.2 ppm; TMS as internal standard). The P–F vibrations are at 971(w), 918 (vs), 877 (s), 869 (s), and 860 (m–s) $cm^{-1}$.

$K[Re(PF_3)_5]$ is a white, crystalline powder, readily soluble in ether and acetone and immediately hydrolysed by water to the weakly acidic $HRe(PF_3)_5$. In the P–F stretching region its IR spectrum [$\tilde{\nu}_{PF}$ = 942 (w), 930 (m), 912 (w), 863 (vs; broad), and 843 (vs, broad) $cm^{-1}$; in acetone] resembles those of the pentakis(trifluorophosphine) complexes $M(PF_3)_5$ where M = Fe, Ru, and Os, and thus indicates a trigonal-bipyramidal structure for the $[Re(PF_3)_5]^{\ominus}$ anion.

Small amounts of hydridopentakis(trifluorophosphine)manganese were also obtained by the reaction sequence:

$$IMn(CO)_5 \xrightarrow[180\,^{\circ}C]{450\ atm\ PF_3} IMn(PF_3)_3(CO)_2 \xrightarrow[(C_2H_5)_2O]{KHg}$$

$$K[Mn(PF_3)_3(CO)_2] \xrightarrow[H_2O]{450\ atm\ PF_3} HMn(PF_3)_5$$

It is a colorless liquid and was identified by its IR spectrum, which is almost the same as that of the rhenium compound [6]. Both the hydrido-trifluorophosphine compounds are more stable, thermally and against oxidizing agents, than the analogous hydrido-carbonyl complexes.

Received: June 28th, 1966 [Z 272 IE]
German version: Angew. Chem. 78, 820 (1966)

[1] Part XVII of Trifluorophosphinemetal Complexes. – Part XVI: *Th. Kruck, N. Derner,* and *W. Lang,* Z. Naturforsch., in press. These results were reported at the EUCHEM Conference on the "Chemistry of Metal Hydrides" at Bristol (England) on April 2nd, 1966.

[2] *Th. Kruck, A. Engelmann,* and *W. Lang,* Chem. Ber., in press (1966).

[3] *Th. Kruck* and *W. Lang,* Angew. Chem. 77, 860 (1965); Angew. Chem. internat. Edit. 4, 870 (1965).

[4] Except where otherwise stated, gas spectra, NaCl optics; s = strong, vs = very strong, m = medium, w = weak

[5] The $^1H$-NMR spectrum was determined on a VARIAN A-60-NMR spectrometer for a 95 % solution in benzene at 20 °C and for a melt at 50 °C. We thank Dr. *K. Schwarzhans* for measuring these spectra.

[6] These experiments were carried out by Dr. *W. Lang.*

## Proton-Catalysed Cleavage of Enol Phosphates and Phosphonates

By Dr. K. Pilgram [*] and Dr. H. Ohse [**]

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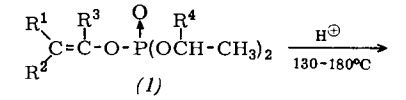
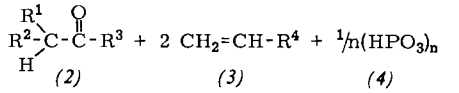
Alkenyl di-sec-alkyl phosphates *(1)* are cleaved at 130 to 180 °C in the presence of catalytic amounts ($\leqslant$ 0.5 %) of concentrated sulfuric acid or *p*-toluenesulfonic acid to ketones *(2)*, alkenes *(3)*, and polymetaphosphoric acid *(4)*.



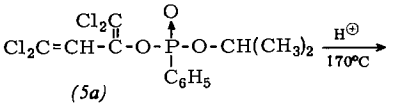
*(1)*



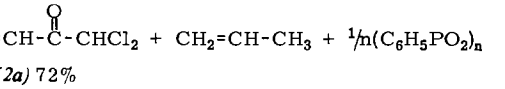
*(2)* *(3)* *(4)*

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *(2)*, Yield (%) |
|---|---|---|---|---|
| Cl | Cl | $-CH=CCl_2$ | $CH_3$ | 74.5 |
| Cl | Cl | $-CH=CCl_2$ | $C_2H_5$ | 61.2 |
| Cl | Cl | $-CCl=CCl_2$ | $C_2H_5$ | 96.3 |
| Cl | Cl | H | $CH_3$ | 75.0 |
| H | Cl | H | $CH_3$ | 33.3 |
| Cl | $CO-N(CH_3)_2$ | $CH_3$ | $CH_3$ | 73.7 |
| H | Cl | 2,4-Dichlorophenyl | $CH_3$ | 95.3 |
| H | H | 2,4-Dichlorophenyl | $CH_3$ | 36.7 |

Alkenyl sec-alkyl phosphonates, *e.g. (5a)*, react analogously:



*(5a)*



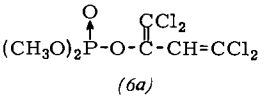
*(2a)* 72%

The rate of this reaction is determined primarily by the nature of the alkyl group and increases along the series:

$$CH_3 \ll C_2H_5 < C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13} \gg \text{iso-}C_3H_7, \text{sec-}C_4H_9$$

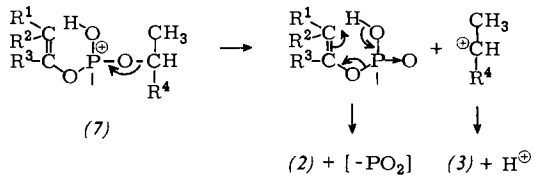
The same order applies to the tendency for olefin formation by dehydration of the corresponding alcohols.

In many cases this method seems to be superior to acid or alkaline hydrolysis of enol phosphates. For instance, none of the ketone *(2a)* is formed from the ester *(6a)* in 57 % sulfuric acid in 3 hr at 80 °C and only a 29 % yield after a further 3 hr at 95 °C. Acid-catalysed cleavage of the isopropyl or sec-butyl ester *(5)* at 170 °C, however, gives a 70 % yield of the ketone within a few minutes.



*(6a)*

It is probable that the phosphonium ion *(7)* formed as intermediate by protonation decomposes by way of an enol phosphoric acid and a carbonium ion into the ketone *(2)*, metaphosphate, olefin *(3)*, and a proton:



(7) → (2) + [-$PO_2$] (3) + $H^{\oplus}$

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German version: Angew. Chem. 78, 820 (1966)

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[**] Present address: Farbenfabriken Bayer, Werk Dormagen (Germany).

## Dehalogenation of Perchloroketones with Triphenylphosphine or Trialkyl or Triaryl Phosphites

By Dr. K. Pilgram[*] and Dr. H. Ohse[**]

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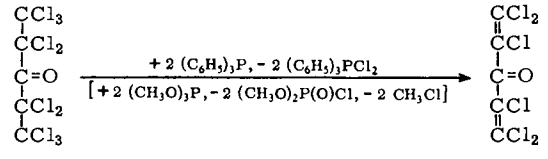
Perchlorodivinyl ketone *(2)*, b.p. 69 °C/0.3 mm, $n_D^{20} = 1.5661$, $d^{20} = 1.6963$[2], is readily obtained (yield 91.2 %) by treatment of perchloro-3-pentanone *(1)*, b.p. 94–95 °C/0.6 mm, $n_D^{15} = 1.5682$, with triphenylphosphine in ether at 5 to 35 °C. The triphenylphosphine dichloride formed is advantageously converted into triphenylphosphine oxide by addition of water before isolation of the ketone *(2)*. Trimethyl phosphite and *(1)* afford dimethyl phosphorochloridate (yield 100 %) as well as the ketone *(2)* (yield 95.3 %). With both reagents there is a common intermediate whose retention time in gas chromatography lies between those of *(1)* and *(2)*; this compound is most likely perchloro(ethyl vinyl ketone).



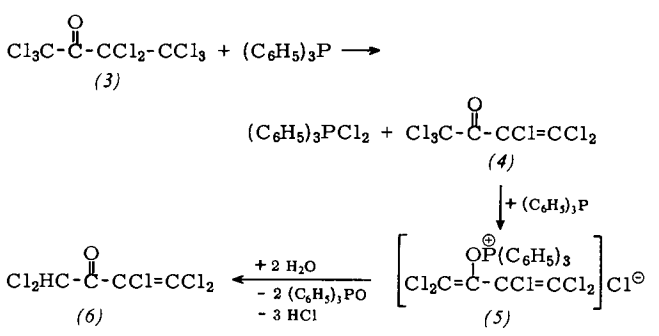
*(1)* → *(2)*

By analogy with the mechanism of dehalogenation[2] of α,β-dibromo compounds with trialkyl phosphites[3,4] and triphenylphosphine[5], we assume that the phosphine (or phosphite) first removes the chlorine atom α to the carbonyl group, this being followed by loss of a β-chlorine atom as an anion.

Perchlorobutanone *(3)* reacts equally smoothly with triphenylphosphine in ethereal solution and, after addition of water, gives 1,1,3,4,4-pentachloro-3-buten-2-one (yield 82.1 %; b.p. 89 °C/9 mm, $n_D^{20} = 1.5440$, $d^{20} = 1.6628$; ref.[6]: b.p. 99–100 °C, $n_D^{20} = 1.5442$). Trichloromethyl trichlorovinyl ketone *(4)* is formed in the first step of this reaction. A second mole of triphenylphosphine then reacts with *(4)* to give an enol phosphonium salt *(5)*, which is extremely sensitive to solvolysis and with water decomposes to 1,1,3,4,4-pentachloro-3-buten-2-one *(6)*, triphenylphosphine oxide, and HCl.

The ketone *(4)* is identical with a sample prepared by a different route[7]. Trialkyl phosphites react with *(3)* by an analogous first step, which leads to *(4)*, alkyl chloride, and dialkyl phosphorochloridate; then a second mole of trialkyl phosphite brings about a Perkow reaction.

Triphenyl phosphite reacts smoothly with *(3)* at room temperature, yielding triphenyl phosphorodichloridate and the ketone *(4)* (yield 96.3 %; b.p. 44 °C/0.2 mm, $n_D^{20} = 1.5319$).



An excess of triphenyl phosphite has no influence, so that the product *(4)* can be distilled continuously when the mixture is heated in an oil bath.

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[*] Present address: Shell Development Co., Modesto, Cal. (U.S.A.).

[**] Present address: Farbenfabriken Bayer, Werk Dormagen (Germany).

[1] *A. Roedig* and *H.-J. Becker*, Chem. Ber. *89*, 1726 (1956).

[2] *H. Hoffmann* and *H. J. Diehr*, Angew. Chem. *76*, 944 (1964); Angew. Chem. internat. Edit. *3*, 737 (1964).

[3] *V. S. Abramov* and *S. Pall*, Chem. Abstr. *52*, 9949 (1958).

[4] *S. Dershowitz* and *S. Proskauer*, J. org. Chemistry *26*, 3595 (1961).

[5] *H. Hoffmann* and *H. J. Diehr*, Tetrahedron Letters *13*, 583 (1962).

[6] *A. Roedig* and *H.-J. Becker*, Chem. Ber. *89*, 906 (1956).

[7] *K. Pilgram* and *H. Ohse*, Angew. Chem. *78*, 820 (1966); Angew. Chem. internat. Edit. *5*, 836 (1966).

## Preparation of N-Functional Derivatives of Glyoxylic Acid

By Dr. H. Gross and Dr. J. Gloede

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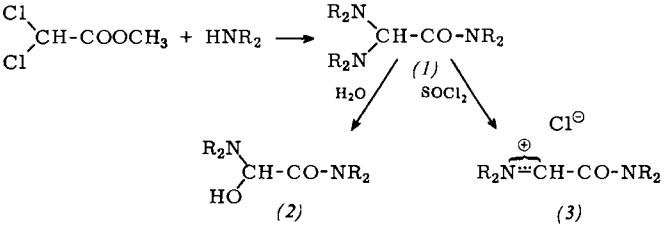
Treatment of dichloroacetic ester with piperidine gives 1-(dipiperidinoacetyl)piperidine *(1a)*, m.p. 87–89 °C, yield 90 %. The morpholine derivative *(1b)*, m.p. 120–122 °C, is obtained analogously (yield 70 %). Both compounds are quite stable in closed vessels but, when kept in air or when recrystallized from aqueous solvents (*e.g.* DMF) are converted into the compounds *(2a)*, m.p. 60–61 °C, yield 89 %), and *(2b)*, m.p. 86–87 °C, yield 72 %, respectively, stable compounds that crystallize well. The OH band of *(2a)* occurs at 3366 $cm^{-1}$ (KBr disc; half-width 17.5 $cm^{-1}$) or at 3420 $cm^{-1}$ (in $CCl_4$; half-width 87 $cm^{-1}$)[1].

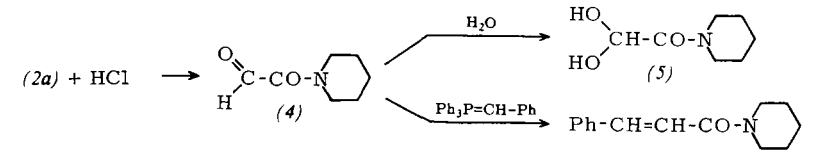


*(a)*, $R_2$ = -$(CH_2)_5$-

*(b)*, $R_2$ = -$(CH_2)_2$-O-$(CH_2)_2$-

Dropping of thionyl chloride into an etheral solution of compound *(1a)* or *(1b)* causes almost quantitative precipitation of the carbenium-imonium salt *(3a)* or *(3b)*, respectively, which can be used for aminomethylations[2].

If compound *(2a)* is treated with 1 mole of ethereal HCl, yields of up to 62 % of 1-glyoxyloylpiperidine *(4)* can be isolated[3] (amide band at 1647 $cm^{-1}$; aldehyde band at 1722 $cm^{-1}$; solvent-free liquid). This product is stable, in contrast to the unstable esters of glyoxylic acid. It forms a stable hydrate *(5)* [m.p. 86–89 °C; amide band at 1653 $cm^{-1}$; OH band at 3362 $cm^{-1}$ (H bonds); KBr disc]. It reacts with benzylidenetriphenylphosphorane, yielding 1-cinnamoylpiperidine (m.p. 119–120 °C; ref.[4] gives 122 °C; no depression with authentic sample).




*1-(2-Piperidinoglycoloyl)piperidine (2a)*:

Methyl dichloroacetate (0.1 mole) and piperidine (0.5 mole) are heated at 110 °C for 2 hr. After cooling, the mixture is extracted with three portions each of 50–60 ml of anhydrous ether, and the ethereal solution is evaporated to dryness. The crude product *(1a)* is dissolved in 50 ml of hot dimethylformamide and treated with 120 ml of water and 0.5 ml of 2 N HCl. Compound *(2a)* separates on cooling. It is recrystallized from dimethylformamide/water; m.p. 60–61 °C.

*1-Glyoxyloylpiperidine (4)*:

Compound *(2a)* (0.1 mole) is dissolved in 100 ml of anhydrous ether, and 24 ml (0.1 mole) of 16 % ethereal HCl is added dropwise at 0 °C. The precipitated piperidinium chloride is removed. The solution is evaporated and then distilled in a high vacuum, affording the product, b.p. 74–76 °C/0.02 mm.

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German version: Angew. Chem. *78*, 823 (1966)

[1] We thank Dr. *D. Kunath*, Berlin-Adlershof, for measurement and discussion of the spectra.

[2] *H. Gross*, *J. Gloede*, and *J. Freiberg*, Liebigs Ann. Chem., in press.

[3] Glyoxylamides have not previously been obtained in the free form, but only as either hydrates or 2,4-dinitrophenylhydrazones after treatment of *N,N*-disubstituted formamides with lithium acetylide [*G. H. Whitfield*, Brit. Pat. 793807; Chem. Abstr. *53*, 227 (1959); Brit. Pat. 797604; Chem. Abstr. *53*, 5137 (1959)] or alkali metals [*H. Bredereck*, *F. Effenberger*, and *R. Gleiter*, Angew. Chem. *77*, 964 (1965); Angew. Chem. internat. Edit. *4*, 951 (1965)].

[4] *B. Herstein*, Ber. dtsch. chem. Ges. *22*, 2265 (1889).

## Poly-4-vinyltriphenylmethyl Polyradicals

By Prof. D. Braun and R. J. Faust

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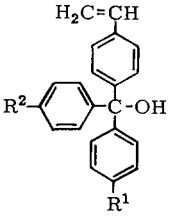
The following monomers were synthesized (in yields of 50 to 70 %) for the preparation of stable carbon polyradicals[*]:
4-Vinyltriphenylmethanol *(1)*, m.p. 75 °C, by reaction of *p*-vinylphenylmagnesium chloride with benzophenone[1];
4-Phenyl-4′-vinyltriphenylmethanol *(2)*, m.p. 74 °C, by the analogous reaction with 4-phenylbenzophenone;
4,4′-Diphenyl-4″-vinyltriphenylmethanol *(3)*, m.p. 95 °C, by analogous reaction with 4,4′-diphenylbenzophenone.

Compounds *(1)* to *(3)* undergo radical polymerization extremely easily and substantially faster than styrene. The rate of polymerization, and at the same time the tendency (presumably due to chain transfer) to cross-linking during polymerization, increase in the order *(1)*, *(2)*, *(3)*. Radical copolymerization with styrene is also much faster than homopolymerization of styrene under the same conditions; the proportion of cross-linked products decreases with increasing styrene content in the monomer mixture and with decreasing monomer concentration.

The homopolymers of *(1)*, *(2)*, and *(3)*, and the copolymers with styrene, react with acetyl chloride, yielding poly-4-vinyltriphenylmethyl chlorides. However, radical polymerization of 4-vinyltriphenylmethyl chlorides could not be achieved.

*(1)*, $R^1 = R^2 = H$
*(2)*, $R^1 = H$, $R^2 = C_6H_5$
*(3)*, $R^1 = R^2 = C_6H_5$




Treatment of the polymeric triphenylmethyl chlorides in benzene solution with incompletely anhydrous zinc powder gives polycations instead of polyradicals, as shown by the absorption spectra in the visible spectral region. These polyions owe their origin to the formation of a strong Lewis acid from traces of water and the zinc chloride formed. The Lewis acid and the still unchanged triphenylmethyl groups of the polymers form cations and hydrogen chloride, which reacts further with the primarily formed radicals, affording triphenylmethyl and chlorotriphenylmethyl groups. Since radical formation is slow, use of the incompletely dry systems results almost exclusively in the faster formation of polycations. However, if the zinc powder is previously treated with potassium-benzophenone solution in benzene until the solution is no longer decolorized, and if the zinc is then well washed with anhydrous benzene, the product can be used for the preparation of polyradicals. Use of potassium is still more effective: no polyanions are then obtained since anion formation is extremely slow. Use of potassium in benzene and dilute solutions (about 5 g/l of poly-4-vinyltriphenylmethyl chloride) leads to soluble polyradicals, but at higher concentrations (about 30 g/l) insoluble, strongly swollen gels are obtained which contain intermolecular hexaphenylethane groups.

The polyradicals react with oxygen and with iodine similarly to their monomeric analogues.

The polyradicals were detected in benzene solution by their ESR spectra; in contrast to the spectra of monomeric triphenylmethyl radicals, these show practically no fine structure, a phenomenon that must be attributed to the high local concentration of radicals in the individual macromolecular coils and to their mutual interaction. The radical concentrations determined by ESR spectroscopy, and the degrees of polymerization determined osmometrically, indicate that on an average every third to fourth monomer unit is a free radical; each macromolecule contains about 100 unpaired electrons.

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German version: Angew. Chem. *78*, 905 (1966)

[*] We propose this designation, in analogy with di- and triradicals, for macromolecules of which numerous monomer units have unpaired electrons; the designation macroradical should, however, be reserved for macromolecules containing only one (usually terminal) unpaired electron.

[1] *D. Braun*, *W. Neumann*, and *J. Faust*, Makromolekulare Chem. *85*, 143 (1965).

## Dimerization of 1-Methylazepine

By Prof. K. Hafner and J. Mondt[1]

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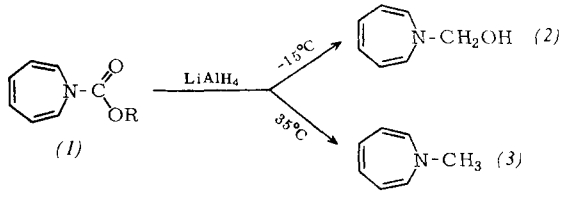
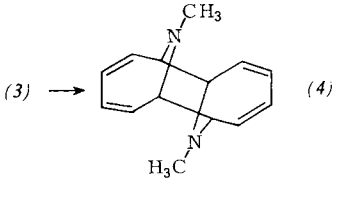
The preparation of alkyl 1-azepinecarboxylates *(1)* by photolysis or thermolysis of azidoformates in benzene or its derivatives has enabled us to study the monocyclic azepine system[2]. On reduction of *(1)*, R = $C_2H_5$, with $LiAlH_4$ in ether at −15 °C we obtained 1-azepinemethanol *(2)*[3] in *ca.* 45 % yield as a thermally unstable, pale yellow oil




*(1)* *(2)* *(3)*

[UV spectrum (in *n*-hexane): $\lambda_{max}$ = 232 mμ, shoulder at 255 mμ], which was isolated as picrate (decomp. > 100 °C)[4]. In boiling ether the same reduction leads to 1-methylazepine *(3)*[3] in 60 % yield as a thermally rather unstable, yellow oil [b.p. 20 °C/$10^{-3}$ mm; structureless UV spectrum, with ε rising towards shorter wavelengths and $\lambda_{max}$ = 236 mμ (ε = 5100) with shoulders at 249 mμ (ε = 4020), 258 (3660), 288 (1950), and 384 (65) (in n-hexane); NMR spectrum (in $CCl_4$), singlet at 7.55 τ ($CH_3$), multiplet at 5.0 to 5.5 τ (6 ring protons)]. Catalytic hydrogenation (Raney Ni; 20 °C) of the azepine *(3)* leads to hexahydro-1-methylazepine[5].

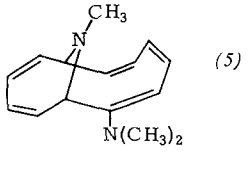
The azepine *(3)* dimerizes rapidly in ether above 0 °C, yielding the colorless 13,14-dimethyl-13,14-diazatricyclo-[6.4.1.$1^{2,7}$]tetradeca-3,5,9,11-tetraene *(4)*, m.p. 171 °C, $\lambda_{max}$ (in n-hexane) = 230 mμ (ε = 15680), 237.5 (16600), and was purified by chromatography with ether on $Al_2O_3$ and recrystallization from methanol[6]. The structure of this dimer follows from the NMR spectrum (in $CDCl_3$), which shows a singlet for the 6 methyl protons at 7.8 τ, a doublet for the 4 bridgehead protons at 6.7 τ, and a multiplet for the 8 olefinic protons centered at 4.1 τ. The dipole moment of the dimer is 0.5 D, which indicates the *trans*-form for *(4)*[7]. The mass spectrum[8] confirms the molecular weight (214); the signal of greatest intensity is at *m/e* 107, which indicates preferential decomposition of *(4)* to the monomer *(3)*; the lower *m/e* values form a pattern characteristic for further decomposition of *(3)*. On catalytic hydrogenation, the dimer *(4)* takes up the amount of $H_2$ calculated for 4 double bonds[8a].




*(3)* → *(4)*

We suggest that dimerization of *(3)* occurs in several stages. 1,3-Dipolar addition of *(3)*, which can be formulated as an azomethine ylide, is improbable in view of the rules of *Woodward* and *Hoffmann*[9].

With hydrogen bromide, the dimer *(4)* gives a dihydrobromide (colorless leaflets, decomp. 240 °C), but with styphnic or picric acid it gives only the monoprotonated product




*(5)*

(styphnate, decomp. 196 °C; picrate, decomp. 195 °C). With methyl iodide in boiling methanol (60 hr) it gives a monomethiodide (decomp. 195 °C), which is converted by Hofmann degradation into the cyclododecapentaene derivative *(5)*, which forms a yellow oil with $\lambda_{max}$ (in n-hexane) = 249.5 mμ; NMR spectrum (in $CCl_4$): two singlets at 7.6 and 7.8 τ (3 $CH_3$), a multiplet centered at 7.15 τ (2 bridgehead protons), and a multiplet centered at 4.15 τ (9 olefinic ring protons).

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German version: Angew. Chem. *78*, 822 (1966)

[1] Diploma Thesis, Universität München, 1965.

[2] *K. Hafner* and *C. König*, Angew. Chem. *75*, 89 (1963); Angew. Chem. internat. Edit. *2*, 96 (1963); *K. Hafner*, Angew. Chem. *75*, 1041 (1963); Angew. Chem. internat. Edit. *3*, 165 (1964); *K. Hafner*, *D. Zinser* and *K. L. Moritz*, Tetrahedron Letters *1964*, 1733.

[3] There are indications that *(2)* and *(3)* are in equilibrium with small amounts of the valence-isomeric 1,2-epimino-1,2-dihydrobenzene derivatives. Aromatization of *(3)* to *N*-methylaniline was observed alongside the dimerization.

[4] Satisfactory analytical results were obtained for all the new compounds.

[5] *R. Lukes* and *J. Malek*, Coll. czechoslov. chem. Commun. *16*, 23 (1951).

[6] Analogous dimerization of *(1)* and 1-cyanoazepine, but only at 200 °C, has recently been reported by *L. A. Paquette* and *I. H. Barrett*, as well as by *A. L. Johnson* and *H. E. Simmons*, J. Amer. chem. Soc. *88*, 2590 (1966).

[7] An X-ray structure analysis of *(4)* is in progress.

[8] We thank Prof. *G. Spiteller*, Göttingen, for measurement and discussion of the mass spectrum of *(4)*.

[8a] *Note added in proof*: We have recently isolated a further dimer of *(3)*, but its structure is not yet known. This compound forms colorless crystals and melts at 66 °C; UV spectrum (in methanol): $\lambda_{max}$ = 242 mμ (ε = 4470). NMR spectrum in $CCl_4$: 2 singlets at 7.15 and 7.8 τ (2 ($CH_3$), multiplets centered at 6.35 τ (4 H) and 4.3 τ (8 H).

[9] *R. Hoffmann* and *R. B. Woodward*, J. Amer. chem. Soc. *87*, 4388 (1965), and earlier papers.

## Transport Reactions of Silicides and Borides of Transition Metals

By Dr. J. Nickl, M. Duck, and J. Pieritz

Forschungslaboratorium für Festkörperchemie, Institut für anorganische Chemie, Universität München (Germany)

We have grown single crystals of silicides and borides by chemical transport reactions. The transport vessels used were silica ampoules (10 mm in diamter, 100 mm in length) in which the starting material was placed at the hot end. The reagents were the elements in massive form or powdered silicides or borides. Chlorine, bromine, or iodine at a pressure of 5 to 120 mm Hg and 20 °C served as gases for both reaction and transport. Before addition of the halogen the ampoules containing the starting material were heated at $10^{-4}$ to $10^{-5}$ mm; the ampoules were sealed off at a pressure of *ca.* $10^{-5}$ mm in an oxyhydrogen flame. The time for transport was 2 to 22 days. The crystals (volume several $mm^3$) obtained were investigated by stereography and X-ray diffraction and finally their stoichiometry was determined by analysis.

The following compounds were found as well-formed single crystals at the *cool* end of the tubes: $TiS_2$, $VSi_2$, $CrSi_2$, $Cr_3Si$, $NbSi_2$, $TaSi_2$, $TiB_2$, $VB_2$, $CrB_2$, CrB, and $ZrB_2$. However, silicides were not obtained from Zr ($ZrSi_2$ – this and other entries in parentheses are starting materials), W (W + Si, $WSi_2$), U (U + Si), and no boride from Nb (NbB), Hf ($HfB_2$), Ta (TaB), or W (WB); in these cases only well-crystallized silicon was formed at the cool end from silicides, and no transport was observable from borides.

Crystals formed at cool end of transport tube.

| Starting materials | Time (days) | Crystals found: Approx. vol. ($mm^3$) | Structure | Lattice parameters (Å) |
|---|---|---|---|---|
| $TiSi_2$ [a] Ti + Si [b] | 2 | $TiSi_2$ 10 | orthorh. ($D_{2h}^{24}$) | $a = 8.24$ $b = 4.77$ $c = 8.52$ |
| $VSi_2$ | 9 | $VSi_2$ 1 | hexag. ($D_6^4$) | $a = 4.56$ $c = 6.36$ |
| $NbSi_2$ [a] | 10 | $NbSi_2$ 1 | hexag. ($D_6^4$) | $a = 4.78$ $c = 6.58$ |
| $TaSi_2$ [c] | 10 | $TaSi_2$ 1 | hexag. ($D_6^4$) | $a = 4.77$ $c = 6.55$ |
| $CrSi_2$ [c] | 9 | $CrSi_2$ 10 | hexag. ($D_6^4$) | $a = 4.42$ $c = 6.35$ |
| Cr + Si [a] | 10 | $Cr_3Si$ 10 | cubic ($O_h^3$) | $a = 4.55$ |
| $TiB_2$ [c] | 5–22 | $TiB_2$ tiny needles | hexag. ($D_{6h}^1$) | $a = 3.03$ $c = 3.23$ |
| $ZrB_2$ [c] | 22 | $ZrB_2$ tiny crystals | hexag. ($D_{6h}^1$) | $a = 3.17$ $c = 3.53$ |
| $VB_2$ [c] | 5–7 | $VB_2$ tiny prisms | hexag. ($D_{6h}^1$) | $a = 3.00$ $c = 3.06$ |
| $CrB_2$ [a] | 15 | $CrB_2$ | hexag. ($D_{6h}^1$) | $a = 2.97$ $c = 3.07$ |
| CrB [c] | 15 | CrB | orthorh. ($D_{2h}^{17}$) | $a = 2.97$ $b = 7.86$ $c = 2.93$ |

Max. temperature (°C): [a] 1050 ($\Delta T \approx 200$); [b] 900 ($\Delta T \approx 150$); [c] 1100 ($\Delta T \approx 120$–150).

At the *hot* end, powders of $TiSi_2$, $VSi_2$, and $CrSi_2$ were partly converted into well-formed crystals, which were larger than those grown at the cool end. When massive chromium and silicon were used, well-formed $Cr_3Si$ crystals grew from both elements; the same crystals grew at the cool end. No mineralization was observed with boride powders.

Crystals grown at the hot or the cool end have highly reflecting faces of low index. Only with $TiSi_2$ was there a tendency to formation of stepped {111} faces (Hopper effect). Transport of the borides was more than about five times slower than that of silicides.

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German version: Angew. Chem. *78*, 822 (1966)

## Elimination of Hydrogen Sulfide from Ferredoxin and Cysteine Methyl Ester[*]

By Prof. Ernst Bayer and W. Parr

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After we had shown that hydrogen sulfide is easily eliminated from cysteine esters and cysteinyl-peptides in the presence of iron salts[1], we attributed the "labile sulfur" in ferredoxin – which is regarded by *Rabinowitz et al.*[2] as "inorganic sulfide" – to elimination of $H_2S$ from the cysteine residues in the ferredoxin. *Malkin* and *Rabinowitz*[3] have recently opposed this view because, contrary to our findings, they failed to obtain $H_2S$ from cysteine methyl ester or from glutathione and, moreover, could not detect dehydroalanine in the ferredoxin. – This contradiction is hard to understand, since β-elimination of $H_2S$ from cysteine methyl ester is a very simple experiment and we identified dehydroalanine in ferredoxin after the elimination of $H_2S$ by three independent methods.

Under the following conditions[**] cysteine methyl ester, in the presence of iron salts, eliminates 1 mole of $H_2S$ per mole of iron salt:

For formation of the cysteine methyl ester-iron complex, solutions of 17.1 mg of cysteine methyl ester hydrochloride in 1 ml of oxygen-free distilled water and of 19.6 mg of Mohr's salt in 1 ml of oxygen-free distilled water are mixed in a 25-ml round-bottomed flask. After addition of 5 ml of 0.5 M Tris hydrochloride buffer (pH 7.30), the mixture is boiled for 15 to 20 min under a reflux condenser to which is attached a Péligot tube containing 7 ml of *p*-amino-*N*,*N*-dimethylaniline reagent (0.5 g of the amine hydrochloride in 500 ml of 5.5 N HCl). For determination of the hydrogen sulfide[4], the Péligot tube is removed and the condenser rinsed down with 15 ml of distilled water. The cooled sample (solution and precipitate) is placed in a 500-ml volumetric flask containing 260 ml of 1.3 % zinc acetate solution and 10 ml of 12 % sodium hydroxide solution. Then 50 ml of *p*-amino-*N*,*N*-dimethylanilinium chloride solution containing the reagent solution from the Péligot tube is added, and the flask is stoppered and shaken until the precipitate has dissolved. After about 10 min, 10 ml of a 0.023 M solution of $FeCl_3$ in 1.2 N HCl is added. The mixture is set aside for 15 min and then made up to the mark with distilled water. After a further 30 min the extinction at 670 mμ is determined. In more than 50 experiments, 1.60 ± 0.10 mg of $H_2S$ was found, corresponding to a molar ratio of added iron salt: $H_2S$ = 1:0.94 ± 0.06. This is exactly the ratio of iron to "labile sulfur" found in ferredoxin.

When the reaction was carried out without Mohr's salt, only 0.38 ± 0.05 mg of $H_2S$ was found. This shows that the reaction is catalysed by formation of the iron complex. Since ferredoxin is an iron complex of a cysteine-rich polypeptide, an analogous reaction must be assumed to occur. $H_2S$ is also eliminated if the iron complex of cysteine methyl ester is prepared without boiling, namely by mixing the solutions and setting them aside in a beaker at room temperature for 16 to 24 hr; however, as a result of incomplete formation of the chelate, and also as a result of side reactions, yields are then only about 20 % of those obtained by the procedure given above. Elimination of $H_2S$ from cysteine methyl ester does not require base catalysis and occurs even in a neutral medium.

On elimination of $H_2S$ from ferredoxin a dehydroalanyl-peptide is formed, from which pyruvic acid should be obtained on total hydrolysis. *Malkin* and *Rabinowitz*[3] were unable to detect pyruvic acid after ferredoxin had been heated with 3 N HCl on the water bath for 1 hr. However, if ferredoxin is treated – as is usual in protein hydrolyses – with 6 N HCl under nitrogen for 24 hr at 110 °C, then 1 mg affords 27.5 μg of pyruvic acid, which can be determined enzymatically with lactate dehydrogenase and NADH. In view of the lability of dehydroalanine under the conditions of hydrolysis the yield of about 30 % of pyruvic acid (calculated for 5 moles $H_2S$ eliminated per mole of ferredoxin of molecular weight 6000) is satisfactory, although it permits no quantitative conclusions to be drawn.

A substantially better method for detection of dehydroalanine consists in reduction of the dehydroalanyl-peptide to the alanyl-peptide with sodium borohydride and subsequent amino-acid analysis[5,6]. As the cysteine content decreases, so the alanine content must increase.

If 1 mg of ferredoxin from *Clostridium pasteurianum* is treated with sodium borohydride under the conditions described by *Pigman et al.*[6], then treated with performic acid by *Hirs*'s technique[7], and hydrolysed with 2 ml of 6 N HCl for 24 hr at 110 °C, the following values are obtained for cysteine and alanine:

1 mg of ferredoxin, 5 days at 22 °C in 1 ml of 0.2 N NaOH containing 11.3 mg ($0.3 \times 10^{-3}$ mole) of $NaBH_4$, then oxidation with performic acid and subsequent hydrolysis:
cysteic acid, 0.176 μmole; alanine, 1.410 μmole.

1 mg of ferredoxin, 8 days at 5 °C in 1 ml of 0.1 N NaOH containing 11.3 mg of $NaBH_4$ ($0.3 \times 10^{-3}$ mole), then oxida-

tion with performic acid and subsequent hydrolysis:
cysteic acid, 0.246 μmole; alanine 1.308 μmole.

1 mg of ferredoxin, only treated with performic acid and then hydrolysed:
cysteic acid, 0.772 μmole, alanine 0.974 μmole.

It can be seen that about 0.4 μmole of cysteine is converted into alanine during the elimination of $H_2S$. The other amino acids are unaffected by these processes.

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German version: Angew. Chem. 78, 824 (1966)

[*] Part 2 of Ferredoxin. – Part 1:[1].

[**] We thank students in the organic chemistry undergraduate courses for series experiments.

[1] *E. Bayer*, *W. Parr*, and *B. Kazmaier*, Arch. Pharmaz. Ber. dtsch. pharmaz. Ges. *298*, 196 (1964).

[2] *W. Lovenberg*, *B. B. Buchanan*, and *J. C. Rabinowitz*, J. biol. Chemistry *238*, 3899 (1963).

[3] *R. Malkin* and *J. C. Rabinowitz*, Biochemistry *5*, 1262 (1966).

[4] *J. K. Fogo* and *H. Popowsky*, Analytic. Chem. *21*, 732 (1949); cf. also[2].

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## Preparation of O,N-Acetals of Acyl Isocyanates

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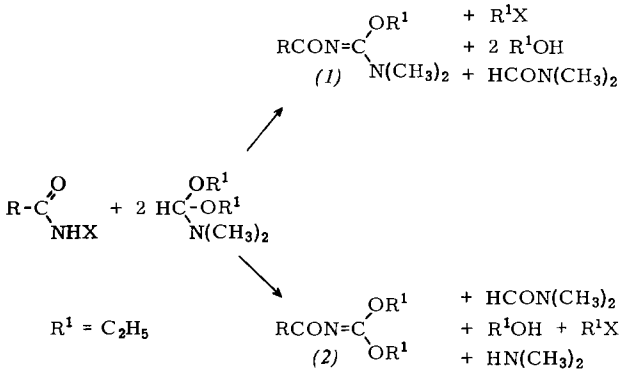
Numerous classes of compound that form addition compounds with tertiary amines can substitute dialkylformamide acetals on the formyl-carbon atom[1,2].

We have treated *N*-halogenocarboxamides (as nitrene precursors) with dialkylformamide acetals and have obtained good yields of *O,N*-acetals *(1)* of acyl isocyanates in an exothermic reaction that is, formally, an electrophilic substitution of the formyl-hydrogen atom. For complete reaction one mole of *N*-halogenocarboxamide requires 2 moles of dialkylformamide acetal, of which, however, 1 mole may be replaced by another tertiary amine. Side reactions occasionally afford, alongside *(1)*, *O,O*-acetals *(2)* of the acyl isocyanates.




| R | X | (1) Yield (%) | (1) B.p. (°C/mm) | (2) Yield (%) | (2) B.p. (°C/mm) |
|---|---|---|---|---|---|
| $CH_3$ | Cl | 75 | 52/0.1 | – | – |
| $C_2H_5$ | Cl | 39 | 55–56/0.1 | 15 | 45–48/0.1 |
| n-$C_3H_7$ | Cl | 44 | 72–75/0.1 | 20 | 58–60/0.1 |
| i-$C_3H_7$ | Cl | 41 | 80–85/1.0 | 21 | 56/0.1 |
| $CH_3$ | Br | 67 | 52/0.1 | – | – |
| $C_2H_5$ | Br | 51 | 55–57/0.1 | – | – |
| i-$C_3H_7$ | Br | 53 | 80–84/1.0 | – | – |

Experiments with compounds of type R(R')CHX, which can be considered as carbene precursors, lead analogously to ketene *O,N*-acetals[3].

*Experimental*: 0.1 mole of carboxylic acid *N*-halogenoamide is mixed with 0.2 to 0.3 mole of dimethylformamide *O,O*-diethyl acetal or with 0.1 mole of the latter and 0.1 mole of triethylamine, with exclusion of moisture and with stirring and cooling (10 °C). An insoluble oil first formed soon dissolves while the solution becomes warm. The mixture is then heated for 2 hr at 80 °C and fractionated in vacuum.

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German version: Angew. Chem. 78, 826 (1966)

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## Triazidomethylium Hexachloroantimonate, $[C(N_3)_3]^+[SbCl_6]^-$

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Because of the energy-rich azide groups, heavy-metal azide halides can undergo various reactions[1]. The compound $[SbCl_4N_3]_2$, which is accessible from $SbCl_5$ and trimethylsilyl azide[2], chlorazide[3], or hydrogen azide[4], reacts when left in boiling $CCl_4$ (1 hr) with formation of the hitherto unknown triazidomethyl cation as hexachloroantimonate in 90 % yield. The salt, pale yellow, slightly hygroscopic needles, insoluble in nonpolar solvents and sensitive to shock or rapid heating, m.p. 145 °C (decomp.), is isolated by filtration.

$$3\ SbCl_4N_3 + CCl_4 \rightarrow [C(N_3)_3]^+[SbCl_6]^- + 2\ SbCl_5$$

The IR spectrum indicates that the cation $[C(N_3)_3]^+$ has $C_{3v}$ symmetry. The three α-N atoms and the carbon atom are coplanar and the azido groups are bent in the same sense at the α-N atoms. The planar arrangement results from $sp^2$ hybridization at the carbon atom, the resonance stabilization corresponding to that of the guanidinium cation. Accordingly, the characteristic IR absorption of the $CN_3$ grouping agrees substantially with that of the guanidinium ion[5].

Characteristic frequencies (in $cm^{-1}$) of the $CN_3$ grouping in $[C(N_3)_3]^+$ and $[C(NH_2)_3]^+$.

| Class | Type | $[C(N_3)_3]^+$ | $[C(NH_2)_3]^+$ |
|---|---|---|---|
| E | $\nu_{as}$ $CN_3$ | 1565 | 1670 |
| $A_1$ | $\nu_s$ $CN_3$ | 1030 | 1010 |
| $A_1$ | $\gamma$ $CN_3$ | 788 | 720 |
| E | $\delta$ $CN_3$ | 529 | 530 |

The four azide stretching vibrations of the ion $[C(N_3)_3]^+$ expected because of its $C_{3v}$ symmetry are 2285 ($\nu_{as}$, $A_1$), 2190 ($\nu_{as}$, E), 1221 ($\nu_s$, $A_1$), and 1050 $cm^{-1}$ ($\nu_s$, E). The IR-active, very characteristic absorption bands[6] of class $F_{1u}$ for the $[SnCl_6]^-$ anion occur at 339 ($\nu_{as}$) and 172 $cm^{-1}$ ($\delta_{as}$). A compound $N{\equiv}C{-}N{=}C(N_3)_2$, which is isoelectronic with $[C(N_3)_3]^+$ and probably has an analogous structure, has been obtained from BrCN and $NaN_3$[7,8].

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German version: Angew. Chem. 78, 825 (1966)

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## Monomeric Boron Imides

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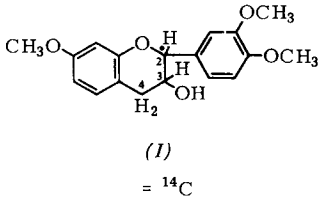
When dichloro(pentafluorophenyl)borane and an equivalent amount of an aromatic amine are kept in boiling benzene for 2 days, they afford the monomeric boron imides *(1)* and *(2)* in 73 and 83 % yield, respectively, together with the calculated quantities of HCl:

$$C_6F_5BCl_2 + ArNH_2 \rightarrow 2\,HCl + C_6F_5B{=}NAr$$

*(1)*, Ar = *p*-$CH_3O$–$C_6H_4$–

*(2)*, Ar = mesityl



*(1)*

= $^{14}C$

The product *(1)* is accompanied, in 13 % yield, by the dimer $(C_6F_5B{-}N{-}C_6H_4{-}OCH_3)_2$ *(3)*, which is a further representative of the series of 1,3,2,4-diazadiboretidines[1–3], but formation of *(2)* is not accompanied by that of the dimer, presumably for steric reasons. Compounds *(1)*, *(2)*, and *(3)* were characterized by elemental analyses and by cryoscopic and osmometric determinations of molecular weight in benzene.

The Raman spectrum of *(1)* includes an intense band at 1703 $cm^{-1}$ with a subsidiary band at 1710 $cm^{-1}$, which we assign to the $^{11}BN$ and $^{10}BN$ stretching vibrations. From the observation that the BN vibration (but not its overtone at 3400 $cm^{-1}$) is IR-inactive we conclude that the BN bond in compound *(1)* is nonpolar and that the BN vibration is independent of the neighboring polar groups. The nonpolarity of the BN bond is assumed to be caused by the strong electron attraction of the $C_6F_5$ group, which not only draws negative charge from the N atom but also strengthens the two possible BN π-bonds.

With pyridine in benzene, compound *(1)* forms a colorless, crystalline 1:1 adduct. Treatment of compound *(1)* with a solution of HCl in diethyl ether cleaves it to *p*-methoxyanilinium chloride and $C_6F_5BCl_2$; the latter is obtained in only moderate yield. With dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate in dioxane, compound *(1)* reacts with liberation of nitrogen and formation of a compound of formula $C_{19}H_{13}O_5N_3F_5B$ (colorless crystals from benzene), which seems to be the product of a Diels-Alder-type reaction with *(1)* as a dienophile.

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German version: Angew. Chem. *78*, 825 (1966)

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## Mechanism of the Rearrangement of Flavan Derivatives on Reduction with $LiAlH_4/AlCl_3$

By Dr. K. Weinges and F. Nader

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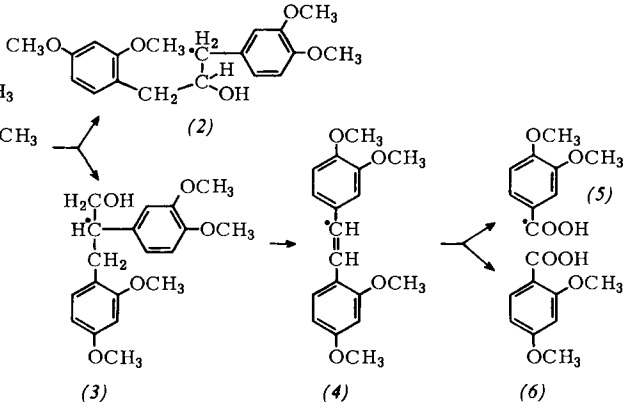
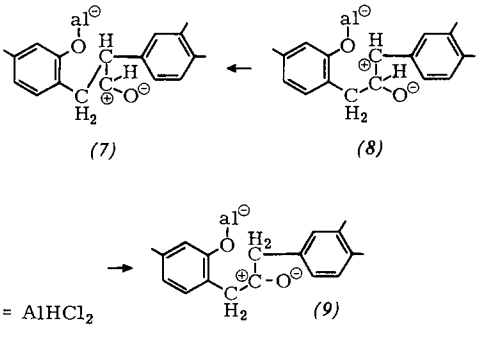
When a flavan containing a 4′-methoxy and a free 3-hydroxy group is reduced with $LiAlH_4/3AlCl_3$, the 1,3-diaryl-2-propanol derivative produced is accompanied by a rearrangement product, namely, the derivative of a 2,3-diaryl-1-propanol[1]. We have studied the course of the rearrangement by means of [2–$^{14}C$]-3′-,4′,7-trimethoxy-3-flavanol *(1)*.

When *(1)* is reduced with $LiAlH_4/3\,AlCl_3$ in tetrahydrofuran and the product is methylated with diazomethane in ether, the compounds *(2)* and *(3)* are formed in the molar ratio 2.3:1 and with a total yield of 61 %. To elucidate the position of the $^{14}C$, the product *(3)* was oxidized to the acid which was then degraded according to the Curtius reaction. The resulting amine gave, on Hofmann elimination, the stilbene *(4)*, oxidation of which afforded veratric acid *(5)* and *O,O*-dimethylresorcylic acid *(6)*. The acids were separated as diphenylmethyl esters. Only the veratric acid *(5)* was radioactive, *i.e.* C-4 of the flavanol must migrate from C-3 to C-2.



*(2)* *(3)* *(4)* *(5)* *(6)*

Probably the hydridodichloroaluminum $AlHCl_2$ formed from $LiAlH_4/3AlCl_3$ attacks the benzyl ether oxygen atom, yielding the carbenium ion *(8)*, which yields the more stable carbenium ions *(7)* and *(9)*. The ion *(7)* arises by migration from C-4, the nucleophilicity of this C atom playing a large part in controlling the yield of *(3)* [the molar ratio *(2)*:*(3)* is 1.2:1 if a further $OCH_3$ group is attached to C-5]. The ion *(9)* arises by hydride shift; that this actually occurs is shown



*(7)* *(8)* *(9)*

al = $AlHCl_2$

by reduction of the flavan *(1)* with $LiAlD_4/3AlCl_3$; it was proved by mass spectrometry and NMR spectrometry that the deuterium in compound *(2)* is then attached to C-2 and C-3 (flavan numbering) in the atomic ratio 3:2.

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## A New Type of Rearrangement in the Lignin Field

By Dr. H. Nimz

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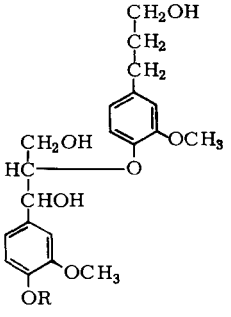
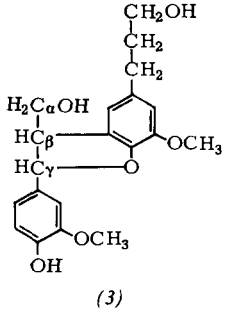
According to present conceptions lignin consists of phenylpropane units linked by C—C and C—O bonds. Glycerol β-aryl ether linkages and phenylcoumaran units are among the most important types of linkage involved.

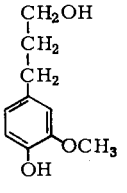
In model experiments on the degradation of lignin we have found a new rearrangement between these two types of linkage. If α-(4-hydroxy-3-methoxyphenyl)glycerol β-dihydroconiferyl ether *(1)* (300 mg) is heated with water (70 ml) under nitrogen for 7 days at 100 °C in a sealed tube, the phenylcoumaran *(3)*[1] (32 %) and dihydroconiferyl alcohol *(4)* (41 %) are formed. Two higher-molecular phenols, whose structures have not yet been determined, can be detected by chromatography as by-products. The ratio of the yields of *(3)* and *(4)* increases with dilution of the starting materials. A corresponding result is obtained if α-(4-hydroxy-3-methoxyphenyl)glycerol β-coniferyl ether [compound *(1)* but with an unsaturated side chain] is heated with water but the methyl ether *(2)* is unchanged under these conditions.



*(1)*, R = H
*(2)*, R = $CH_3$



*(3)*



*(4)*

The rearrangement *(1)* → *(3)* has so far been observed only under the conditions described above. When heated with 2 N NaOH, compound *(1)* gives a styryl ether with loss of water and formaldehyde[2,3]; on using hot, dilute mineral acid (0.2 N HCl in dioxane/water[4]) we obtained from *(1)* neither the compound *(3)* nor products formed therefrom. The course of acetolysis of *(1)* with acetyl bromide is obscure, whereas with acetic anhydride/$BF_3$ nuclear acylation results[5].

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German version: Angew. Chem. *78*, 821 (1966)

[1] *K. Freudenberg* and *H. H. Hübner*, Chem. Ber. *85*, 1181 (1952).

[2] *J. Gierer* and *I. Norén*, Acta chem. scand. *16*, 1713 (1962).

[3] *H. Nimz*, Chem. Ber., in press.

[4] *E. Adler*, *J. M. Pepper*, and *E. Eriksoo*, Ind. Engng. Chem. *49*, 1391 (1957).

[5] *H. Nimz*, Liebigs Ann. Chem. *691*, 126 (1966); the compound of unknown structure described in that paper has meanwhile been identified as an acetophenone derivative.

## Color of Solutions of Aluminum Bromide in Benzenoid Hydrocarbons

By Prof. H.-H. Perkampus and G. Orth

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In the presence of protons, aromatic compounds and Lewis acids form proton-addition complexes[1] which are responsible for the color of the solutions. However, the π-complexes are supposed to be colored even in absence of protons; *e.g.*, *Brown et al.*[2] state that the complex benzene/$Al_2Br_6$ is pale yellow and the complex mesitylene/$Al_2Br_6$ orange-yellow.

We observed no coloration when such solutions were prepared in a high vacuum with thorough drying of the solvent (over potassium) and of the apparatus. Above 323 mμ the extinction of solutions of $Al_2Br_6$ in benzenoid hydrocarbons is essentially zero.

A criterion for the water content of the benzene used is its conductivity; that of completely anhydrous benzene is $8\times10^{-15}$ $ohm^{-1}$ $cm^{-1}$; on dissolution of $Al_2Br_6$ the conductivity rises to $7.2\times10^{-12}$ $ohm^{-1}$ $cm^{-1}$ at $c = 6.0\times10^{-3}$ M and shows a distinct temperature-dependence.

Similarly, for pure, anhydrous benzene the dielectric constant is 2.2832 at 20 °C; for a benzene solution of $Al_2Br_6$ it is 2.3178 at $c = 6.0\times10^{-3}$ M. Conductivities, dielectric constants, and extinctions were measured on the same solution without breaking the vacuum.

Solutions of $Al_2Br_6$ in intensely dried benzenoid hydrocarbons (benzene, toluene, mesitylene) are therefore colorless. In all experiments during which a color was observed, traces of moisture must thus have been present. Since the extinction coefficient of the proton-addition complexes is 10000 to 30000 l $mole^{-1}$ $cm^{-1}$, mere traces of water suffice for coloration of the solutions.

Received: July 15th, 1966 [Z 296 IE]
German version: Angew. Chem. *78*, 908 (1966)

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## Aliphatic Amines from Carbon Monoxide, Steam, and Ammonia

By Prof. H. Kölbel and Dr. J. Trapper

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Aliphatic amines are formed in the catalytic reaction of CO with $H_2$ and added $NH_3$[1]. We have developed a single-stage amine synthesis in which steam is used instead of hydrogen:

$$3n\ CO + n\ H_2O + NH_3 = C_nH_{2n+1}NH_2 + 2n\ CO_2$$
$$(\Delta H = -52.2n \text{ kcal/mole amine})$$

Similarly to the reaction without added ammonia[2], the synthesis is carried out on a fixed reduced iron catalyst[*] in an electrically heated tube of 15 mm internal diameter and 60 cm length.

In the formation period of the catalyst the temperature is increased from 200 °C to 250 °C in *ca.* 300 h. The synthesis can then be continued for weeks with constant conversions and throughputs (average conditions during a long-time run see Table 1; optimal results: CO conversion 90–95 %, $NH_3$ conversion 70–80 % at a flow rate of 350–370 Sl/h per 1 l of catalyst at 11 atm).

Table 1. Amine synthesis data. (Initial gas composition in vol-%: 53.8 % CO, 20.6 % $H_2O$, 0.9 % $NH_3$, 23.7 % Ar; 11 atm; catalyst: 100 g Fe + 0.2 g Cu + 0.6 g $K_2CO_3$).

| Averaged over (h) | 54 | 56 | 120 |
|---|---|---|---|
| Temperature (°C) | 219–226 | 226–235 | 251 |
| Throughput (Sl/h per 1 l contact) | 48 | 45 | 58 |
| CO conversion (%) | 80 | 80 | 73 |
| $NH_3$ conversion (%) | 31 | 35 | 23 |

The synthesis product consists of primary, unbranched monoamines with exclusively terminal $NH_2$ groups together with saturated and unsaturated, predominantly unbranched hydrocarbons (molar ratio amines : hydrocarbons ≈ 1:5). In side reactions formation of alcohols and carboxylic acids can occur.

Table 2. Amine content of five fractions in operation aimed at production of lower amines.

| Fraction no. | Mean chain length (C atoms) | Proportion of amines (wt.-%) rel. to total product | Proportion (wt.-%) of total amine yield |
|---|---|---|---|
| 1 | 3 | 7.5 | 41.0 |
| 2 | 5 | 2.1 | 11.4 |
| 3 | 9 | 2.3 | 12.7 |
| 4 | 20 | 4.3 | 24.2 |
| 5 | 40 | 2.0 | 10.7 |
| | Total | 18.2 | 100 |

Secondary amines are present at most in traces. The yield of primary, unbranched amines was 10–15 g per $Sm^3$ of CO converted or 4.2 g per g of $NH_3$ converted. The homologues methylamine up to dodecylamine were identified. Increasing potassium carbonate content of the catalyst (from 0.2 % to 0.6 %) results in increased formation of amines (from 18 % to 28 %).

The reaction is of the 0.6th order with respect to ammonia. The preferential formation of primary 1-amines apparently indicates that the first reaction steps follow a mechanism proposed by *Anderson*[3] and that the ammonia chemisorbed on the catalyst (which is similar to the catalysts used in $NH_3$ synthesis) is added with termination of the C-chain and elimination of water.

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German version: Angew. Chem. 78, 908 (1966)

[*] Promoter content ≤ 1 wt.-% ($K_2CO_3$ + Cu); prepared by precipitation.

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[2] *H. Kölbel* and *F. Engelhardt*, Brennstoff-Chem. *32*, 150 (1951); Erdöl u. Kohle *5*, 1 (1952); *H. Kölbel*, *J. Kuschel*, and *H. Hammer*, Liebigs Ann. Chem. *632*, 8 (1960); *H. Kölbel* and *K.K. Bhattacharyya*, *ibid. 618*, 67 (1958); *H. Kölbel*, *W. H. E. Müller*, and *H. Hammer*, Makromolekulare Chem. *70*, 1 (1964).

[3] *H. Kölbel*, *G. Patzschke*, and *H. Hammer*, Brennstoff-Chem. *47*, 4 (1966).

## Reaction of Isocyanates, Isothiocyanates, or Carbon Disulfide with Methylenediamines

By Dr. H. Ulrich and Dr. A. A. R. Sayigh

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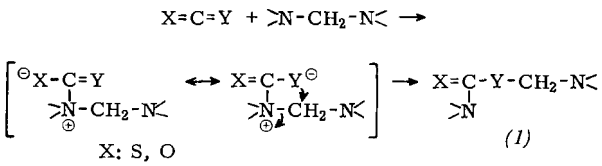
The reaction of formaldehyde *O,N*-acetals[1], *O,O*-acetals[2], and mercaptals[2] with isocyanates in the presence of Lewis acids has already been reported. We have now found that formaldehyde *N,N*-acetals (*i.e.* methylenediamines) react with isocyanates, isothiocyanates, or carbon disulfide (molar ratio 1:1 in benzene) already at room temperature in the absence of a catalyst. The 1:1-adducts were obtained in yields of 80–93 %.




*(1)*

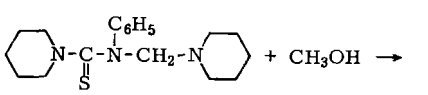
| *(1)* | Amine component in >N–$CH_2$–N< | X=C=Y | Temp. (°C) | F.p. (°C) | $-CH_2-$ signal (ppm) [a] |
|---|---|---|---|---|---|
| *(a)* | Morpholine | Phenyl isocyanate | 25–39 | oil | 4.32 |
| *(b)* | Piperidine | *p*-Toluenesulfonyl isocyanate | 26–45 | oil | 4.14 |
| *(c)* | Morpholine | *p*-Toluenesulfonyl isocyanate | 23–35 | 115–120 | 4.18 |
| *(d)* | *N*-Methyl-aniline | *p*-Toluenesulfonyl isocyanate | 23–39 | oil | 4.78 |
| *(e)* | Piperidine | *p*-Chlorobenzene-sulfonyl isocyanate | 27–42 | oil | 4.12 |
| *(f)* | Piperidine | Phenyl isothio-cyanate | 26–34 | 75–78 | 4.73 |
| *(g)* | Diethylamine | Phenyl isothiocyanate | 27–37 | oil | 4.75 |
| *(h)* | Piperidine | $CS_2$ [b] | 40 | 58–60[3] | 5.2 |
| *(i)* | Morpholine | $CS_2$ [b] | 40 | 121–122 | 5.25 |
| *(j)* | Diethylamine | $CS_2$ [b] | 40 | oil | 5.2 |

[a] Relative to tetramethylsilane (25 % in $CDCl_3$).

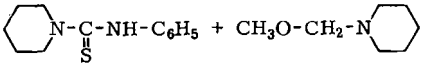
[b] Used as solvent.

The structures of the thermolabile adducts *(1)* (cleavage into the starting materials on heating to *ca.* 100 °C) were proved by elemental analyses and NMR spectra (see table).

The isocyanate and isothiocyanate adducts *(1)* (X = O or S; Y = RN or $RSO_2N$) react with compounds containing active hydrogen, *e.g.* water, alcohols, amines, with cleavage of the newly formed C–N bond. For example, if compound *(1f)* is dissolved in methanol, the thiourea derivative *(2f)*, m.p. 98–99 °C, is formed rapidly and quantitatively.




*(1f)*




*(2f)*

Compound *(2b)* is converted by an additional mole of *p*-toluenesulfonyl isocyanate into the 2:1 adduct, m.p. 85 to 90 °C.

Received: July 25th, 1966 [Z 297 IE]
German version: Angew. Chem. 78, 827 (1966)

[1] *R. Oda*, *M. Nomura*, *S. Tanimoto*, and *T. Nishimura*, Bull. Inst. Chem. Research, Kyoto Univ. *34*, 224 (1956); Chem. Abstr. *51*, 6528 (1957).

[2] *H. v. Brachel* and *R. Merten*, Angew. Chem. *74*, 872 (1962); Angew. Chem. internat. Edit. *1*, 592 (1962).

[3] This compound has been described, without proof of structure, by *R. A. Donia*, *J. A. Shotton*, *L. O. Bentz*, and *G. E. P. Smith*, *Jr.*, J. org. Chemistry *14*, 952 (1949).

## Preparation of Chlorobis(trifluoromethylthio)-methanesulfenyl Chloride, $(F_3CS)_2CCl-SCl$, and Chlorofluoro(trifluoromethylthio)methanesulfenyl Chloride, $F_3CS-CFCl-SCl$

By Dr. A. Haas and W. Klug

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Universität Göttingen (Germany)

Carbonyl fluoride, $COF_2$, reacts with alkali fluorides MF (M = K, Rb, or Cs) in acetonitrile at room temperature, giving trifluoromethoxides, $MOCF_3$ [1].

After the analogous reaction of thiocarbonyl fluoride, $CSF_2$, with CsF we could isolate no $CsSCF_3$. Instead, a deep red solution is rapidly obtained, even at −44 °C, with quantitative consumption of the $CSF_2$. On fractional distillation this liquid yields $CH_3CN$, a yellow liquid *(1)*, b.p. 43 °C, and as main product a dark red liquid *(2)*, b.p. 111 °C. The IR spectra, colors, and boiling points show that the yellow liquid *(1)* is the "pseudodimer" $F_3CS-CF=S$ of $CSF_2$, and that the red liquid *(2)* is bis(trifluoromethyl) trithiocarbonate, $(F_3CS)_2CS$ [2]. All the CsF added is recovered.

In absence of solvent, $CSF_2$ and CsF (molar ratio 1:60) in a sealed tube at −78 °C quantitatively give a white powder which changes gradually at room temperature to a yellow to red, transparent mass. When the volatile constituents are removed at room temperature in a high vacuum, a white solid remains which is soluble in chloroform. From the chloroform solution methanol precipitates a viscous, rubber-like product. Quantitative analysis and molecular-weight determination show this to be a polymer of $CSF_2$ [3].

Reaction of $CSF_2$ and CsF without solvent is extremely fast at 0 °C; the ester *(2)* was the sole product found.

$CSF_2$ reacts analogously with KF or $NH_4F$, but the ratio $MF:CSF_2$ may not be varied indefinitely, as it can for CsF. Also, the reactions are appreciably slower and require higher temperatures.

Compounds *(1)* and *(2)* react with chlorine even at −60 °, giving the sulfenyl chlorides *(3)* and *(4)* rapidly and quantitatively:

$F_3CS-CFCl-SCl$ *(3)*

$(F_3CS)_2CCl-SCl$ *(4)*

These materials, yellow liquids with pungent odor, were identified and characterized by elemental analyses, IR spectra, and NMR measurements.

*(3)*: B.p. 113 °C. IR: $\nu_{max}$ = 1165 $cm^{-1}$ (vs, br) [4], 1102 (vs, br), 1039 (vs), 1012 (sh), 792 (vs), 528 (s), 467 (m), 410 (m). The $^{19}F$–NMR spectrum consists of a doublet ($CF_3$) and a quadruplet (CF) with chemical shifts of $\delta_{CF_3}$ = 38.1 ppm, $\delta_{CF}$ = 57.6 ppm [5], and coupling constants $J_{F-F}$ = 22.0 Hz. The starting material *(1)* also gives a doublet and a quadruplet, $\delta_{CF_3}$ = 42.97 ppm, $\delta_{CF}$ = −89.6 ppm, $J_{F-F}$ = 18.0 Hz.

*4*: B.p. 40 °C/0.1 mm. IR: $\nu_{max}$ = 1745 $cm^{-1}$ (m), 1165 (vs, br), 1097 (vs, br), 1011 (sh), 801 (s), 754 (vs), 712 (m), 513 (m), 466 (m), 446 (m). $^{19}F$–NMR: $\delta_{CF_3}$ = 39.1 ppm. Starting material *(2)*: $\delta_{CF_3}$ = 42.0 ppm.

Received: July 25th, 1966 [Z 294 IE]
German version: Angew. Chem. *78*, 906 (1966)

[1] *M. E. Redwood* and *C. J. Willis*, Canad. J. Chem. *43*, 1893 (1963).

[2] *N. R. Haszeldine* and *J. M. Kidd*, J. chem. Soc. (London) *1955*, 3871.

[3] *H. C. Walter*, U.S.-Pat. 3032537 (May 1st, 1962), Du Pont.

[4] vs = very strong, br = broad, s = strong, sh = shoulder, m = medium.

[5] Measured for a 50% solution in $Cl_3CF$ which acted as internal standard.

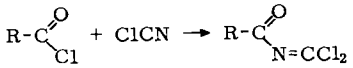
## New Synthesis of *N*-(Dichloromethylene)-carboxamides

By Dr. D. Pawellek

Wissenschaftliches Laboratorium der A-Fabrik,
Farbenfabriken Bayer AG., Leverkusen (Germany)

Reaction of sulfur dichloride with cyanogen chloride gives chlorosulfenyl isocyanide dichloride [1]. We have treated carbonyl chlorides with cyanogen chloride, obtaining *N*-(dichloromethylene)carboxamides *(1)*. The new process has the advantages of easily accessible starting materials compared with the chlorination of isonitriles [2], isothiocyanates [3], and *N*-acyldithiocarbamic esters [4].

The table shows some examples of compounds thus obtained.



*(1)*

| R | B.p. (°C/mm) M.p. (°C) | Yield (%) | IR bands ($cm^{-1}$) $-CO-N\langle$ | $-N=C\langle$ | $=CCl_2$ |
|---|---|---|---|---|---|
| $ClCH_2$[3] | 80/20 | 60–70 | – | – | – |
| $Cl_2CH$[3] | 82/14 | 70–80 | 1750 | 1650 | 925 |
| $Cl_3C$[3] | 85/18 | 70–80 | 1760 | 1650 | 925 |
| $ClCO(CH_2)_2$ | 101–103 | 28 | 1765 | – | 905 |
| $C_6H_5$[3] | 114/20 | 20–30 | 1775 | 1650 | 910 |

For the synthesis of *N*-(dichloromethylene)chloroacetamide, 152 ml of chloroacetyl chloride was placed in an enamelled shaking autoclave (capacity 0.7 l), and 300 ml of cyanogen chloride (molar proportions 1:3) were pressed in. After 2 hours' heating at 50 °C/5 atm the pressure was released and unchanged cyanogen chloride was condensed in cooled receivers. The product was isolated in 64% yield by fractional distillation of the residual reaction mixture. Synthesis of the other products (cf. table) was achieved analogously; further, *N*-(dichloromethylene)methoxymethylamine, b.p. 40 °C/25 mm, was prepared in 10% yield from chloromethyl methyl ether and cyanogen chloride.

These compounds decompose when stored, even in the dark, and faster when heated, into acid chloride and (trimerizing) cyanogen chloride. The temporary appearance of isocyanide dichlorides could be demonstrated by IR spectroscopy in reacting mixtures of cyanogen chloride and acetyl chloride.

Extension of the reaction of chloroacetyl chloride to other nitriles was successful only with 4-cyanomorpholine, then yielding α-chloro-*N*-[chloro(morpholino)methylene]acetamide, b.p. 110–115 °C/15 mm, $-CO-N\langle$ band at 1680 $cm^{-1}$, $-N=C\langle$ band at 1590 $cm^{-1}$ under the above conditions.

Received: July 25th, 1966 [Z 302 IE]
German version: Angew. Chem. *78*, 908 (1966)

[1] *R. G. R. Bacon*, *R. S. Irwin*, *J. M. Pollock*, and *A. D. E. Pullin*, J. chem. Soc. (London) *1958*, 764; erroneously considered by these authors to be ClS–CCl=NCl.

[2] *J. U. Nef*, Liebigs Ann. Chem. *270*, 267 (1892).

[3] *B. Anders* and *E. Kühle*, German publ. Pat. Appl. 1178422 (1964).

[4] *J. B. Douglas* and *T. B. Johnson*, J. Amer. chem. Soc. *60*, 1486 (1938).

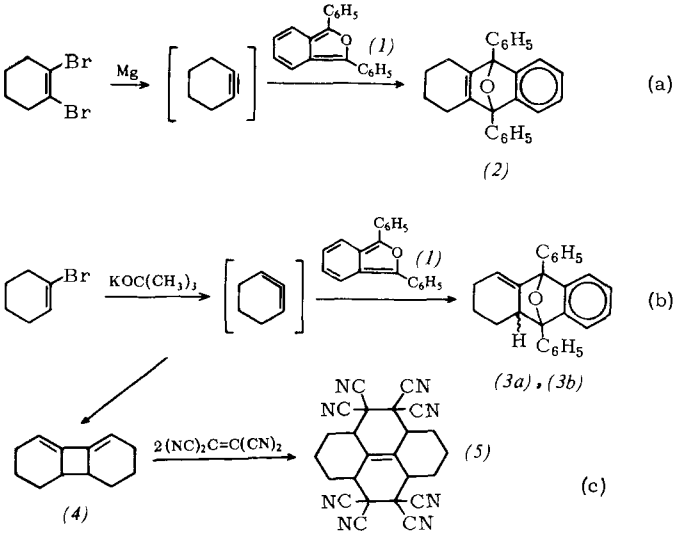
## On the Intermediate Occurrence of 1,2-Cyclohexadiene

By Prof. G. Wittig and Dr. P. Fritze

Institut für Organische Chemie,
Universität Heidelberg (Germany)

1,3-Diphenylbenzo[*c*]furan *(1)* has proved of particular value for the detection of lower-membered cycloalkynes[1]. In order to ascertain that it is cyclohexyne which is trapped, in accordance with equation (a), and not perhaps 1,2-cyclohexadiene, we have generated the cyclic allene by an independent route and allowed it to react with *(1)*.

Sublimed potassium t-butoxide was treated with 1-bromocyclohexene in dimethyl sulfoxide in the presence of *(1)* for several hours at 40 °C. Chromatography on $Al_2O_3$ then gave, among other products, two compounds, *(3a)* (m.p. 137–138 °C) and *(3b)* (m.p. 195–196 °C), in a total yield of 37 %; these are isomers of compound *(2)* (m.p. 170–171 °C) and are clearly differentiated from it by mixed melting point determinations and by IR and NMR spectroscopy. Whereas only aliphatic and aromatic protons can be recognized in the spectrum of *(2)*, the spectra of *(3a)* and *(3b)* both show a multiplet at $\tau = 4.3$, due to an olefinic proton. This indicates that the *exo*- and *endo*-isomers of 1,2-cyclohexadiene adducts have been formed. Control experiments confirmed that the *allene* was trapped: compound *(2)* does not isomerize to *(3a)* or *(3b)* under the conditions used.




Treatment of 1-bromocyclohexene with potassium t-butoxide on dimethyl sulfoxide in the absence of *(1)* affords in 7 % yield a hydrocarbon (m.p. 53–54 °C) whose structure *(4)* was proved by its mass spectrum, elemental analysis, NMR, infrared, and ultraviolet spectra ($\lambda_{max} = 237$ mμ, log ε = 4.176), and a diene reaction with tetracyanoethylene to give *(5)*[2]. In contrast, reaction of 1,2-dibromocyclohexene with lithium amalgam or magnesium gives a trimer, $(C_6H_8)_3$, and a tetramer, $(C_6H_8)_4$, whose structures and probable modes of formation have been determined[3].

Analogous experiments have been carried out on compounds with 7- and 8-membered rings[4].

Received: July 28th, 1966 [Z 298 IE]
German version: Angew. Chem. *78*, 905 (1966)

[1] *G. Wittig* and *A. Krebs*, Chem. Ber. *94*, 3260 (1961); *G. Wittig* and *R. Pohlke*, *ibid. 94*, 3276 (1961).

[2] Cf. *W. J. Ball* and *S. R. Landor*, J. chem. Soc. (London) *1962*, 2298.

[3] *G. Wittig* and *U. Mayer*, Chem. Ber. *96*, 342 (1963); *G. Wittig* and *J. Weinlich*, *ibid. 98*, 471 (1965).

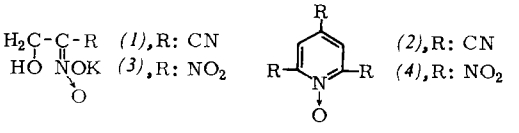
[4] *P. Fritze*, *J. Schüller*, and *H. L. Dorsch*, Dissertations, Universität Heidelberg, 1966.

## Synthesis of 2,4,6-Tricyanopyridine 1-Oxide from Nitroacetonitrile

By Prof. K.-D. Gundermann and Dr. H.-U. Alles

Organisch-Chemisches Institut, Bergakademie-Technische Hochschule, Clausthal-Zellerfeld (Germany)

In order to obtain a further protected 2-nitroacrylic acid derivative[1], we treated potassium *aci*-nitroacetonitrile, m.p. 150–155 °C (decomp.), obtained from nitroacetonitrile in anhydrous ether and an equivalent amount of a solution of potassium methoxide in anhydrous methanol, in 40 % aqueous solution with about the two-fold molar amount of formaldehyde solution at room temperature; on vacuum evaporation of the mixture we isolated potassium 3-hydroxy-2-*aci*-nitropropionitrile *(1)*, yield 75 %, m.p. 188–120 °C (decomp.) (from methanol/ether). When kept for 24 hr in the seven-fold volume of 2 N sulfuric acid, this salt evolves nitrogen oxides and gives 2,4,6-tricyanopyridine 1-oxide *(2)*, yield *ca.* 50 %, m.p. 222 °C (from acetone/water). The structure of the oxide *(2)* was ascertained by elemental analysis, molecular-weight determination, NMR spectrum (only a sharp singlet at $\tau = 8.82$ ppm), mass spectrum (peak at $M-16$; characteristic for *N*-oxides[2,*]), and IR spectrum.




Reduction of the oxide *(2)* for 3 hr with iron powder and glacial acetic acid/acetone at 95 °C, extraction of the basic components with sodium hydroxide/ether/acetone, evaporation of the ethereal solution, heating of the residue with HCl in anhydrous methanol, and treatment of the concentrated methanol solution with potassium carbonate gave the known trimethyl 2,4,6-pyridinetricarboxylate in *ca.* 60 % yield.

*Duden* and *Ponndorf*[3] obtained a compound $C_5H_2N_4O_7$ of then unknown structure from potassium 2,2-dinitroethanol *(3)* and dilute sulfuric acid; from its mode of formation and IR and NMR spectra this is also a substituted pyridine 1-oxide, namely, *(4)*. The compounds *(2)* and *(4)* are strong electron acceptors and with, *e.g.*, dimethylaniline give deep red or violet π-complexes.

Studies of the general applicability and mechanism of this new synthesis of substituted pyridine 1-oxides are in progress; reaction presumably occurs by way of Dewar-pyridine derivatives.

Received: July 25th, 1966 [Z 300 IE]
German version: Angew. Chem. *78*, 906 (1966)

[*] Prof. *W. Lüttke* and Prof. *G. Spiteller*, Göttingen, to whom we are indebted for measurement of the NMR and mass spectra, first suggested, on the basis of the spectroscopic results, that compound *(2)* was a symmetrical tricyanopyridine 1-oxide and not, as we had then assumed, 3,5,7-tricyanooxazepine.

[1] *K.-D. Gundermann* and *H.-U. Alles*, Angew. Chem. *77*, 812 (1965); Angew. Chem. internat. Edit. *4*, 788 (1965).

[2] *T. A. Bryce* and *J. R. Maxwell*, Chem. Commun. *1965*, 206.

[3] *P. Duden* and *G. Ponndorf*, Ber. dtsch. chem. Ges. *38*, 2031 (1905).

## 2,4,6-Triphenylphosphabenzene

By Dr. G. Märkl

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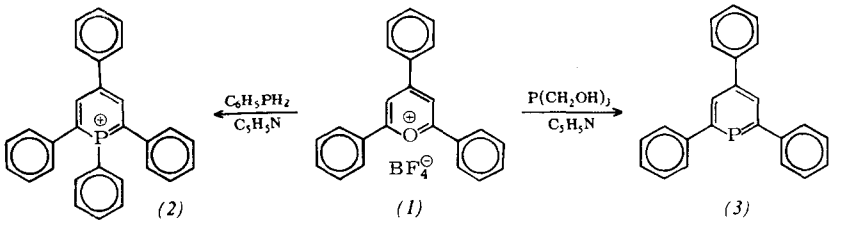
Universität Würzburg (Germany)

The reaction of phenylphosphine with 2,4,6-triphenylpyrylium tetrafluoroborate *(1)*[1] is to be interpreted as involving the intermediate formation of a cation *(2)* that is unstable under the reaction conditions.

We have synthesized the first derivative of phosphabenzene, namely, 2,4,6-triphenylphosphabenzene *(3)*, from the tetrafluoroborate *(1)* and tris(hydroxymethyl)phosphine[2,3] (molar ratio 1:1.25). When these reactants are heated for 2 hr in boiling pyridine, then cooled and treated with a little water,




*(2)* *(1)* *(3)*

+ 3 $CH_2O$ + $H_2O$ + $HBF_4$

Products

*(3)* crystallizes in 24–30 % yield as pale yellowish needles, m.p. 172–173 °C (from much ethanol or a little chloroform/ethanol). It is not autoxidizable. The molecular weight was found to be 326 in benzene by vapor-pressure osmometry, and 324 by mass spectrometry (MS 9)[2]. $^1H$–NMR spectrum in $CDCl_3$, band complex at $\tau$ = 2.2–3.0 (15 H), doublet at $\tau$ = 1.9 (2 H), $J$ = 6 Hz.

The signal of the $^{31}P$ nuclear magnetic resonance[4], $\delta$ = −178.2 ppm (in pyridine, $\delta H_3PO_4$ = 0) is at unexpectedly low field.

In comparison with the UV spectra of 1,3,5-triphenylbenzene ($\lambda_{max}$ = 254 mμ, $\varepsilon$ = 56000) and 2,4,6-triphenylpyridine ($\lambda_{max}$ = 254, 317 mμ ($\varepsilon$ = 49500, 9390), that of compound *(3)* in methanol ($\lambda_{max}$ = 278 mμ, $\varepsilon$ = 41000) shows a bathochromic shift that agrees qualitatively with observations on phosphacyanines of tervalent phosphorus with coordination number two[5].

Received: July 26th, 1966 [Z 301 IE]
German version: Angew. Chem. *78*, 907 (1966)

[1] *Ch. C. Price*, Chem. and chem. Ind. (Kagaku to Kogyo) *16*, 109 (1963); *Ch. C. Price, T. Parasaran*, and *T. Lakshminarayan*, J. Amer. chem. Soc. *88*, 1034 (1966).

[2] I thank Farbwerke Hoechst for a gift of tris(hydroxymethyl)-phosphine and for measurement of the mass spectrum.

[3] *H. Hellmann, J. Bader, H. Birkner*, and *O. Schumacher*, Liebigs Ann. Chem. *659*, 49 (1962).

[4] I am grateful to Dr. *E. Fluck*, Heidelberg, for measurement of the $^{31}P$–NMR spectrum.

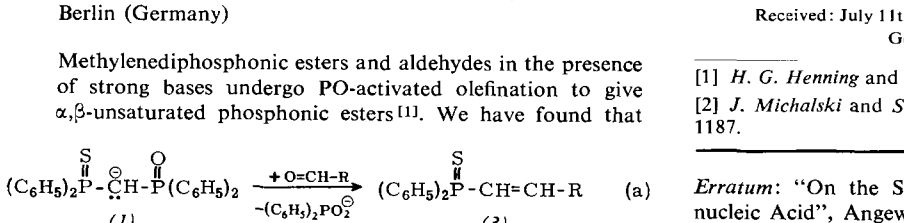
[5] *K. Dimroth* and *P. Hoffmann*, Angew. Chem. *76*, 433, 512 (1964); Angew. Chem. internat. Edit. *3*, 384 (1964); Chem. Ber. *99*, 1325 (1966); see also *R. Allmann*, Angew. Chem. *77*, 134 (1965); Angew. Chem. internat. Edit. *4*, 150 (1965).

## Preparation of α,β-Unsaturated Phosphines and Phosphine Sulfides

By D. Gloyna and Dr. H. G. Henning

II. Chemisches Institut, Humboldt-Universität, Berlin (Germany)

Methylenediphosphonic esters and aldehydes in the presence of strong bases undergo PO-activated olefination to give α,β-unsaturated phosphonic esters[1]. We have found that this type of reaction can be applied also to unsymmetrical methylenediphosphorus compounds, the carbonyl-oxygen atom of the aldehyde being transferred to the more strongly positive phosphorus atom. Thus by reactions (a) and (b) we obtained diphenylphosphinic acid in average yields of 90 %,




together with unsaturated phosphine sulfides *(3)* or phosphines *(4)*. As shown in eq. (a), no PS-activated olefination[2] occurred.

The phosphines *(4)*, which were isolated in the pure state, could be converted into unsaturated phosphine sulfides *(3)* by warming them with sulfur in benzene or acetone, or into the corresponding phosphine oxides with 5 % hydrogen peroxide in acetone.

*(4)* + S → *(3)* (c)

The influence of the diphenylphosphino group on the smooth reaction (b), and the steric course of reactions (a) and (b), are being investigated.

| R | M.p. (°C) | Compounds *(3)* by eq. (a) yield (%) | Compounds *(3)* by eq. (c) yield (%) | Compounds *(4)* M.p. (°C) | Compounds *(4)* by eq. (b) yield (%) |
|---|---|---|---|---|---|
| Phenyl | 110 | — | 67.2 | 57–58 | 63.5 |
| *o*-Methoxyphenyl | 125–126 | 75.7 | 70.9 | 58–59 | 59.4 |
| Styryl | 139–140 | 63.6 | 58.7 | 90–91 | 64.2 |
| 2-Thienyl | 106–107 | 70.9 | 60.9 | 58–59 | 52.3 |
| 2-Pyridyl | 129–130 | 73.8 | 80.4 | 82–83 | 69.2 |
| *p*-Phenylenedi- | 282–283 (decomp.) | — | 77.3 | 221–223 [*] | 64.7 |

[*] Under argon in a sealed tube.

α,β-*Unsaturated phosphines (4)*: A solution of 10 mmole of methylenebis(diphenylphosphine) monoxide *(2)* and 20 mmole of potassium t-butoxide in 60 ml of anhydrous benzene was boiled under argon for *ca.* 10 min, then treated with a solution of 10 mmole of pure aldehyde (5 mmole for dialdehydes) in 20–30 ml of anhydrous benzene and set aside for 1 hr. The cooled mixture was shaken with 50 ml of water. On acidification the aqueous phase yielded diphenylphosphinic acid, and the benzene phase on evaporation yielded the phosphines *(4)* which, depending on the radical R, were recrystallized from acetone/$H_2O$, methanol, or DMF/$H_2O$.

Olefinations with compound *(1)* were effected similarly; the phosphine sulfides were recrystallized from ethanol or methanol.

Received: July 11th, 1966; revised: August 8th, 1966 [Z 304 IE]
German version: Angew. Chem. *78*, 907 (1966)

[1] *H. G. Henning* and *D. Gloyna*, Z. Chem. *6*, 28 (1966).

[2] *J. Michalski* and *S. Musierowicz*, Tetrahedron Letters *1964*, 1187.

*Erratum*: "On the Secondary Structure of Soluble Ribonucleic Acid", Angew. Chem. internat. Edit. *5*, 591 (1966), by *H. Doepner, H. Seidel*, and *F. Cramer*.

The 5th row of the table on p. 591 should read:

| Av.no.of base pairs per molecule | (77–14)/2 = 31.5 | (77–25)/2 = 26 | (73–17)/2 = 28 | (73–22)/2 = 25.5 |
|---|---|---|---|---|

## Chemisorption of Gases on Evaporated Metal Films

*G. Wedler*, Hannover (Germany)

Chemisorption of gases depends not only on the chemical composition of the adsorbing surface, but also to a great extent on its structure and cleanliness. Extremely pure metal surfaces suitable for chemisorption investigations can be obtained by deposition of thin metal films at about $10^{-10}$ mm Hg on degassed glass surfaces.

Electron-microscopic and X-ray studies with numerous 100-Å-thick nickel films that had been condensed at 77 °K and annealed at 60 °C showed that these films consist of crystals of approximately uniform size and oriented preferentially with the {111} face parallel to the underlying surface. X-Ray measurements and also the mean free paths of the conduction electrons (determined from the dependence of resistivity on film thickness) show that these nickel films are in an ordered state. Adsorption phenomena observed on such films are thus characteristic of the compact catalyst material.

Chemisorption of gases was studied by simultaneous measurement of the change of electric resistance and work function of the films, as well as by direct calorimetric measurement of differential heats of adsorption.

For the system nickel/hydrogen, in contrast to the report in the literature that the heat of adsorption is strongly dependent on the coverage of the surface by hydrogen, we observed a heat of adsorption of *ca.* 17.5 kcal/mole independent of the coverage, provided that 100-Å-thick, completely fresh nickel films were used as adsorbent; only when a complete monomolecular layer had been built up did the heat of adsorption decrease with increasing coverage. If the nickel films had previously been covered with oxygen or carbon monoxide up to about a quarter of a monolayer, then the heat of adsorption of hydrogen – which was chemisorbed as atoms – amounted to *ca.* 21 kcal/mole at the beginning of the experiment; the heat of adsorption decreased in this case with increasing coverage, in contrast to the behavior with initially fresh films.

In contrast to the systems nickel/hydrogen and nickel/carbon monoxide[1], with which substantially only chemisorption occurs on the metal surface, we observed marked uptake of hydrogen in the lattice, *i.e.* a volume effect, for the system titanium/hydrogen[2]. With the system nickel/water vapor[3] a reaction clearly occurs between the adsorbent and the adsorbate, with formation of NiOH groups on the surface.

[Lecture at Erlangen (Germany) on May 13th, 1966] [VB 14 IE]
German version: Angew. Chem. *78*, 827 (1966)

[1] *G. Wedler* and *M. Fouad*, Z. physik. Chem. N.F. *40*, 1, 12 (1964).

[2] *G. Wedler* and *H. Strothenk*, Ber. Bunsenges. physik. Chem. *70*, 214 (1966); Z. physik. Chem. N.F. *48*, 86 (1966).

[3] *R. Suhrmann, J. M. Heras, L. Viscido de Heras*, and *G. Wedler*, Ber. Bunsenges. physik. Chem. *68*, 511, 990 (1964).

## Preparation and Properties of Substances with *N*- or *S*-Perhalogenomethyl Groups

*E. Klauke*, Leverkusen (Germany)

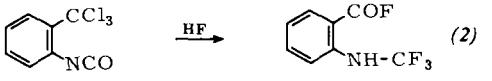
Trichloromethanesulfenyl chloride, $Cl_3C-SCl$ *(1)*, is fluorinated selectively in anhydrous HF to dichlorofluoromethanesulfenyl chloride. Replacement of further chlorine atoms by fluorine requires stronger fluorinating agents, *e.g.* $SbF_3$ or NaF. Whereas 3,6-dichloro-1,4,2,5-dithiadiazine is formed on treatment of *(1)* with $NH_3$[1], dichlorofluoro- and chlorodifluoro-methanesulfenyl chloride and ammonia give the corresponding amides $FCl_2C-SNH_2$, b.p. 54–56 °C/50 mm Hg, and $F_2ClC-SNH_2$, b.p. 89.5 °C/760 mm, respectively.

Perhalogenomethyl arenethiosulfonates can be cleaved to thiols with HCl. However, trichloromethanethiol decomposes to phosgene with loss of HCl. Thiophosgene and other thiocarbonyl dihalides are also obtained by thermolysis of perhalogenomethyl thiosulfonates.

$$Ar-SO_2S-CCl_2F + HCl \rightarrow Ar-SO_2Cl + FCl_2C-SH$$

Reaction products of *(1)* are of practical importance as leaf fungicides. Replacement of the $CCl_3$ by the $CCl_2F$ group leads to preparations with appreciably broader activity spectra[2].

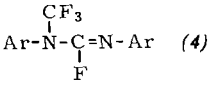
*o*-(Trichloromethyl)phenyl isocyanate undergoes Cl–F exchange in anhydrous HF; isomerization occurs simultaneously and *o*-*N*-(trifluoromethyl)aminobenzoyl fluoride *(2)* can be isolated.



*(2)*

*N*-(Trifluoromethyl)aniline derivatives *(3)* are readily prepared from aromatic isocyanide dichlorides[3].

$$Ar-N=CCl_2 \xrightarrow{HF} Ar-NH-CF_3 \quad (3)$$



*(4)*

In the preparation of *N*-(trifluoromethyl)anilines *(3)*, fluoroformamidines, *e.g. (4)*, are obtained as dimerization products of the intermediate isocyanide difluorides, the amounts varying according to the nature of the substitution and the reaction conditions. *N*-(Trifluoromethyl)anilines *(3)* are smoothly acylated by sulfenyl chlorides, but not by carbonyl chlorides. Chlorocarbonyl isocyanide dichloride and HF give trifluoromethyl isocyanate.

[Lecture at Göttingen on May 20th, 1966] [VB 12 IE]
German version: Angew. Chem. *78*, 829 (1966)

[1] *A. Senning*, Angew. Chem. *75*, 450 (1963); Angew. Chem. internat. Edit. *2*, 325 (1963).

[2] *E. Kühle, E. Klauke*, and *F. Grewe*, Angew. Chem. *76*, 807 (1964).

[3] *H. Holtschmidt*, Angew. Chem. *74*, 848 (1962); Angew. Chem. internat. Edit. *1*, 632 (1964); *E. Kühle*, Angew. Chem. *74*, 861 (1962); Angew. Chem. internat. Edit. *1*, 647 (1964).

## Types of Bonding of Sulfur in Vulcanization Processes

*W. Scheele*, Hannover (Germany)

In vulcanization processes part of the sulfur is always bound in polysulfide groups ($S_p$-sulfur). The amount of $S_p$-sulfur passes through a maximum during the process; later products contain, *inter alia*, sulfide groups, predominantly as part of five-membered rings either with or without double bonds. The amount of $S_p$-sulfur present in the vulcanizate after a reaction time $t$ can be expressed by the empirical equation (1):

$$[S_p] = at^b e^{-ct} \quad (1)$$

The quantity $b$ is normally a constant of the system, whereas $a$ and $c$ depend on the experimental conditions (*e.g.*, $c$ is related to the rate of uptake of sulfur). The coordinates of the $S_p$ maxima, $[S_p]_{max}$ and $t_{max}$, calculated from eq. (1), are in excellent agreement with experiment.

If the formation and degradation of $S_p$-sulfur are first-order processes, a kinetic expression can be developed, integration of which leads to:

$$[S_p] = \varepsilon \frac{k_1[S_8]_0}{(k_1-k_2)} [e^{-k_1 t} - e^{-k_2 t}] \quad (2)$$

$k_1$ and $k_2$ are the rate constants for decrease in $[S_8]$ and of $[S_p]$, respectively, and $[S_8]_0$ is the initial sulfur concentration. The factor $\varepsilon$ is the quotient of the experimental $[S_p]$ maxima and those calculated on the assumption that all the sulfur contained in a cross-link ($p$ + 2 atoms) reacts further, namely, $[S_p]_{max}/[S_p + 2]_{max}$. The rate constant $k_2$ is obtained by use of $t_{max}$, as in eq. (3):

$$k_1 t_{max} = \ln \omega (\omega - 1)^{-1}, \text{ where } \omega = k_2/k_1 \quad (3)$$

The total rate of formation of all the subsequent products, $\Sigma$ [P], is given by

$$d \Sigma [P]/dt = k_2[S_p] \quad (4)$$

Inserting the expression for $[S_p]$ from eq. (2) and integrating gives

$$\Sigma [P] = \varepsilon [S_8]_0 \left[ \frac{1}{(k_2-k_1)} (k_1 e^{-k_2 t} - k_2 e^{-k_1 t}) + 1 \right] \quad (5)$$

On the other hand, inserting the expression for $[S_p]$ from eq. (4) into eq. (1) gives:

$$\Sigma [P] = (k_2 a/c^2) [1 - e^{-ct} - ce^{-ct}] \quad (6)$$

The kinetics thus developed were tested on vulcanization of natural rubber in the presence of ZnO, zinc benzothiazoyl sulfide, and zinc myristate or stearate in three series of experiments, in which the temperature, the inital concentration of sulfur, or the content of accelerator were varied.

For determination of the $S_p$-sulfur the vulcanizate was degraded with lithium tetrahydridoaluminate; $p$ sulfur atoms were split off as $H_2S$ from the alkenyl alkyl polysulfide bridge bonds each containing ($p$ + 2) sulfur atoms, while in each case two sulfur atoms remain on the polymer chain as thiol groups; it should be noted that that the ZnS formed in the vulcanization must be separately determined and taken into account.

The relation between $S_p$ content of the vulcanizate and reaction time calculated from eq. (2) is in excellent agreement with experiment; calculation of the final concentration ($t = \infty$) of the subsequent products by means of eqs. (5) and (6) gave values also in good agreement with experimental results. These facts can be considered as confirmation of the kinetics developed, since no assumptions were made in deriving eq. (1), on which eq. (6) is based.

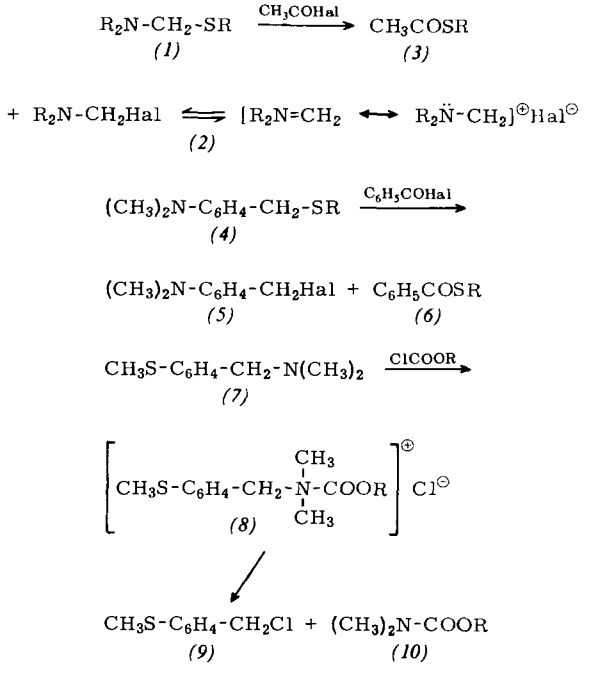
[Lecture at Hannover, May 26th, 1966] [VB 10 IE]
German version: Angew. Chem. 78, 828 (1966)

## Cleavage of Aryl-substituted Tertiary Amines by Acyl Halides

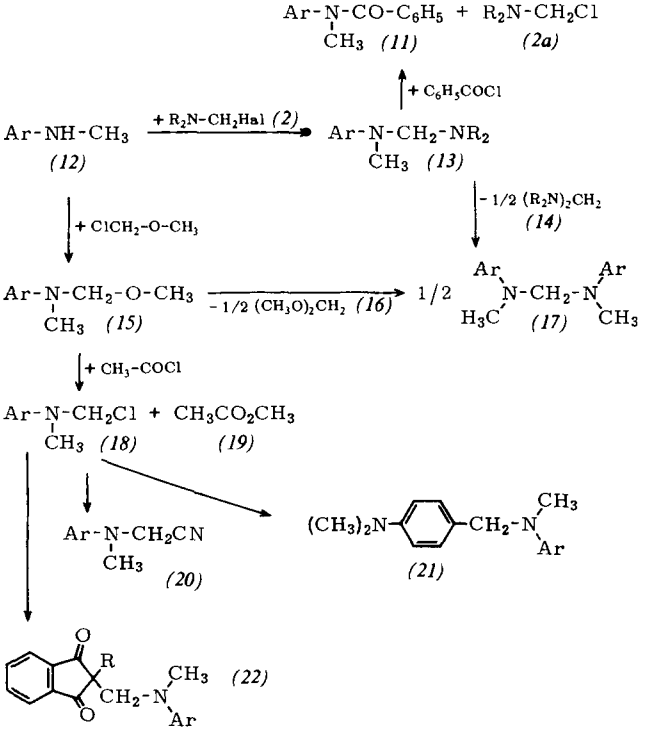
*H. Böhme*, Marburg (Germany)

The reaction of *S,N*-acetals *(1)* with carbonyl halides in indifferent solvents leads to α-halogenated amines *(2)*, together with thiocarboxylic esters *(3)*. By the analogous fission of phenylogous *S,N*-acetals of type *(4)* we have isolated the first of the rather unstable, phenylogous α-halogenated amines *(5)*, which were characterized by reaction with secondary amines to the previously described phenylogous aminals.

Phenylogous *S,N*-acetals of type *(7)* react with carbonyl chlorides and with chloroformic esters at low temperatures (about −60 °C), yielding addition products, *e.g. (8)*, that decompose at room temperature to *p*-(methylthio)benzyl chloride *(9)* and *N,N*-dimethylurethane (R = $C_2H_5$) *(10)*. Other benzylamines behave similarly: the stability of the addition compounds increases as the *para*-substituent is changed in the order $(CH_3)_2N$, $CH_3O$, $CH_3S$, H, $CH_3SO_2$.



Reaction of α-halogenated amines *(2)* and 2,4,6-trichloro- or 2,4,6-trimethyl-*N*-methylanilines *(12)* makes accessible the unsymmetrical aminals *(13)*, which on distillation (80 °C/$10^{-2}$ mm) symmetrize to compounds *(17)* and *(14)* and on cleavage with a carbonyl chloride give *N,N*-dialkylchloromethylamine *(2a)* together with a substituted benzanilide *(11)*. *O,N*-Acetals *(15)* were similarly prepared from chloromethyl methyl ether and the aniline *(12)*, and they also symmetrize



at about 80 °C, yielding compounds *(17)* and *(16)*; on cleavage with acetyl chloride the acetals *(15)* yield *N*-(chloromethyl)aniline derivatives *(18)* and carboxylic esters *(19)*; the compounds *(18)* with hydrogen cyanide afford cyanides *(20)*, with dimethylaniline afford diamines *(21)*, and with monosubstituted indanediones afford compounds of type *(22)*.

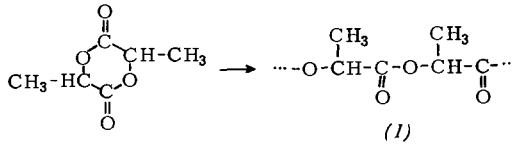
[Lecture at Marl on June 15th, 1966] [VB 13 IE]
German version: Angew. Chem. *78*, 828 (1966)

## Methods and Problems in the Study of Optically Active Polymers

*R. C. Schulz*, Mainz (Germany)

For the preparation of optically active polymers asymmetric monomers were polymerized with radical or ionic initiators [*e.g.*, menthol and borneol acrylate and methacrylate, menthol *N*-vinylurethane, *N*-substituted *N*-(α-methylbenzyl)-acrylamides, *N*-vinylureas derived from α-amino acids], and asymmetric substituents were introduced into optically inactive polymers in polymer-analogous conversions.

High-molecular crystalline polyesters *(1)* with softening points of about 170 °C were obtained by ring-opening polymerization of L-dilactide:



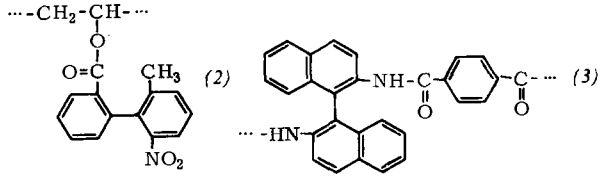
*(1)*

In this reaction the configurations of all the asymmetric C atoms are retained and are the same, so that a completely isotactic polymer results. The optical rotatory dispersion and circular dichroism were measured in several solvents. The Cotton effect, which is observed only for poly-L-lactide, indicates a secondary structure. The rotatory dispersion can be described equally well by the modified two-term Drude equation and by the Moffit-Yang equation; the constants are similar to those for helical proteins and poly-L-amino-acids, but the signs are reversed.



*(2)*

All optically active polymers described previously contain asymmetric C atoms. However, treatment of (+)-2′-methyl-6′-nitrobiphenyl-2-carbonyl chloride with polyvinyl alcohol yields the first polymer *(2)* whose optical activity is due to atropisomerism.



*(2)* *(3)*

This polymer gives the same Cotton effects as monomeric model compounds.

The specific rotation of the polymer corresponds precisely to the analytically determined content of atropisomeric substituents. From the rotatory dispersion and the circular dichroism it can be concluded that there is no mutual optical interaction between the side groups of this polymer, that the polymer structure has no influence on the specific rotation, and that in solution the macromolecules are randomly coiled.

Racemization of atropisomeric model compounds is first order, but the polymer racemizes appreciably more slowly and not according to first-order kinetics.

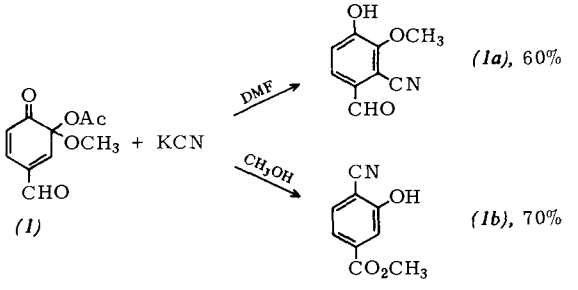
Polymers of type *(3)*, with atropisomeric groups in the main chain, have been obtained by interfacial polycondensation of (+)-1,1′-binaphthyl-2,2′-diamine with terephthaloyl dichloride.

[Lecture at Mainz (Germany), June 23rd, 1966] [VB 16 IE]
German version: Angew. Chem. *78*, 909 (1966)

## Chemistry of *o*-Quinol Acetates

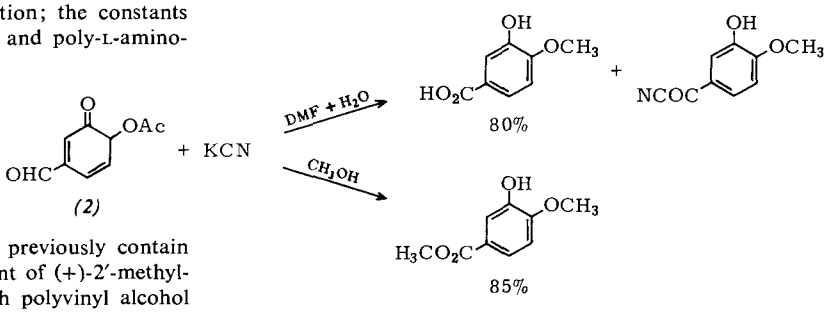
*F. Wessely*, Vienna (Austria)

Whereas, in all cases studied so far, reaction of *o*-quinot acetates with KCN leads to *m*-hydroxybenzonitriles, reaction of compound *(1)* with KCN depends on the solvent. It gives a *m*-hydroxy nitrile *(1a)* only in dimethylformamide, formation of this product being explained by 1,6-addition to the conjugated system of *(1)*. However, in methanol compound *(1b)* is formed, a result for which a complicated rearrangement must be responsible. Both reactions proceed rapidly at room temperature.



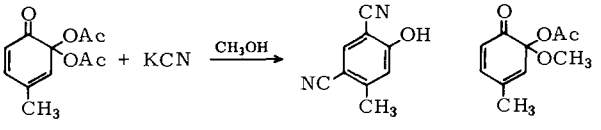
*(1)* *(1a)*, 60% *(1b)*, 70%

On treatment of compound *(2)* with KCN the product is practically independent of the solvent. The reaction leads to conversion of the aldehyde group into a carboxyl group, which can be esterified by the alcohol used as solvent.



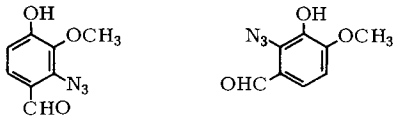
80% 85%

For the mechanism of the reaction leading from *(1)* to *(1b)* it is important that the quinol acetate *(3)* and KCN in methanol give a 55 % yield of compound *(3a)*, whereas only a very small yield of *(3a)* is obtained from the quinol acetate *(4)* under the same conditions. The structure of compound *(3a)* has resemblances to that of compound *(1b)*.



*(3)* *(3a)* *(4)*

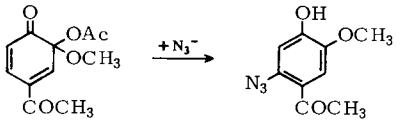
Reaction of *(1)* and *(2)* with trimethylsilyl azide in methanol, or with the azide ion, leads to compounds *(1c)* and *(2a)*. Quinol acetates carrying alkyl groups on C-4 or C-5 do not give such products. Thus the azide ion adds to an *o*-quinol acetate only if the latter is activated by a formyl group. The



*(Ic)*, 60%



*(2a)*, 95%



*(5)*

*(5a)*

quinol acetate *(5)* adds the azide ion with formation of compound *(5a)*.

[Lecture at Kiel (Germany), June 30th, 1966] [VB 21 IE]

German version: Angew. Chem. *78*, 910 (1966)

## Chemical Problems in the Pyrometallurgical Reprocessing of Nuclear Fuels

*S. R. Austin*, Clausthal-Zellerfeld (Germany)

The principle of pyrometallurgical reprocessing was explained on the basis of the fuel cycle for the Experimental Breeder Reactor No. II (EBR-II) in Idaho, U.S.A., developed by the Chemical Engineering Division of the Argonne National Laboratory.

The process consists in a melt refining at *ca.* 1400 °C, in which the rare earths and other non-noble fission products are oxidized and further products (*e.g.* Cs, Rb, Cd, I) are volatilized. M tallic uranium is obtained with sufficient purity for operation of EBR-II, which is designed as a fast plutonium breeder. The more noble fission products (Mo, Tc, Ru, *etc.*) are reduced and extracted by molten zinc from a $CaCl_2/MgCl_2/MgF_2$ melt containing the residue from the melt refining process. Uranium which enters into this by-process is recovered by reduction and precipitation with magnesium-zinc alloys.

For development and optimization of this and other pyrometallurgical and pyrochemical processes various chemical matters require clarification, including the following points:

1) Phase relations of the relevant metal and salt systems, in particular solubilities in molten metals and salts.

2) Free energy ($\Delta G$) of the relevant chemical reactions.

3) Activities and partial molar excess thermodynamic functions in molten metals and salts.

In view of the numerous individual problems (interest attaches to, *e.g.*, the properties of U, Pu, Th, and at least 20 elements that occur as fission products, in various molten metals and salts), it is evident why there are still gaps in our knowledge. Our experimental work was confined to a study of the rare earths in molten salts. For instance, the thermodynamic activities in molten $KCl/NdCl_3$ mixtures showed strong negative deviations from ideality,which can probably be explained by appearance of $[NdCl_6]^{3\ominus}$ complexes in the melt. The excess chemical potential $\mu^E$ of $NdCl_3$ is $-1$ kcal/mole at a mole fraction $x = 0.25$, and $-12$ kcal/mole at $x = 0$.

[Chemical colloquium at Clausthal-Zellerfeld (Germany), July 15th, 1966] [VB 9 IE]

German version: Angew. Chem. *78*, 910 (1966)

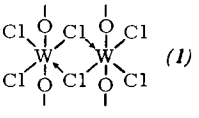
# SELECTED ABSTRACTS

**Ability selectively to dissolve carcinogenic hydrocarbons** has been observed by *M. Wilk* and *E. L. Wynder* for suspensions of isolated mitochondria from mouse liver in an aqueous buffered medium (triethanolamine · HCl / $MgCl_2$ / $KH_2PO_4$ / EDTA; pH 7.2 at 25 °C).

Non-carcinogenic hydrocarbons are not dissolved by mitochondria and have no influence on respiration; however, respiration of the mitochondria is strongly hindered after they have taken up 3,4-benzopyrene or 7,12-dimethylbenz-[*a*]anthracene. Uptake of these substances could be followed by fluorescence spectroscopy. A promotor action by the polycyclic aromatic hydrocarbons is assumed to set in on the mitochondria which are the structural elements for cell respiration. This view is supported by depression of respiration of isolated mitochondria by pure cocarcinogens such as croton oil./Z.Naturforsch.*21b*, 161 (1966) / –De. [Rd 509 IE]

**The oxide fluorides $AsOF_3$, $SbOF_3$, and $SbO_2F$** have been prepared by *K. Dehnicke* and *J. Weidlein*. The fluoride nitrates $AsF_3(ONO_2)_2$, $SbF_3(ONO_2)_2$, and $SbF(ONO_2)_4$ are accessible from the fluoride chlorides $AsF_3Cl_2$, $SbF_3Cl_2$, and $SbFCl_4$ by use of chlorine nitrate and on thermal decomposition afford the hitherto unknown oxide fluorides $AsOF_3$, $SbOF_3$, and $SbO_2F$. $AsOF_3$ is a white, hygroscopic solid, amorphous according to its X-ray diagram, and insoluble in nonpolar solvents; at 240 °C it decomposes without melting; it forms no adduct with pyridine. $SbOF_3$ has similar properties; it is stable up to about 200 °C but, in contrast to $AsOF_3$, forms a 1:1 adduct with pyridine. Decomposition of $SbO_2F$ does not begin until 350 °C; no adduct is formed with pyridine. According to the IR spectra $AsOF_3$ and $SbOF_3$ are associated by means of M–O–M bridges (M = As or Sb) (symmetry $C_{3v}$), but $SbO_2F$ has $C_s$ symmetry. / Z. anorg. allg. Chem. *342*, 225 (1966) / –Sch. [Rd 534 IE]

**Tungsten(V) oxide trichloride** *(1)* has been synthesized by *G. W. A. Fowles* and *J. L. Frost*. Reducing W(VI) oxide tetrachloride with Al powder in a sealed tube at 100 to 140 °C and subsequent removal of the $AlCl_3$ and starting material by sublimation affords the olive-green substance *(1)*, which is only weakly paramagnetic and according to its IR spectrum and X-ray powder diagram has a structure analogous to that of Nb(V) oxide trichloride (tetragonal unit cell: $a = 10.7$ and $c = 3.84$ Å). It forms deeply colored



*(1)*

complexes with pyridine and acetonitrile. In accord with its polymeric structure the product *(1)* is insoluble in solvents such as $C_6H_6$ or $CH_2Cl_2$. / Chem. Commun. *1966*, 252 / –Ma. [Rd 529 IE]

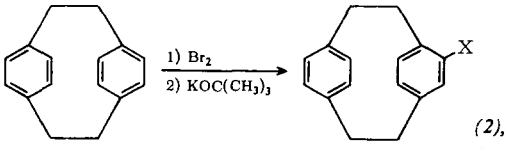
**Electrochemical oxidation of iodide to iodate** at graphite electrodes has been investigated by *R. Landsberg*, *R. Nitzsche*, and *W. Geissler*. Analysis of the potential curves indicated that the reaction leading to iodate is of the first order with respect to iodide; the order with respect to hydroxide ions is 0.23 at pH 6 to 10.6, but zero at higher pH values. The following reaction mechanism is proposed:

$$OH^-_{aq} \rightleftarrows (OH^-)_{ad}$$

$$I^- + (OH^-)_{ad} \rightarrow (IOH^-)_{ad} + e^-$$

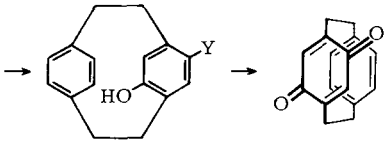
/ Electrochim. Acta *11*, 495 (1966) / –Hz. [Rd 520 IE]

**A paracyclophane with intramolecular electron donor-acceptor action** has been prepared by *D. J. Cram* and *A. C. Day*. Treating [2.2]paracyclophane *(1)* with one equivalent of bromine gives a high yield of the fairly pure monobromo compound *(2)*, which is converted by K t-butoxide in dimethyl sulfoxide through a benzyne intermediate into the phenol *(3)*. This couples with diazotized sulfanilic acid, yielding the azo dye *(4)* which is reduced by sodium hydrogen sulfite to the unstable aminophenol *(5)*. The




*(1)*

*(2)*, X : Br
*(3)*, X : OH



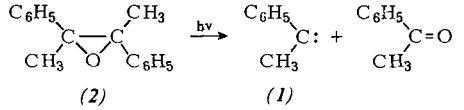

*(4)*, Y : $N{=}N\text{-}C_6H_4\text{-}SO_3H\text{-}p$
*(5)*, Y : $NH_2$

*(6)*

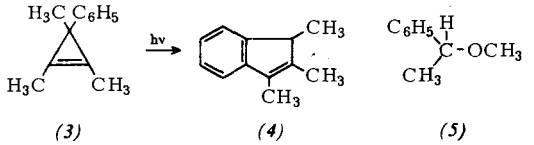
quinone *(6)* is then obtained by oxidation with $Fe_2(SO_4)_3$ in $H_2SO_4$ (total yield *ca.* 10 %); it absorbs at 340 mμ (ε = 600), which is interpreted as a charge-transfer band. / J. org. Chemistry *31*, 1227 (1966) / –Bu. [Rd 511 IE]

**Metastable $K^+$ ions produced by electron impact** have been found in the mass spectrometer by *Florence Fiquet-Fayard*. The first species, which appears above 24.5 ± 2 eV, is interpreted as $K^+$ in the configuration $3s^23p^54s$, whose 4*s* electron has a spin opposite to that of the electron missing from the 3*p* shell, so that this condition is metastable as a result of the selection rule $\Delta S = 0$. The second species, which appears between 33.5 and 36.5 eV, is assigned to the state $3s^23p^5n$, where *n* is a principal quantum number higher than 4; the probability of return of the more highly excited electron is appreciably smaller the greater the value of *n*; the appearance potential of such states is thus close under the second ionization potential, which for potassium is 36.15 V. / J. Chim. physique *63*, 401 (1966) / –Hz. [Rd 518 IE]

**Methylphenylcarbene (α-methylbenzylidene)** *(1)*, hitherto unknown, has been obtained, together with acetophenone, by *H. Kristinsson* by irradiation of *trans*-α,α'-dimethylstilbene oxide (2,3-dimethyl-2,3-diphenyloxirane) *(2)*. This fragmentation is analogous to that occurring on photolysis of stilbene oxide or tetraphenyloxirane which yields phenylcarbene or diphenylcarbene, respectively. Irradiation of the oxide *(2)* (40 hr, 35 °C, low-pressure Hg lamp) in 2-butyne affords 1,2,3-trimethyl-3-phenylcyclopropene *(3)* (10 %),




*(2)* *(1)*




*(3)* *(4)* *(5)*

which is largely rearranged photochemically into 1,2,3-trimethylindene *(4)*. Photolysis of the oxide *(2)* in methanol/benzene leads to methyl α-methylbenzyl ether *(5)* (50 %). / Tetrahedron Letters *1966*, 2343 / –Ma. [Rd 528 IE]

**Fractionation and purification of tRNA** by column chromatography on Sephadex G 25 has been achieved by *K. H. Muench* and *P. Berg*. The procedure leads to 24-fold enrichment and 25 to 40 % purity in one passage (10-l column for 3.5 g of mixed tRNA). The two-phase solvent mixture consists of 6 parts of 1.25 M potassium phosphate buffer (pH 6.88), 2 parts of 2-ethoxyethanol, 1 part of 2-butoxyethanol, 0.01 part of triethylamine, and a little 2-mercaptoethanol. The Sephadex columns are prepared by use of the lower solvent layer and are then equilibrated with the upper layer. After the tRNA mixture has been added, elution is carried out with the upper layer and then with a gradient of the upper layer containing 0.01 to 0.05 part of triethylamine. Between these gradients and the lower layer the distribution coefficient of the tRNA varies from about 0.08 to 0.8. The procedure is also suitable for separation of amino acid-specific tRNA's in pure sub-fractions. / Biochemistry *5*, 970 (1966) / –Hö. [Rd 517 IE]

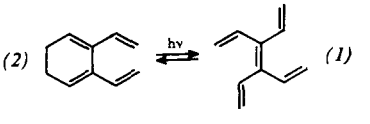
**A new synthesis of (tertiary alkyl)amines** has been described by *P. Kovacic, R. J. Hopper, S. S. Chaudhary, J. A. Levisky*, and *V. A. Liepkalns*. Amination of methylcyclohexane and *p*-cymene by trichloramine in presence of $AlCl_3$ in $CH_2Cl_2$ or ethylene dichloride at 0 to 10 °C affords 1-methylcyclohexylamine *(1)* and 1-methyl-1-*p*-tolylethylamine *(2)*, respectively; for the latter synthesis t-butyl bromide (in amount equimolar with the catalyst) should be added. Molecular proportions for the amination are substrate:trichloramine:$AlCl_3$ = 1:0.1:0.2. No basic product is formed in absence of $AlCl_3$; yields are much reduced in absence of the t-butyl halide. *(1)*: yield 83 %; *(2)*: yield 80 %, b.p. 76–77 °C/5.2 mm. The following reaction sequence is assumed:

$$RH \xrightarrow{-H^{\ominus}} R^{\oplus} \xrightarrow{+NH_2^{\ominus}} RNH_2$$

/ Chem. Commun. *1966*, 232 / –Ma. [Rd 527 IE]

**Cesium fluoride is a donor of particularly active fluoride ions,** as is shown by *D. P. Graham, V. Weinmayr*, and *W. B. McCormack*. Thus anionic polymerization of tetrafluoroethylene has been achieved for the first time by use of CsF, yielding oily fluorocarbons that contain 8 to 14 C atoms. The carbanion complexes formed by addition of CsF to polyfluoroolefins are about as reactive as Grignard compounds. For instance, perfluoro-2-methyl-2-butanol (a water-clear liquid, b.p. 67 °C) was prepared in 86 % yield from tetrafluoroethylene, CsF, and hexafluoroacetone. In this case CsF activates the ketone as well as the olefin. Remarkably, perfluorocarboxylic acids can be obtained by simple carbonylation, *e.g.* perfluoroisobutyric acid in 56 % yield from hexafluoropropene, CsF, and $CO_2$. / J. org. Chemistry *31*, 955, 957, 958 (1966) / –Bu. [Rd 512 IE]

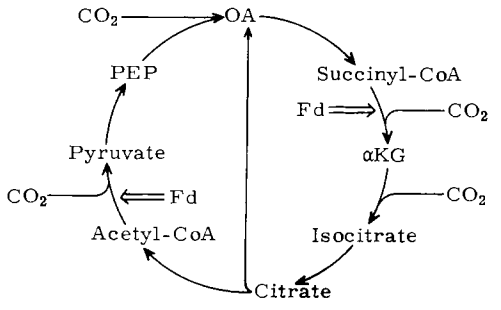
**Tetravinylethylene (3,4-divinyl-1,3,5-hexatriene)** *(1)* was isolated in 6 to 7 % yield by *L. Skattebøl* after irradiation (λ = 2537 Å) of a 10 % solution of 2,3-divinyl-1,3-cyclohexadiene *(2)* in pentane at –78 °C; *ca.* 25 % of polymeric product was also formed. Irradiation of the product *(1)* regenerated *(2)*; in the presence of a sensitizer (benzophenone) none of the open-chain product *(1)* was ob-




*(2)* *(1)*

tained, but formation of the polymer was accelerated. The structure of product *(1)* was deduced from IR, UV, and NMR spectra. After hydrogenation of the crude product, 3,4-diethylhexane was isolated. / Tetrahedron Letters *1966*, 2257 / –Ma. [Rd 530 IE]

**A photosynthetic, reductive carboxylic acid cycle** due to anaerobic microorganisms (*Chlorobium thiosulfatilum*) is contrasted by *M. C. W. Evans*, *B. B. Buchanan*, and *D. I. Arnon* with the Calvin cycle of plants. The total synthesis leads to 1 mole of oxaloacetate (OA) from 4 moles of $CO_2$, as well as regenerating 1 mole of oxaloacetate as starting material for the cycle. The four reactions for fixation of $CO_2$ are: 1) formation of α-ketoglutarate (αKG) from succinyl-coenzyme A, 2) formation of isocitrate from αKG, 3) synthesis of pyruvate from acetyl-coenzyme A, and 4) formation of OA from phosphoenolpyruvate (PEP). Reactions 1) and 3) depend on reduced ferredoxin (Fd), which is regenerated in a light reaction. The cycle makes use of the reversibility of reactions of the citric acid cycle. / Proc. nat. Acad. Sci. U.S.A. *55*, 928 (1966) / –Hö. [Rd 516 IE]




**The recognition of codes by pure tRNA species** from *Escherichia coli B* has been studied by *D. A. Kellog* and his collaborators. They concluded that appearance of several tRNA's specific to one amino acid is not necessarily related to degeneration of the genetic code, but that one pure aminoacyl-tRNA "recognizes" several codons. Thus *E. coli B* contains three (or two) valyl-tRNA, all three (two) of which include a GUU anticodon. Nevertheless there are differences between them: valyl-tRNA I and II are preferentially bound to ribosomes through the ribotrinucleotides GUA, GUG, and GUU; valyl-tRNA III reacts with GUU and GUC. A similar situation exists with alanyl-tRNA, of which I is bound through GCA and GCG and rather worse by GCU, whereas II is bound equally well by GCA, GCG, GCC, and GCU. A pure phenylalanyl-tRNA reads the codons UUU and UUC. As already known, methionyl-tRNA species occupy a special position: I corresponds to UUG, CUG, and AUG, II only to AUG; only I can be formylated and plays a part in starting peptide chains. / Proc. nat. Acad. Sci. U.S.A. *55*, 912 (1966) / –Hö. [Rd 515 IE]

**Isoleucyl-tRNA synthetase** from *Escherichia coli* has been enriched 300 times by *A. N. Baldwin* and *P. Berg*. The enzyme appears homogeneous in ultracentrifugal and chromatographic experiments, has a molecular weight of 112000, and binds one molecule of isoleucyl-AMP per molecule (AMP = adenosine-5′ phosphate). The complex enzyme-isoleucyl-AMP is more stable than the pure enzyme towards denaturation by heat, trypsin, and thiols. The first step (a) in the reaction catalysed by the enzyme occurs with isoleucine ($K_M = 5\times10^{-6}$ mole/l) as well as with valine ($K_M = 4\times10^{-4}$ mole/l), but only isoleucine is transferred to isoleucine-specific tRNA [step (b)]. The complex enzyme-valyl-AMP is,

$$\text{Isoleucine} + \text{ATP} \rightleftarrows \text{Isoleucyl-AMP} + \text{Pyrophosphate} \quad \text{(a)}$$

$$\text{Isoleucyl-AMP} + \text{tRNA}_{\text{Ile}} \rightarrow \text{Isoleucyl-tRNA} + \text{AMP} \quad \text{(b)}$$

on the contrary, decomposed into enzyme, valine, and AMP under catalysis by isoleucine-specific tRNA. This reaction is characteristic of isoleucine-specific tRNS which is inactive after any chemical change investigated (*e.g.* esterification with isoleucine, periodate oxidation of the free 2′- and 3′-hydroxyl groups, removal of the terminal adenosine, or fission near the 5′-end).

The authors suggest that this is a safety mechanism to prevent confusion between the two homologous amino acids isoleucine and valine. / J. biol. Chemistry *241*, 831, 839 (1966) / –Hö. [Rd 514 IE]

**Two conformers of the 3-nitro-1,2,4,5-tetraisopropylbenzene radical anion** have been detected by *T. M. McKinney* and *D. H. Geske* by means of ESR spectroscopy following electrochemical reduction. The two conformers differ in the angular orientation of the nitro group with respect to the ring plane. The free energy of conversion of the form with the greater into that with the lesser angle in acetonitrile was determined as $\Delta G_{298} = (-5 \pm 1)\times10^2$ cal/mole. The radical anion of 2-nitro-1,3,5-triisopropylbenzene does not display conformational isomerism. / J. chem. Physics *44*, 2277 (1966) / –Hz. [Rd 519 IE]

***N*-Unsubstituted hydrazones,** which are otherwise difficultly accessible, have been prepared by *G. R. Newkome* and *D. L. Fishel* from *N,N*-dimethylhydrazones by exchange with anhydrous hydrazine in absolute alcohol. The unsubstituted hydrazones are obtained very pure and in excellent yields. In particular, they are free from azines and can be kept without decomposition in the free state. Some hitherto unknown hydrazones (*e.g.* those of α-tetralone, yield 96 %, m.p. 38–40 °C, and of 1-indanone, yield 79 %, m.p. 77 to 78 °C) have been obtained in this way. The method fails for sterically hindered or aromatic carbonyl compounds that in the *ortho*-position to the carbonyl group have substituents (*e.g.* halogen) that are easily removed by nucleophiles. The last-mentioned compounds afford 1*H*-indazole when treated with hydrazine. / J. org. Chemistry *31*, 677 (1966) / –Bu. [Rd 513 IE]

# BOOK REVIEWS

**Advances in Heterocyclic Chemistry.** Vol. 4. Edited by *A. R. Katritzky* with collaboration by *A. J. Boulton* and *J. M. Lagowski*. Academic Press, New York-London 1965. 1st edit., 462 pp., bound $15.–.

Volume 4 of the series is divided into five chapters, each written by an acknowledged expert. The first three chapters are devoted to sections of heterocyclic chemistry that have not been previously reviewed.

The first chapter treats the addition of water to nitrogen heterocycles that was first observed among pteridines (Qualitative Aspects: *A. Albert* and *W. L. F. Amarego*, 42 pp., Quantitative Aspects: *D. D. Perrin*, 30 pp.). It is followed by one chapter each on isothiazoles whose first simple member was prepared in 1956 (*R. Slack* and *K. R. H. Woolridge*, 13 pp.) and on oxazolones (*R. Filler*, 32 pp.). In a further chapter *H. J. den Hertog* and *H. C. van der Plas* (24 pp.) give an account of the hetarynes, which constitute a new class of energy-rich organic compounds, not isolable in substance.

Hetarynes are of importance chiefly as intermediates in abnormal nucleophilic heteroaromatic substitution reaction. Normal nucleophilic substitution (addition-elimination mechanism) of six-membered aromatic heterocycles (azines) such as pyridine, pyrimidine, *s*-triazine, *etc.*, is the subject of by far the longest contribution (*R. G. Shepherd* and *J. L. Fedrick*, 278 pp.). Since there was an article of nucleophilic heteroaromatic substitution in Vol. 3 of this series, the

question arises whether further treatment after such a short time is justified. In spite of considerable overlap between the two articles the reviewer accepts the duplication: first, because elucidiation of substitution of this type is in very rapid development (90 % of the experimental contributions belong to the last ten years); and, secondly, because of the extraordinary thoroughness of *Shepherd* and *Fedrick*'s article (about 800 references).

The good repute that "Advances in Heterocyclic Chemistry" earned by the first three volumes will certainly not be diminished by Volume 4.

*Th. Kauffmann* [NB 496 IE]

**Agar Gel Electrophoresis.** By *R. J. Wieme*. Elsevier Publishing Company, Amsterdam-London-New York 1965. 1st edit., 425 pp., 116 figs., 25 tables, bound, DM 61.50 (about $15.–).

An explanation of the physical basis of electrophoresis and a review of suitable gels are followed by a description of the methods used in practice for zone electrophoresis on agar gel, *e.g.* fully enclosed gel and agar plates that contain a layer of agar gel or agar sol. Analytical electrophoresis is the kernel of the exposition, which describes in detail the methods used with agar plates. Three types are differentiated: electrophoresis with a voltage drop of 5 V/cm or of 15 V/cm, and electrophoresis in liquid agar sol. The literature is comprehensively and critically surveyed, so that this monograph serves as a handbook of methods. Moreover, analysis of the pherograms is explained in detail: localization of the zones in dried agar film by physical and, particularly, by chemical methods (specific color reactions) and their quantitative evaluation are treated in detail. In addition the interesting methods for localization of substances having enzymatic properties are described, and finally precipitation by antiserum (immuno-electrophoresis). In conclusion an exposition of the application of agar plate methods for the separation of a diversity of substr tes occupies 171 pages, particular attention being naturally p id to proteins and enzymes.

The author's wide experience is eviden in many sections of the book. All who use electrophoresis will benefit from reading this excellent book and it is to be hoped that it will help to show the enquiring research worker the manifest advantages of agar gel electrophoresis. For the next edition, which can be confidently anticipated, the reviewer would like to express a few wishes: The methods used with agar plates (normal voltage, high voltage, and agar sols) are carefully described under these three variants, and it would be very useful if the relative results achieved by them were explained for electrophoresis of one normal serum, with illustrations of the colored pherogram and also of the usual protein diagram.

There is no one ideal method of electrophoresis – each method has its advantages and disadvantages, whose relative importance is determined in part by the problem set. The present book enables the advantages of agar gel electrophoresis to be exploited, and thanks are due to the author for describing his field of work.

*W. Bockemüller* [NB 497 IE]

**Organic Reaction Mechanisms.** By *R. Breslow*. W. A. Benjamin, Inc., New York-Amsterdam 1965. 1st edit. ix + 232 pp., numerous figs., paperback $4.35.–, bound $7.70.

The gap between a textbook and the original literature is great. For a study of organic reaction mechanisms this gap can be bridged by *R. Breslow*'s original and didactically successful contribution. In seven chapters (Bonding in Organic Compounds; Reaction Mechanisms and Reaction Rates; Nucleophilic Aliphatic Substitution; Ionic Elimination and Addition Reactions; Aromatic Substitution; Reactions of Carbonyl Compounds; Reactions Involving Free Radicals) the reader is introduced to nearly all the basic facts and aspects of reaction mechanism. Even difficult subjects, such as MO treatment of conjugated compounds, transition state theory, electronegativity, hybridization, and general acid catalysis are presented simply and clearly. The experiments on which theory is based are always emphasized. The discussions of "special topics" which follow each chapter include the most recent advances and familiarize the reader with such research areas as Hückel's rule, enzyme catalysis, carbonium ion rearrangements, cycloadditions, π-complexes and aromatic substitution, redox reactions, and polar effects in radical reactions.

Production and formulae, with a few exceptions (p. 224), are excellent. As regards content, exception can be taken only to the identification of resonance with valence bond theory on p. 9, for according to *Heilbronner* the former is closer to MO theory.

Students will benefit from this book in their preparation for advanced ex inations, and all others for refreshing their memory, since only textbook knowledge of organic and physical chemistry is required. An attraction, but also a problem, of the book is the brief, concise presentation: this makes reading it a pleasure, but is too demanding for the beginner.

*C. Rüchardt* [NB 500 IE]

**Fortschritte der Arzneimittelforschung** [Advances in Drug Research]. Vol. 8. Edited by *E. Jucker*. Birkhäuser Verlag, Basel-Stuttgart 1965. 1st edit., 530 pp., numerous figs. and tables, bound, DM 115.– (about $29.–).

This volume, like earlier ones, contains comprehensive reviews of problems in drug research.

*G. Woolfe* devotes 42 pages to "The Chemotherapy of Amoebiasis". After a short introduction to the test methods used *in vivo* and *in vitro*, there is a discussion of the chemistry, pharmacology, and clinical use of emetine and the newer effective antibiotics and chemotherapeutic substances (Paromomycin, Biallylamicol, Entobex, Mantomid, Diloxanide, and Mebinol). Although the new substances represent an advance for the physician and the patient, emetine and dehydroemetine are still essential for extraintestinal infections (198 references). – "Biochemical Effects of Drugs Acting on the Central Nervous System" are reviewed by *L. Decsi* in 100 pages. The first part is devoted to metabolism in the central nervous system and chemical transport. There follows a discussion of the biochemical action of substances that excite or depress the central nervous system. The final discussion indicates that there is as yet no satisfactory conclusion in spite of the extremely large number of publications in this field (1841 references).

*H. Uehleke* reviews "Biological Oxidation and Reduction on Nitrogen of Aromatic Amino and Nitro Compounds" in 62 pages. The mechanism and reaction products are discussed first. The second section deals with the toxic action of the products, and in particular with the formation of methemoglobin and with the role the products can play in cancer formation by carcinogenic aromatic amines (473 references).– "Narcotic Antagonists" are reviewed by *S. Ascher* and *L. S. Harris* (58 pages). They report first on the chemistry of antagonists to morphine and substances of similar activity. After a short discription of the methods usually used to determine antagonist action, attention is directed to the relations between chemical structure and activity and to the pharmacology and clinical use. This review (223 references) closes with a criticism of the receptor theory as explanation for the effect. – *M. W. Whitehouse* devotes 106 pages to a comprehensive review of "Some Biochemical and Pharmacological Properties of Anti-Inflammatory Drugs", referring to the often unsolved problems of the pathology and therapy of "rheumatic"diseases. A short introduction on the experimental methods of testing anti-inflammatory or antirheumatic activity is followed by a discussion of presently known effects on the biochemistry of the organism and of relations between chemical constitution and activity. A review of the known changes in the biochemistry of the organism due to rheumatic diseases, and consideration of the conclusions that can be drawn from the results reported, close this contribution (404 references).

The aim of *J. A. Montgomery* in his article "On the Chemotherapy of Cancer" was to discuss the types of substance studied (alkylating agents, antimetabolites, hormones, antibiotics, plant extracts) and to relate their constitution to their activity so far as possible. A section on the therapy and its problems closes the review (68 pages, 496 references). – An extensive subject index, and cumulative indexes of authors and articles in the series, make this volume a useful reference work. The production, with the very numerous structural formulae, is excellent, as in previous volumes.

*O. Schaumann* [NB 493 IE]

**Kunststoff-Handbuch. Aufbau, Verarbeitung, Eigenschaften und Anwendung der synthetischen Werkstoffe** (Handbook of Synthetic Industrial Materials. Structure, Processing, Properties, and Applications). Edited by *R. Vieweg* and 14 co-editors for the single volumes. Carl Hanser Verlag, München. Vol. III: Abgewandelte Naturstoffe (Modified Natural Products). Edited by *R. Vieweg* and *E. Becker*. 1965. xv + 470 pp., 237 figs., 80 tables, linen DM 98.– (about $25.–); on subsctiption to the complete work, DM 79 (about $20.–).

Well-known specialists here report on a field which often is, quite unjustifiably, somewhat neglected in discussions of synthetic industrial materials, namely on materials derived by modification from natural sources such as wood, cellulose, and casein. Although the production of these materials has not increased as rapidly as that of synthetic resins and plastics, their significance (yearly production over 100000 tons in Germany alone) can by no means be overlooked. The greater part of this book is devoted, as expected, to the derivatives of cellulose. Who would want to do without Vulcanized Fiber, cellulose glass, celluloid, acetylcellulose, and other esters and ethers of cellulose? All these are treated by competent specialists who give a clear and easily grasped presentation of their chemical technology, properties, processing, and applications.

The chapter on injection molding compositions of cellulose esters is particularly well written. In the otherwise excellent treatment of cellulose ester films the coverage of the non-German literature is somewhat scanty. As a general principle as much literature should be cited in such compilations as possible, since the documentation of artificial resins and plastics is not yet developed to a satisfactory extent.

The sections on laminated wood and artificial horn, materials produced in smaller amounts smce they can be formed only by cutting, round the book off very well.

Like Volume IV (on polyvinyl chloride) [1], this book also well meets the needs of resea ch and technology. Chemists, physicists; and engineers interested in the scientific aspects, as well as procesing and applications engineers, can gain valuable information from this volume on behavior, uses, and properties of this class of synthetic materials.

*O. Horn* [NB 499 IE]

[1] Cf. Chemie-Ing. Techn. *36*, 1341 (1964).

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# A New Group of Antischistosomal Compounds

BY DR. PAUL SCHMIDT AND DR. MAX WILHELM
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*A number of compounds containing the 5-nitro-2-thiazolyl group are suitable for the treatment of schistosomiasis; 1-(5-nitro-2-thiazolyl)-2-imidazolidinone is particularly effective. The compounds are taken up selectively by the schistosomes causing the disease and by their eggs, and destroy both. – A review of earlier attempts to control this tropical disease is also presented in this communication.*

## 1. Schistosomiasis (Bilharziasis)

After malaria, schistosomiasis is the most widespread disease of tropical and subtropical regions. It is caused by trematode parasitic flukes of the genus *Schistosoma* that live in pairs in the blood vessels of man and some other mammals. The male and the female worms are tightly intertwined, the thread-like female virtually enveloped in the ventral fold of the larger male, which effects the attachment and movement of the pair in the lumen of the vascular system by means of its suckers (Fig. 1). Schistosomes derive their nourishment from the blood. They can usually survive 20 years, up to a maximum of 30 years, and reach a length of 0.8–1.2 cm.

Fig. 1. Schistosome pair.

There are three types of schistosome mainly responsible for schistosomiasis in man, each of which gives rise to a typical clinical picture:

*Schistosoma haematobium*, the cause of urogenital schistosomiasis, affects the bladder and anal regions; the symptoms are localized in the urinary tract often involving the kidneys and, in women, the genital tract also.

*Schistosoma mansoni*, the cause of intestinal schistosomiasis, principally affects the mesenteric vessels. Symptoms occur in the intestinal tract, the spleen, and the liver. Dysentery and portal hypertension are frequent consequences.

*Schistosoma japonicum*, the cause of splenohepatic schistosomiasis, inhabits less clearly circumscribed regions than do the other types, but is found mainly in the spleen and liver. *S. japonicum* is responsible for a complex of exclusively splenohepatic symptoms whose development is, however, faster and more spectacular than in *S. mansoni* infections.

The life cycle of the three main types of the parasite involves four stages of development:

1. The female deposits its eggs, principally in the small vessels of the intestine or the urinary organs. The eggs remain lodged there and the blocked sections of the vessels atrophy. Some of the eggs diffuse into the surrounding tissues, where they cause characteristic inflammation. Small granulomas form around eggs or groups of eggs ("pseudo-tuberculomas"). If, however, the eggs reach the lumen of the bladder or intestine they are excreted in the urine or feces. In this way, the disease is transmitted further.

2. Larvae (miracidia) hatching from the eggs when they have found their way into water swim around and eventually bore into the intermediate host, a water-snail.

3. In the water-snail thousands of bifid-tailed cercaria with boring glands develop from each miracidium by asexual reproduction. Several weeks after the infection of the snail, *i.e.* after penetration by the miracidium, the

very numerous cercaria swarm out into the water, where they either swim freely or remain on the surface. On contact with human skin or mucous membrane they enter the organism by means of their acid glandular secretion. By way of the lymph or blood vessels the young parasites reach the liver, where they become sexually mature within a few weeks in the branches of the portal vein.

4. Once paired, the worms migrate to the mesenteric or intestinal veins, where they remain or pass into the plexus of veins of the lesser pelvis. Development is thus complete and the cycle begins again.

## 2. Distribution

According to estimates made by the World Health Organisation, the number of persons suffering from schistosomiasis amounts to 200–300 million. *S. haematobium* is found throughout North Africa from Morocco to the Nile valley, in West Africa from Senegal to Angola, as well as in East and South Africa and Madagascar. Outside Africa, these parasites occur on the Arabian peninsula and in Iraq. *S. Mansoni* occurs particularly in the eastern fringe areas of Africa, from Lower Egypt to South Africa, in Madagascar and in the Yemen, and also in Brazil, Venezuela, and on some of the islands in the West Indies. *S. japonicum* is very widespread in China and is found in certain parts of Japan and the Philippines.

## 3. Antischistosomal Therapy

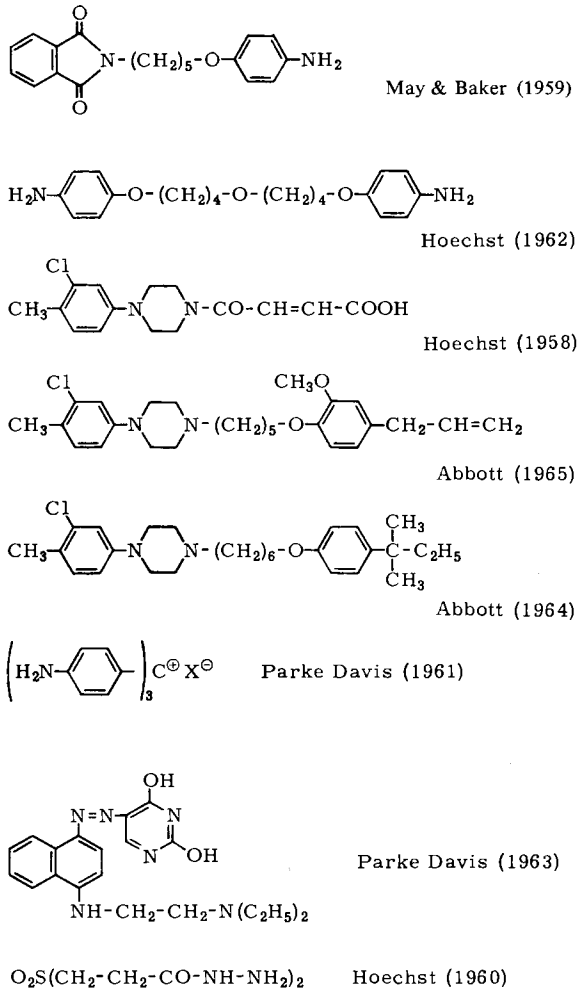
In order to control schistosomiasis successfully the life cycle of the parasites must be interrupted at one or more stages of their development. This could be achieved by eradication of the intermediate host, the water-snail, or by treatment of infected humans with drugs that attack the schistosomes and prevent the production and deposition of eggs.

Each of these courses is beset with considerable difficulties. Eradication of the snails requires a molluscicide that attacks the intermediate host specifically without damaging fish and plants living in the same waters. Much thought and energy have been spent on attempts to find a method of preventing the development of the parasites in the principal host; several substances have shown activity in animal experiments but have so far proved unsuitable for clinical use.

In the past, only two groups of substances have been used, with varying success; these are compounds of tervalent antimony and derivatives of thioxanthone (10*H*-dibenzo[*b*,*c*]thiin-10-one).

The use of tartar emetic in the treatment of bilharziasis was introduced by *Christophersen* [1] as long ago as 1918. Compounds of tervalent antimony are active *in vitro* as well as *in vivo*, regardless of the species of schistosome and of the host. The therapeutic effect is limited only by the fact that relapses occur if the dosage administered is too low; since the substance is highly toxic, however, effective therapeutic doses may not be tolerated.

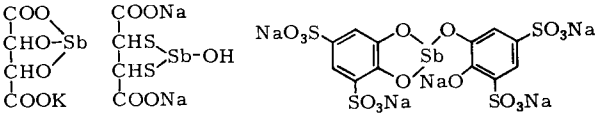
[1] *J. B. Christophersen*, Lancet *195*, 325 (1918).




Scheme 1. Antischistosomal drugs tested.

Attempts to detoxify tartar emetic have always failed because both the antiparasitic effect and the toxicity depend on the amount of antimony administered. Raising the dose improves the action on the parasite but also increases the toxicity, irrespective of the chemical form of the drug. Moreover, antimony compounds must be administered parenterally, which is a further disadvantage.

Scheme 2 shows the antimony compounds customarily used in the treatment of schistosomiasis, namely tartar emetic *(1)*, Astiban® *(2)* (Hoffmann-La Roche), and Fuadin® *(3)* (Winthrop). Astiban is less toxic than tartar emetic and has been well received in various countries [2].

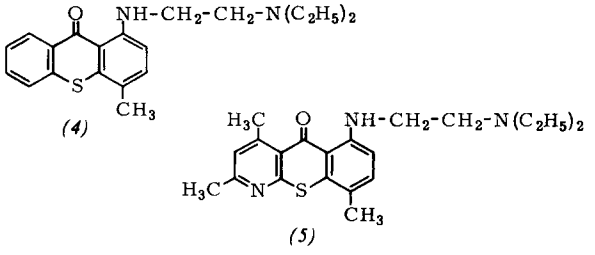



Scheme 2. Antimony-containing antischistomal drugs.

Of the antimony-free schistosomicidal agents, only the thioxanthone derivatives have proved useful in practice. Around 1932, xanthone and thioxanthone derivatives

[2] *E. A. H. Friedheim et al.*, Amer. J. trop. Med. Hyg. *3*, 714 (1954); *P. Cavier*, Biol. medicale *49*, 201 (1960).

containing dialkylaminoalkylamino side-chains were produced as antiprotozoal drugs. These compounds also displayed a therapeutic effect in mice infected with *S. mansoni*[3], but they were not sufficiently active against *S. haematobium* in man. They may be given orally but are relatively toxic. The best-known compound *(4)* in this group is marketed under the names Miracil D® (Bayer) and Nilodin® (Burroughs Wellcome).




Scheme 3. Thioxanthone preparations.

Our preparation CIBA 17,581-Ba *(5)*[4] exhibited good therapeutic action in mice infected with *S. Mansoni*, but clinically had the same disadvantages as Nilodin® and was consequently abandoned. However, we continued to use this compound for some time afterwards as a comparative substance in experiments *in vivo*. Recently, Sterling-Winthrop found that a metabolite of *(4)* in which the methyl group is hydroxylated is equally effective but ten times less toxic[5].

## 4. Experimental Testing

Before any experimental work can be undertaken in the field of schistosomiasis, a suitable model for microbiological testing must be available. The customary *in vitro* test methods such as are used to determine the antibacterial activity of antibiotics have only a limited value in the case of schistosomes, because the damage to the parasites does not become visible until a fairly late stage. During the relatively long period before the drug begins to take effect (at least 2 days), environmental factors may come into play and lead to artefacts in the results. It is thus better to leave the flukes in their natural surroundings, *i.e.* in the blood vessels of the infected host.

In the years 1948/1949, workers in English and German Institutes succeeded in reproducing the natural development cycle of *S. mansoni* in the laboratory. The preferred experimental animal is the white mouse, which usually harbours about 20 paired adult worms in the vessels of the intenstinal tract six weeks after infection with 100 cercaria. As in man, eggs are found in the feces, and also in the liver. With animals uniformly infected in this way it becomes possible to test drugs under reproducible conditions.

[3] *W. Kikuth et al.*, Naturwissenschaften *33*, 253 (1946); Amer. trop. Med. Parasitol. *42*, 256 (1948).

[4] *K. Meier*, unpublished work.

[5] *D. Rosi et al.*, Nature (London) *208*, 1005 (1965).

## 5. Natural and Synthetic Nitro Compounds

Since 1948 we have been synthesizing and screening nitro compounds, in particular heterocyclic nitro compounds, in the hope of finding effective antibacterial and/or antiparasitic substances. It was about this time that chloramphenicol, an antibiotic with a nitro substituent on an aromatic nucleus, was discovered.

Later it became evident that natural organic nitro compounds are much more common than had previously been supposed. They are consitutents of plant material or metabolites of microorganisms. The nitro group may be bound aliphatically or aromatically. 3-Nitropropionic acid, for instance, occurs fairly frequently in Nature; in the plant it is bound in the form of glycosides, *e.g.* in the roots of the sweet violet (*Viola odorata*). The antibiotic azomycin (2-nitroimidazole) is an example of a naturally-occurring heterocyclic nitro compound; it combines rather low toxicity in warm-blooded animals with potent antibacterial activity.

A large number of nitro compounds has been synthesized in recent years, some of which are suitable for use as insecticides, herbicides, or fungicides. Among the nitroheterocycles, some nitrofuran derivatives, in particular, have proved useful as bactericides and antiprotozoal agents in human and veterinary medicine. Some simple nitrothiazole derivatives are also employed as antiprotozoal agents, especially in veterinary medicine.

We have been concerned particularly with nitro derivatives of the furan, thiophene, imidazole, pyrazole, thiazole, pyridine, and pyrimidine compounds, and with some dinitroheterocycles and anellated nitroheterocycles. Some of these substances possess interesting antibacterial and antiparasitic properties, but none of them meets the demands made nowadays on drugs.

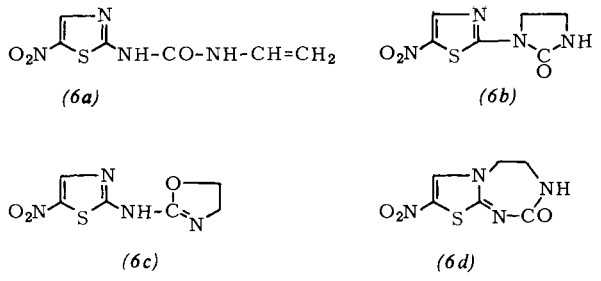
## 6. Nitrothiazoles

### a) Synthesis and Elucidation of the Structure of 1-(5-Nitro-2-thiazolyl)-2-imidazolidinone

Some years ago we began an intensive study of the nitrothiazole series. Condensation of 2-chloroethyl isocyanate with 2-amino-5-nitrothiazole *(7)* led to *N*-(2-chloroethyl)-*N'*-(5-nitro-2-thiazolyl)urea *(8)*, which displayed an interesting activity against protozoa. Under neutral or alkaline conditions hydrogen chloride was split off from this compound *(8)*, and a product with the molecular formula $C_6H_6N_4O_3S$ was formed that distinguished itself by its marked activity against *S. mansoni* in the *in vivo* test described above. After daily doses of 2 mg per mouse for one week no living flukes were found on subsequent autopsy[6].

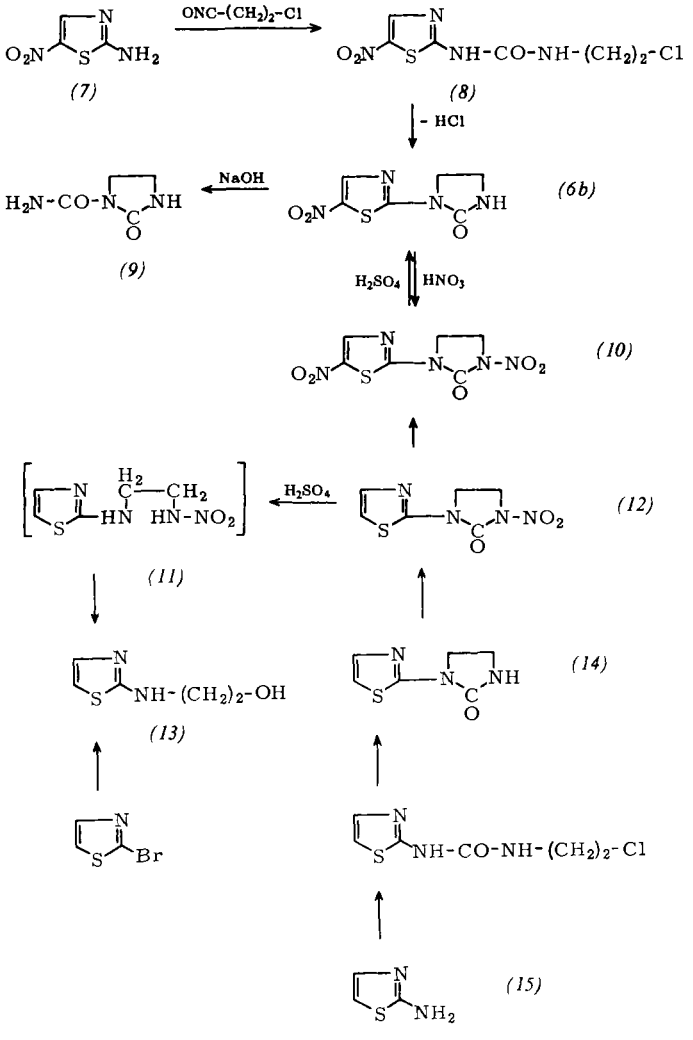
The molecular formula and the nature of the starting materials indicated that the effective compound would have one of the following formulae:

[6] *C. R. Lambert, M. Wilhelm, U. Striebel, F. Kradolfer*, and *P. Schmidt*, Experientia *20*, 452 (1964).



(6a) (6b) (6c) (6d)

In contrast to *N*-ethyl-*N'*-(5-nitrothiazolyl)urea *(27)*, the compound thus obtained is insoluble in cold 1 N sodium hydroxide solution. The characteristic signals of the allyl group are not present in its $^1$H-NMR spectrum. Thus formula *(6a)* is excluded. Degradation reactions (see Scheme 4) indicated that we are dealing with structure *(6b)*, and not structures *(6c)* or *(6d)* [7].



Scheme 4. Degradation of 1-(5-nitro-2-thiazolyl)-2-imidazolidinone.

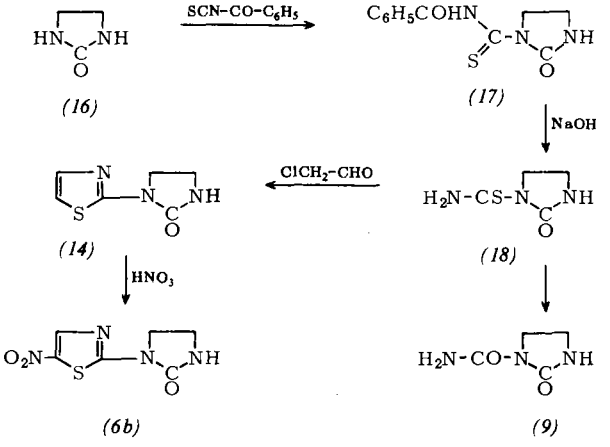
1-(2-Thiazolyl)-2-imidazolidinone *(14)* was obtained by treatment of 2-aminothiazole *(15)* with 2-chloroethyl isocyanate and subsequent cyclization, and on nitration under mild conditions yielded the *N*-nitroimidazolidine *(12)*. The imidazolidinone ring of this substance was cleaved by treatment with dilute acid, 2-(2-thiazolylamino)ethanol *(13)* being formed. This degradation product was also obtained from 2-bromothiazole and ethanolamine. We believe that the degradation proceeds by the way of the *N*-nitroamine *(11)*.

[7] *M. Wilhelm, F. H. Marquardt, Kd. Meier*, and *P. Schmidt*, Helv. chim. Acta, in press.

The *N*-nitroimidazolidinone derivative *(12)* was converted by one mole of nitric acid into the dinitro derivative *(10)*, which was also obtained on nitration of our compound *(6b)*; the dinitroimidazolidinone *(10)* was converted by dilute sulfuric acid into the original mononitroimidazolidinone derivative *(6b)*.

The thiazole ring of our product *(6b)* was opened by sodium hydroxide solution, and 2-oxoimidazolidine-1-carboxamide *(9)* was isolated as fission product; this had already been described by *Jankiewicz-Wasowska* [8] and was synthesized by us by a different route.

These two degradation reactions are strong evidence for the structure *(6b)*. Additional proof was provided by synthesis from 2-imidazolidinone:



Scheme 5. Synthesis of 1-(5-nitro-2-thiazolyl)-2-imidazolidinone *(6b)*.

Condensation of 2-imidazolidinone *(16)* with benzoyl isothiocyanate yielded compound *(17)*, and removal of the benzoyl group with alkali then gave the thiocarboxamide *(18)*, which with chloroacetaldehyde gave 1-(2-thiazolyl)-2-imidazolidinone *(14)*. Subsequent nitration again yielded our compound *(6b)*, which was active against schistosomes.

The structure indicated by the reactions was confirmed by X-ray structure analysis.

### b) Structure and Activity of Similar Thiazole Derivatives

The interesting properties of the nitrothiazole derivative *(6b)* induced us to prepare many similar compounds, but very few of them exerted a good schistosomicidal action [9] (cf. Table 1).

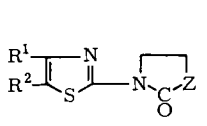
Even a small change in the thiazole ring, such as the introduction of an alkyl or aryl group [compounds *(19)* and *(20)*], gives rise to inactive products. The nitro group in position 5 seems to be essential for activity; if it is omitted, as in *(14)*, or replaced by chlorine, sulfamoyl, or *p*-chlorophenylazo [*(21)*, *(22)*, and *(23)*], the schistosomicidal properties are lost.

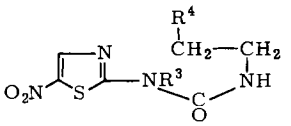
Alkyl substitution in the imididazolidinone ring, as in *(25)*, diminishes the activity; if the ring is enlarged, as in *(24)*, the activity is retained. The open-chain starting material *(8)* is about one-third as active as compound *(6b)*, but the ethylurea derivative *(27)* is inactive. The chloroethyl compound *(8)* probably is partly converted into *(6b)* in the organism.

[8] *J. Jankiewicz-Wasowska*, Roczniki Chem. *34*, 85 (1960).

[9] *M. Wilhelm* and *P. Schmidt*, Acta tropica Suppl. *9*, 3 (1965).

Table 1. Action of thiazole derivatives on *Schistosoma mansoni* in mice (+++ strong, ++ medium, + weak, 0 inactive).



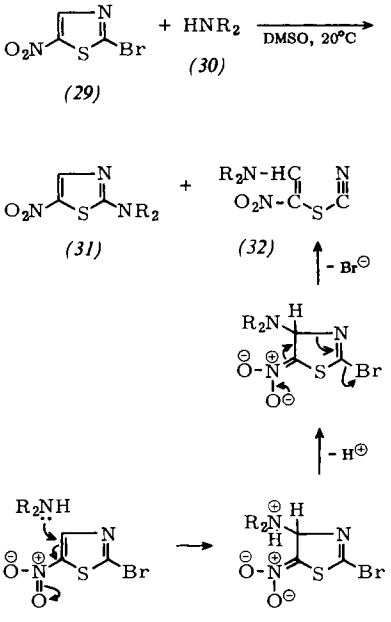


| Compound | $R^1$ | $R^2$ | Z | $R^3$ | $R^4$ | Activity |
|---|---|---|---|---|---|---|
| *(6b)* | H | $NO_2$ | NH | | | +++ |
| *(19)* | Alkyl | $NO_2$ | NH | | | 0 |
| *(20)* | Aryl | $NO_2$ | NH | | | 0 |
| *(14)* | H | H | NH | | | 0 |
| *(21)* | H | Cl | NH | | | 0 |
| *(22)* | H | $SO_2-NH_2$ | NH | | | 0 |
| *(23)* | H | $N=N-C_6H_4$-*p*-Cl | NH | | | 0 |
| *(24)* | H | $NO_2$ | $CH_2$--NH | | | +++ |
| *(25)* | H | $NO_2$ | *N*-Alkyl | | | ++ |
| *(26)* | H | $NO_2$ | $CH_2$ | | | 0 |
| *(8)* | | | | H | Cl | + |
| *(27)* | | | | H | H | 0 |
| *(28)* | | | | $CH_3$ | H | 0 |

We then wondered whether a tertiary nitrogen atom must be present; however, this is apparently insufficient since *N'*-ethyl-*N*-methyl-*N*-(5-nitro-2-thiazolyl)urea *(28)* is inactive.

If the NH group of the imidazolidinone ring is replaced by a methylene group, as in *(26)*, the activity is lost.

The nitrothiazole ring is not particularly stable and is destroyed by warm sodium hydroxide solution. *Ilvespää*[10] isolated fission products by treating 2-bromo-5-nitrothiazole with amines:



Scheme 6. Cleavage of 5-nitrothiazole derivatives.

Condensation of 2-bromo-5-nitrothiazole *(29)* with secondary amines *(30)* often gives two isomeric products *(31)* and *(32)*. The infrared spectrum of *(31)* shows the bands of the expected condensation product, 2-dialkylamino-5-nitrothiazole, whereas a sharp band at 4.63 μ and a very intense band at 6.18 μ in the spectrum of *(32)* indicate a thiocyanate group and a C=C linkage. The presence of the thiocyanate group in compound *(32)* could be shown also by the appearance of a red color upon treatment with iron(III) salts, whereas compound *(31)* displayed no color reaction in this test. The nuclear magnetic resonance spectra of the two compounds are very similar and correspond to what was expected.

The formation of compound *(32)* can be explained by the fact that the secondary amine *(30)* adds to the carbon atom at position 4, which has been rendered positive by the nitro group; the ring then opens, hydrogen bromide being eliminated. Sterically hindered amines give a notably higher yield of compound *(32)* than do simple amines; for instance, dicyclohexylamine yielded virtually only the thiocyanate *(32)*, R = $(CH_2)_6$, whereas only 2-dimethylamino-5-nitrothiazole was obtained when dimethylamine was used. Thus the amine can attack position 2 or 4 of 2-bromo-5-nitrothiazole, substitution at position 2 being more difficult for bases with strong steric hindrance. If the activation energy required to effect substitution at position 2 is high, addition takes place at position 4 and the ring subsequently opens.

As expected, the ring remains intact when primary amines are used.

## 7. Clinical Results

After exhaustive pharmacological, toxicological, and biochemical study, 2-(5-nitro-2-thiazolyl)-2-imidazolidinone *(6b)* (Ambilhar®) was administered for the first time in late 1963 to patients infected with *S. haematobium*. An abrupt decline in the number of viable schistosome ova in the patients' urine was observed, and their general condition improved rapidly, accompanied by an increase in body weight; soon no viable eggs were found in the urine of the patients, indicating that the flukes had been destroyed[11].

Since these first clinical trials, thousands of cases of schistosomiasis have been treated. It soon became apparent that our compound is active against all three types of human schistosome and assures a parasitological cure, provided the treatment is carried out correctly[12]. The effective therapeutic dose is 25 mg/kg administered daily over a period of 5–7 days.

## 8. Mode of Action

1-(5-Nitro-2-thiazolyl)-2-imidazolidinone is particularly active against the mature forms of the parasite, females being clearly more susceptible than males. The first detectable result is the effect on oviposition, which is inhibited already by $^1/_4$ to $^1/_5$ of the schistosomicidal dose[13].

It therefore seemed worthwhile to investigate the absorption of the drug by the host and by the parasite[14]. For this purpose, mice that had been experimentally infected with *S. mansoni* were treated with $^{14}C$-labeled nitrothiazolylimidazolidinone. Autoradiography of the

[10] *A. O. Ilvespää*, Helv. chim. Acta, in press.

[11] *C. R. Lambert* and *F. S. Cruz Ferreira*, Bull. World Health org. *32*, 73 (1963).

[12] *C. R. Lambert*, Acta tropica *23*, 1 (1966).

[13] *H. P. Striebel* and *F. Kradolfer*, Acta tropica Suppl. *9*, 54 (1965).

[14] *R. Hess*, *J. W. Faigle*, and *C. R. Lambert*, Nature (London) *210*, 964 (1966).

host tissues and of the parasites showed that the radioactivity was concentrated largely in the mature flukes and in the eggs. Females absorbed more of the radioactive substance than did males. The level of radioactivity was appreciably higher in the deposited eggs than in the surrounding tissues, as is shown in the micro-autoradiogram of a liver section reproduced in Figure 2. There was a high concentration also in the mucous lining of the stomach and in the intestines.

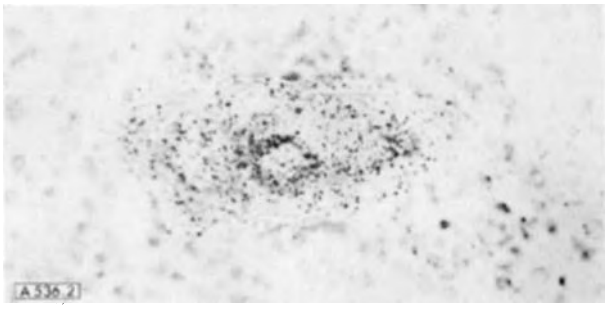



Fig. 2. Micro-autoradiogram (540×) of schistosome ova in the liver of a mouse 24 hours after treatment with 1 g/kg *p.o.* of Ambilhar®.

In the light of our findings, it may be assumed that the mode of action is as follows. Owing to the presence of the imidazolidinone ring [or of the perhydrodiazinone ring in *(24)*], the nitrothiazole derivative is selectively absorbed by the schistosomes and their eggs; the nitro group then exerts its influence on metabolism, perhaps by blocking a redox enzyme. This assumption is all the more plausible in view of the fact that metabolites and synthetic substances without the nitro group displayed no activity.

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# Methods for the Synthesis of Uniform Polymers

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*The difficulties encountered in the preparation of polymers that are uniform chemically, structurally, and in their molecular weight are due mainly to the wide variety of possible polymers. This article gives a review of attempts to synthesize homogeneous polymers by chain reactions and by stepwise synthesis. Syntheses on templates are extremely important in living cells; methods have recently been found for syntheses of this type that are independent of natural processes. Uniform polymers can also be obtained by reactions on existing polymers. In replicating polymers, this in principle requires the modification of only one polymer molecule.*

## 1. Introduction

### a) The Problem

Polymers are substances formed by the linkage of low molecular weight compounds (monomers) and containing continuous sequences of covalent bonds as in long-chain hydrocarbons (but all the atoms need not be C atoms). The number of monomer units present in a polymer molecule (*i.e.* its degree of polymerization) may be as large as desired. Polymers are characterized by the many possibilities regarding the nature and number of monomer units, the manner in which they are combined, and the side reactions accompanying the synthesis of the polymer.

Owing to this variability, it is very difficult to prepare monodisperse polymers, *i.e.* polymers whose molecules are identical in structure and size. Any side reactions occurring during the preparation of the polymer will affect a much larger proportion by weight of the reaction mixture than in reactions involving only small molecules. Finally, it has been found that the difficulty of isolation and purification increases with the molecular weight of the polymer. For a long time, the chemistry of synthetic polymers was concerned almost exclusively with ill-defined, heterogeneous, amorphous substances. On the other hand, many uniform polymers occur in Nature, some with very high degrees of polymerization, the correct structure of which is essential to the life processes. It was expected that homogeneous synthetic polymers would have better mechanical properties and thermal stability.

This expectation was confirmed when a number of structurally identical, crystallizable polymers had been prepared in the laboratory. Methods have now been developed for the preparation of polymer molecules of uniform length. Even very complex polymers similar to those in Nature and exhibiting biological activity can now be synthesized uniformly with or without the aid of natural substances [1].

### b) The Concept of Uniformity

It is usual to speak of chemical uniformity, structural uniformity, and uniformity of molecular weight. A polymer is chemically uniform if each molecule has the same composition. Homopolymers, by definition, contain only one type of monomer unit (apart from the ends of the chains), so that these polymers satisfy the

[1] Cf. *J. H. Winter*: Die Synthese von einheitlichen Polymeren. Springer, Berlin-Heidelberg-New York, in press.

above condition. However, if a polymer contains more than one type of monomer unit (copolymers), it can be chemically uniform only if the monomer units are present in the same ratio in all molecules and are joined together in a regular manner. (Random distribution of the different monomer units merely presents an illusion of chemical uniformity.) In most polymer syntheses, each monomer unit is linked to *two* other monomer units; the resulting chains should therefore be unbranched. This linearity of the chains is an important criterion of chemical uniformity. Another criterion is the uniformity of the end groups.

In connection with the structure of the polymers, let us consider first their microstructure. The mode of linkage of monomer units of the type $-(A-A')-$ in the polymer chain is important. An arrangement often encountered is

$$-(A-A')-(A-A')-(A-A')-.$$

In polyvinyl compounds and polyolefins, this is known as the head-to-tail arrangement (the substituted C atom being the head). Another factor is the spatial arrangement of the substituents on the C atoms in the chain (*e.g.* the methyl group in polypropylene). These C atoms are asymmetric centers. Following *Natta*, the simplest regular arrangements (with uniform head-to-tail linkage) of the monomer units are known as the isotactic (*d,d,d,d*... or *l,l,l,l*...) and syndiotactic (*d,l,d,l,d,l*...) arrangements of the substituents (Fig. 1)[2].

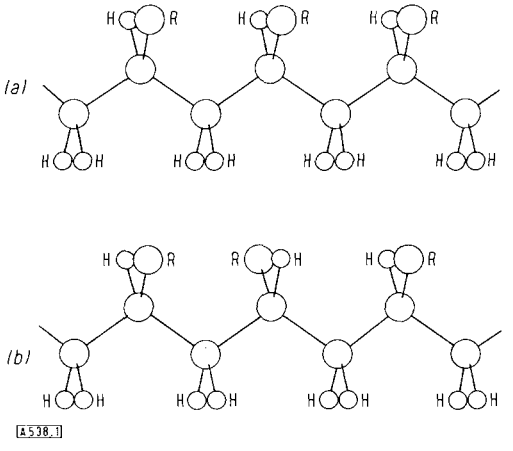



Fig. 1. Model of tactic polymers with head-to-tail monomer units; it is arbitrarily assumed that the chains are extended linearly. (a) isotactic, (b) syndiotactic arrangement of the substituents.

The presence of carbon-carbon double bonds offers the possibility of *cis-trans* isomerism. Configurations of this type in a polymer may again be uniform or nonuniform. The mobility of the chain atoms with respect to one another (*e.g.* "free" rotation about C–C single bonds) enables polymers to assume different conformations, and this is another structural factor. Whereas polymers in solution and in the amorphous state are mainly in the form of random coils, they form certain preferred chain conformations on crystallization. Special mention should be made of the helix structure, which is encountered in many natural macromolecules and in synthetic polymers with regular microstructures.

[2] *G. Natta*, J. Polymer Sci. *16*, 143 (1955).

The measured molecular weight of a polymer generally is an average value. Depending on the method used, the value obtained may be the number-average molecular weight $\overline{M}_n$ or the weight-average $\overline{M}_w$, the latter always being greater. The closer the ratio $\overline{M}_w/\overline{M}_n$ to unity, the more uniform is the molecular weight of the polymer.

## 2. Syntheses Based on Classical Methods

### a) Chain Reactions

The synthesis of a polymer by a chain reaction begins with a reaction (initiation) between an activated substance R* (free radical or ion) as the initiator (sometimes as part of a "catalyst") and a cyclic or unsaturated monomer molecule. As a result, two valences are made available in the monomer by the opening of the double bond or of the ring. The initially activated substance

Free-radical polymerization:

$$R^{\bullet} + n\,CH_2{=}CHCl \xrightarrow[\text{Initiation}]{} R\text{-}CH_2\text{-}C^{\bullet}HCl + (n-1)\,CH_2{=}CHCl$$

$$\xrightarrow[\text{Propagation}]{} R\text{-}(CH_2\text{-}CHCl)_{n-1}\text{-}CH_2\text{-}C^{\bullet}HCl$$

Cationic polymerization:

$$H^{\oplus}\cdots(BF_3OH)^{\ominus} + n\,H_2C\text{-}CH_2 \xrightarrow{\text{Initiation}}$$

$$\left[HO\text{-}CH_2\text{-}CH_2^{\oplus}\cdots(BF_3OH)^{\ominus}\right] + (n-1)\,H_2C\text{-}CH_2$$

$$\rightarrow HO\text{-}CH_2\text{-}CH_2^{\oplus}\cdots(BF_3OH)^{\ominus} + (n-1)\,H_2C\text{-}CH_2$$

$$\xrightarrow[\text{Propagation}]{} H(O\text{-}CH_2\text{-}CH_2)_{n-1}\text{-}O\text{-}CH_2\text{-}CH_2^{\oplus}\cdots(BF_3OH)^{\ominus}$$

Anionic polymerization:

$$R^{\ominus}\cdots Li^{\oplus} + n\,H_2C{=}C(CH_3)(CO{-}OCH_3) \xrightarrow{\text{Initiation}}$$

$$\left[R\text{-}CH_2\text{-}C(CH_3)(CO{-}OCH_3)\cdots Li^{\oplus}\right] + (n-1)\,H_2C{=}C(CH_3)(CO{-}OCH_3)$$

$$\rightarrow R\text{-}CH_2\text{-}C(CH_3)(CO{-}OCH_3)\cdots Li^{\oplus} + (n-1)\,H_2C{=}C(CH_3)(CO{-}OCH_3) \xrightarrow{\text{Propagation}}$$

$$R\text{-}\left[CH_2\text{-}C(CH_3)(CO{-}OCH_3)\right]_{n-1}\text{-}CH_2\text{-}C(CH_3)(CO{-}OCH_3)\cdots Li^{\oplus}$$

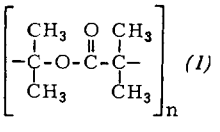
usually becomes linked to the monomer by one of these valences, while the other is used for linkage with another monomer unit, and this process continues (chain growth or propagation).

Whether a chemically uniform polymer can be formed depends on the choice of initiators or catalysts, the monomers, and the other substances present in the reaction mixture. For example, organic peroxides give free radicals that tend to cause side reactions (this tendency is much smaller for azo compounds). Ionic catalysts often react with functional groups in the monomer. As a general rule, the smaller the number of monomer types and of other reacting substances (including impurities) and the higher the activation energies of possible side reactions relative to that of the propagation steps, the easier will be the formation of a chemically homogeneous polymer.

Reactions with high activation energies are relatively unimportant at low temperatures. Reactions of the growing polymers with one another are suppressed by dilution and by polymerization to low conversions. Thus essentially linear homopolymers and copolymers can be obtained by all types of polymerization.

In copolymerization it is not unusual for a monomer unit A at the active end of the polymer to react only with difficulty or not at all with the monomer A, but to react readily with the monomer B, and *vice versa*. The resulting polymer, irrespective of the monomer concentrations, then has an alternating monomer sequence ...A–B–A–B–A–B... An example is the free-radical copolymerization of olefins with sulfur dioxide to form polysulfones [3]. However, the same result can be obtained if only one of the two monomers does not react readily with itself. The concentration of this monomer must then be kept high relative to the other during polymerization.

Thus dimethylketene and acetone, which by itself does not polymerize under these conditions, react alternately at −60 °C in toluene with butyl-lithium as catalyst to give a highly crystalline polyester *(1)* [4].

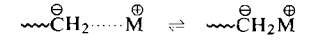


*(1)*

Dimethylketene and benzaldehyde react similarly [5]. Alternating copolymerization of ethylene with *cis*-2-butene [6] and cyclopentene [7] (and possibly also butadiene [8]) can also be achieved by the use of Ziegler-Natta catalysts. In order to prevent homopolymerization of the ethylene, the other component must always be present in excess.

The activation energy for the incorporation of monomers depends on the mode of addition (*i.e.* head-to-tail, head-to-head). The uniform head-to-tail addition is generally favored on steric grounds, since this is the position in which the substituents present the least hindrance to one another. However, this also means that the monomer unit at the active end of the polymer has a directing influence on the incoming monomer. In polymers in which the substituents on the centers of asymmetry can assume *d* or *l* arrangements, the activation energy for head-to-tail polymerization, for example, in the isotactic position is different from that for the syndiotactic position. In free chain growth, as generally occurs in free-radical polymerization, syndiotactic steps have the lower activation energy. Polymethyl methacrylate prepared by free-radical polymerization contains 75 % of syndiotactically arranged substituents when prepared at room temperature [9], and almost 100 % when prepared at −78 °C.

"Free chain growth" means that the monomer can approach the active polymer ends and can combine directly with the free valences of the terminal monomer units. If the chain growth is not free, the activation energies of the propagation steps change, so that the probabilities of the various steps may change. For example, highly crystalline polyvinyl chloride (crystallinity 80 %) is obtained even at 50 °C by free-radical polymerization in butyraldehyde, whereas the crystallinity is only 10 % in the absence of butyraldehyde [10]. It may be assumed that the butyraldehyde becomes attached to the polymer radical and influences the addition of monomer. Effects of this type are more pronounced in ionic polymerization, where the oppositely charged ion (counterion) can influence the conditions at the active polymer ends. At least two states are possible at the active polymer ends, *i.e.* the state of a dissociated ion pair and that of an undissociated ion pair [11, 12].



In the dissociated state, relatively free, fairly rapid growth occurs at the active chain end. As in free-radical polymerization, this leads to a sterically irregular arrangement of the monomer units, which becomes increasingly syndiotactic as the temperature is lowered. At undissociated ion pairs, on the other hand, the probabilities of the different types of linkage are reversed, so that isotactic addition occurs.

An interesting example is the polymerization of methyl methacrylate with lithium catalysts. At −60 °C in a nonpolar solvent such as hexane, the product is predominantly isotactic [13, 14]. In this system the ion pair at the growing

[3] For recent work see *R. E. Cook, F. S. Dainton*, and *K. J. Ivin*, J. Polymer Sci. *26*, 351 (1957); *29*, 549 (1958).

[4] *G. Natta, G. Mazzanti, G. Pregaglia*, and *M. Binaghi*, J. Amer. chem. Soc. *82*, 5511 (1960).

[5] *G. Natta, G. Mazzanti, G. Pregaglia*, and *G. Pozzi*, J. Polymer Sci. *58*, 1201 (1962).

[6] *G. Natta, G. Dall'Asta, G. Mazzanti*, and *F. Ciampelli*, Kolloid-Z. u. Z. Polymere *182*, 50 (1962).

[7] *G. Natta, G. Dall'Asta, G. Mazzanti, I. Pasquon, A. Valvassori*, and *A. Zambelli*, Makromolekulare Chem. *54*, 95 (1962).

[8] *G. Natta, A. Zambelli, I. Pasquon*, and *F. Ciampelli*, Makromolekulare Chem. *79*, 161 (1964).

[9] *W. G. Gall* and *N. G. McCrum*, J. Polymer Sci. *50*, 489 (1961).

[10] *I. Rosen, P. H. Burleigh*, and *J. F. Gillespie*, J. Polymer Sci. *54*, 31 (1961).

[11] *C. Geacintov, J. Smid*, and *M. Szwarc*, J. Amer. chem. Soc. *83*, 1253 (1961).

[12] *H. Hostalka, R. V. Figini*, and *G. V. Schulz*, Makromolekulare Chem. *71*, 198 (1964).

[13] *T. G. Fox, B. S. Garrett, W. E. Goode, S. Gratch, J. F. Kincaid, A. Spell*, and *J. D. Stroupe*, J. Amer. chem. Soc. *80*, 1768 (1958).

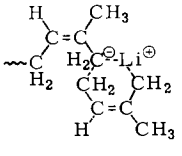
[14] *D. Braun, M. Herner, U. Johnsen*, and *W. Kern*, Makromolekulare Chem. *51*, 15 (1962).

polymer end is undissociated. In polar solvents such as dimethoxyethane, on the other hand, the ion pair is strongly dissociated; the influence of the counter-ion is therefore practically eliminated, free growth can occur, and predominantly syndiotactic polymer is formed.

The tendency towards dissociation of the ion pairs is determined by the polarity of the solvent and the degree of solvation of the ions [15]. The tendency towards solvation increases with decreasing ionic radius and with increasing polarity of the solvent, sometimes also of the monomer.

In growth on the undissociated ion pair, the incoming monomer is probably first coordinately bound [16]. It is therefore oriented with respect to the polymer end, and can add to the chain stereospecifically. A process of this type is particularly likely with monomers containing functional groups that serve merely to enhance the coordination and orientation. This is probably why monomers containing ether, carbonyl, amino, or similar groups or with a second double bond are particularly suitable for stereospecific polymerization. Examples are vinyl alkyl ethers, alkenyl alkyl ethers, alkoxystyrenes, vinylcarbazoles, and β-chlorovinyl ether, which can be polymerized cationically, and butadiene, isoprene, styrene, 2-vinylpyridine, esters of sorbic acid, acrylates, and methacrylates, which can be polymerized anionically to give stereoregular polymers.

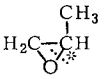
An energetically favored six-membered ring in the *cis*-position may be initially formed with the monomer [17] as the activated coordination complex [*(2)*], (*e.g.* in the ionic polymerization of isoprene).



*(2)*

Even in orientation of the monomer on the ion pair, the terminal monomer unit, and the polymer chain as a whole, still has some directing effect [18]. On the whole, the stereospecificity of a catalyst depends on the interaction of all the substances taking part in the reaction.

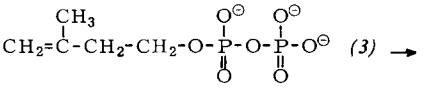
The syntheses of optically active polymers are particularly impressive. For example, propylene oxide generally is a racemic mixture, which gives an inactive product on polymerization with potassium hydroxide as catalyst. However, if diethylzinc that has previously been treated with a little water and (+)-borneol is used as the catalyst, the D-(+)-propylene oxide is polymerized preferentially to give an optically active polymer [19]. The remaining monomer mixture is optically active, since the L-isomer predominates. Owing to the asymmetry in the catalyst (due to the borneol), the activation energies for the incorporation of the two isomers are different (asymmetric induction).



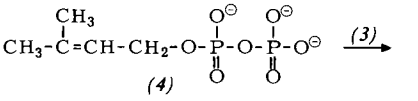
D or L

The first generally convincing stereospecific polymerizations were carried out by *Natta et al.* [20] using Ziegler catalysts. Stereoregular polymers can be prepared with these catalysts even at 100 °C. The mixed catalysts contain a compound of a transition metal in one of its lower oxidation states and an organic compound of a metal from Groups I to III of the periodic system [21]. A typical example is the system $TiCl_3$–$Al(C_2H_5)_2Cl$. The titanium compound forms a crystalline phase of colloidal dimensions, and complexes are formed on the crystal surfaces with the aluminum compound. The active centers from which the polymer grows, generally by an anionic mechanism, are located here. The monomer is again assumed to be coordinately bonded to the active centers [22]. The presence of crystal surfaces undoubtedly contributes to the high stereospecificity of these systems. Important examples are the essentially linear polyethylene and the predominantly isotactic polypropylene obtained by this method at high temperatures [23].

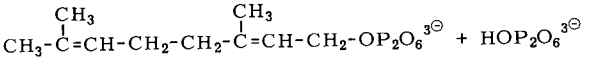
The catalysts with the greatest specificity are produced by Nature in the form of the enzymes. An example of an enzyme-catalysed chain reaction is the synthesis of natural rubber, which was elucidated by *Lynen et al.* [24]. In the chain initiation, the monomer 3-methyl-3-butenyl pyrophosphate *(3)* is isomerized to 3-methyl-2-butenyl (dimethylallyl) pyrophosphate *(4)* by the enzyme isomerase. Another enzyme catalyses the linkage with the next molecule of substrate *(3)*, the pyrophosphate group being eliminated.



*(3)*



*(4)*



Since a new allyl pyrophosphate group is simultaneously introduced, further molecules of the substrate can be introduced in the same manner. The double bond assumes the *cis*-configuration.

Polymers of uniform molecular weight generally are difficult to obtain by chain reactions, since the reactivity of the active polymer end is practically independent of the chain length. Further, chain termination and chain transfer also frequently take place independently of the

[15] *S. S. Medvedev* and *A. R. Gantmakher*, J. Polymer Sci. *C4*, 173 (1963).

[16] *G. Natta*, Angew. Chem. *71*, 205 (1959).

[17] *R. S. Stearns* and *L. E. Forman*, J. Polymer Sci. *41*, 381 (1959).

[18] *T. Higashimura, T. Watanabe, K. Suzuoki, S. Okamura*, and *I. Iwasa*, J. Polymer Sci. *C4*, 361 (1963).

[19] *T. Tsuruta, S. Inoue, M. Ishimori*, and *N. Yoshida*, J. Polymer Sci. *C4*, 267 (1963).

[20] *G. Natta, P. Pino, P. Corradini, F. Danusso, E. Mantica, G. Mazzanti*, and *G. Moraglio*, J. Amer. chem. Soc. *77*, 1708 (1955).

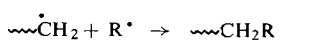
[21] *K. Ziegler, E. Holzkamp, H. Breil*, and *H. Martin*, Angew. Chem. *67*, 541 (1955).

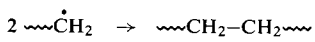
[22] Cf. *G. Natta*, J. Polymer Sci. *48*, 219 (1960).

[23] Cf. *G. Natta, A. Zambelli, I. Pasquon, G. Gatti*, and *D. DeLuca*, Makromolekulare Chem. *70*, 206 (1964).

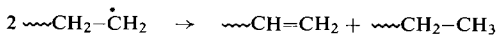
[24] *F. Lynen* and *U. Henning*, Angew. Chem. *72*, 820 (1960).

molecular weight. In free-radical polymerization, the principal termination reactions are the combination of a polymer radical with an initiator radical or with another polymer radical

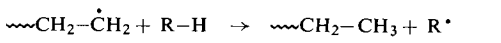




and the disproportionation of polymer radicals



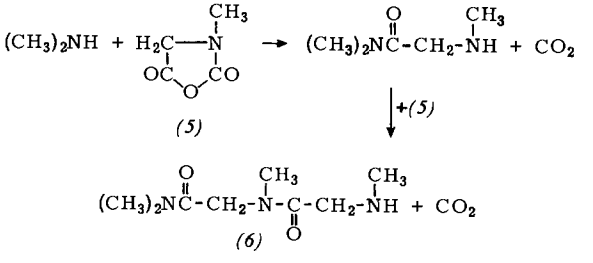
However, the polymer radical may also become saturated by abstraction of an atom or group from another molecule, so that the reaction chain is carried on by the new radical formed (chain transfer):



All these processes occur randomly. In ionic polymerization and in polymerization on Ziegler-Natta catalysts, chain transfer also occurs, mainly to the monomer, as well as catalyst decomposition, side reactions at the active polymer ends, and depolymerization, which also proceed randomly.

Polymers of uniform molecular weight are therefore formed only if none of these reactions take place. Moreover, the growth of all polymer chains must begin as nearly as possible simultaneously and proceed at the same rate. Several cases are now known in which these conditions are approximately satisfied.

For example, in the polymerization of sarcosine *N*-carboxylic anhydride *(5)*, $CO_2$ is eliminated, and a polypeptide *(6)* [25] having a uniform molecular weight is formed. The chain reactions are initiated with protonic substances. Each propagation step leads to the formation of a peptide that is also

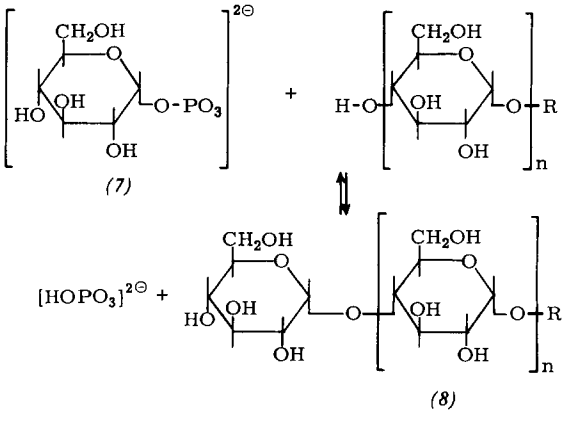


protonic, but very stable in this form in the absence of the monomer. No side reactions occur in acetophenone with secondary amines as initiators. The chains grow at the same rate, so that the molecular weight of the product is fairly uniform [26].

The polymerization of ethylene oxide with protonic substances proceeds similarly, and can also lead to polymers with narrow distributions of molecular weight ($M_n$ = 44000, $M_w/M_n$ = 1.1) [27].

Anionic polymerizations with metal cations are other examples. Many organo-alkali metal compounds, when used as catalysts, give such stable ion pairs that the polymer ends remain active (the polymers remain "living") [28]. However, these processes are very sensitive to impurities. The reaction conditions must be such that either all the polymer anions grow freely or all the ion pairs at the polymer ends are undissociated. For example, in the case of a polystyrene anion with a sodium cation, the dissociation of the ion pairs can be suppressed by the addition of sodium salts that are soluble in the reaction medium [29]. The polymerization then proceeds more slowly, but uniformly. Rapid mixing of the catalyst and the monomers is important, particularly when initiation is slow [30]. In pre-initiation, the whole of the catalyst is first allowed to react with small quantities of monomer [31]. In this way all the chains are initiated, but the degrees of polymerization remain low. The actual polymerization then takes place simultaneously for all polymer molecules as the monomer is added. The "living" polymers must be deactivated by termination when the desired degree of polymerization has been reached; the latter is given by the ratio of the number of monomer molecules to the number of catalyst molecules.

The enzyme-catalysed synthesis of amylose *(8)*, which proceeds *in vitro* in the presence of phosphorylase, can also be carried out in accordance with the above principle [32]. The substrate is glucose-1-phosphate *(7)*, which polymerizes in a chain reaction with elimination of phosphate.



Initiators, such as maltosaccharides containing more than two glucose units, are required. The initiation can be carried out rapidly, and amyloses with very uniform degrees of polymerization (up to 500) can be obtained.

However, polymers of perfectly uniform molecular weight can never be obtained by the above methods. Nevertheless, narrow distributions (Poisson distributions) of the molecular weights are obtained.

### b) Stepwise and Stagewise Synthesis of Polymers

In many polymer syntheses, the two sites of linkage of the monomer react practically independently. Thus

[25] *S. G. Waley* and *J. Watson*, Proc. Roy. Soc. (London) *A199*, 499 (1949).

[26] Cf. *W. J. Ritschard*, Makromolekulare Chem. *29*, 141 (1959); *B. Hargitay*, *A. J. Hubert*, and *R. Buyle*, *ibid. 56*, 104 (1962); *R. D. Lundberg* and *P. Doty*, J. Amer. chem. Soc. *79*, 3961 (1957).

[27] *B. Wojtech*, Makromolekulare Chem. *66*, 180 (1963).

[28] *M. Szwarc*, *M. Levy*, and *R. Milkovitch*, J. Amer. chem. Soc. *78*, 2656 (1956).

[29] *H. Hostalka*, *R. V. Figini*, and *G. V. Schulz*, Makromolekulare Chem. *71*, 198 (1964).

[30] *R. V. Figini*, *H. Hostalka*, *K. Hurm*, *G. Löhr*, and *G. V. Schulz*, Z. physik. Chem. N.F. *45*, 269 (1965); *F. Wenger*, Makromolekulare Chem. *64*, 151 (1963).

[31] Cf. also *D. J. Worsfold* and *S. Bywater*, Canad. J. Chem. *36*, 1141 (1958).

[32] *E. Husemann*, *B. Fritz*, *R. Lippert*, *B. Pfannemüller*, and *E. Schupp*, Makromolekulare Chem. *26*, 181 (1958).

these are not chain reactions in the sense described. A typical example is the polycondensation of a hydroxy acid to a polyester:

$$n\,\mathrm{HO{-}R{-}COOH} \rightarrow \mathrm{H(O{-}R{-}CO)_{n\text{-}1}{-}O{-}R{-}COOH} + (n\text{-}1)\mathrm{H_2O}$$

The process is a mixture of *stepwise* polycondensation (in which one monomer unit is introduced at a time) and *stagewise* polycondensation, in which two polymer fragments combine. This type of monomer will be denoted by a–R–b. Similarly, monomers of the types a–R–a and b–R′–b, each containing two identical functional groups a or b per molecule, combine in an alternating sequence

a–R–ab–R′–ba–R–ab–R′–b.

What has been said about polycondensations is also true when the functional groups combine by addition.

The position of the monomer units of the type a–R–b is fixed by the functional groups. The monomer also determines the centers of asymmetry if these can be introduced unchanged into the polymer, *i.e.* if no racemization or *cis-trans* rearrangement takes place during the synthesis. This can be achieved by the use of mild reaction conditions, in particular low temperatures, by the use of very pure materials, and by catalysis of the linkage reactions.

If it is desired to obtain polymers of this type with uniform molecular weights, the stepwise and stagewise syntheses must not occur randomly, but must proceed in a definite manner. In the case of monomers of the types a–R–a and b–R′–b, one may be used in such a large excess that on grounds of probability only a single linkage step (in both directions in this case) takes place:

$$\mathrm{a{-}R{-}a} + 2\,\mathrm{b{-}R'{-}b} \rightarrow 2\,\mathrm{b{-}R'{-}ba{-}R{-}ab{-}R'{-}b} \qquad (9)$$

or

$$\mathrm{b{-}R'{-}b} + 2\,\mathrm{a{-}R{-}a} \rightarrow \mathrm{a{-}R{-}ab{-}R'{-}ba{-}R{-}a} \qquad (10)$$

If the products *(9)* or *(10)* are now separated from the excess of monomer and then allowed to react with a large excess of the other monomer, the next (double) step also takes place in a controlled manner. Polymer fragments can be joined in accordance with the same principle ("duplication process")[33]:

$$(9) + 2\,(10) \rightarrow (10)\text{–}(9)\text{–}(10)$$

In the cases described, two functional groups can react in each monomer molecule and in each polymer fragment. If only one functional group were present per fragment, it would be easier to obtain uniform polymers, but these would be unable to react further:

$$\mathrm{R{-}a} + \mathrm{b{-}R'} \rightarrow \mathrm{R{-}ab{-}R'}$$

However, it is possible to chemically alter the activities of functional groups, to block them, or to remove them altogether, as well as to introduce new functional groups.

It is therefore also possible to use effectively monofunctional compounds. In the bifunctional monomers a–R–a and b–R′–b, for example, some of the functional groups a may be chemically changed (a′) in such a way that they no longer react with b, and some of the groups b (b′) so that they no longer react with a. The resulting monomers can give only one dimer:

$$\mathrm{a'{-}R{-}a} + \mathrm{b{-}R'{-}b'} \rightarrow \mathrm{a'{-}R{-}ab{-}R'{-}b'} \qquad (11)$$

After conversion of b′ into b or of a′ into a in *(11)*, the process can be continued as follows:

$$\mathrm{a'{-}R{-}ab{-}R'{-}b} + \mathrm{a{-}R{-}a'} \rightarrow \mathrm{a'{-}R{-}ab{-}R'{-}ba{-}R{-}a'} \qquad (12)$$

or

$$\mathrm{a'{-}R{-}ab{-}R'{-}b} + \mathrm{a{-}R{-}ab{-}R'{-}b'} \rightarrow \mathrm{a'{-}R{-}ab{-}R'{-}ba{-}R{-}ab{-}R'{-}b'} \qquad (13)$$

This procedure may be continued as long as the required isolation and purification can still be carried out. It is possible in this way to produce very complex aperiodic polycondensates, *e.g.* polyesters[34], polypeptides, and polynucleotides[35]. The method has very often been used for the synthesis of peptides[36]. The 20 most important naturally occurring amino acids, of which all but glycine are optically active, are used. To prevent racemization, polymerization must be carried out under particularly mild conditions. For example, an amino acid whose amino group is protected by the t-butoxycarbonyl (BOC) group is allowed to react with another amino acid whose amino group is unprotected, but whose carboxyl group is esterified with ethanol. The compounds can be condensed in the presence of dicyclohexylcarbodiimide (DCCI):

$$\mathrm{BOC{-}NH{-}R{-}COOH} + \mathrm{H_2N{-}R'{-}COOC_2H_5} \xrightarrow{\mathrm{DCCI}} \mathrm{BOC{-}HN{-}R{-}COO{-}NH{-}R'{-}COOC_2H_5} + \mathrm{H_2O}$$

After removal of *e.g.* the BOC group, the reaction can be continued. The yields obtained in such syntheses are generally about 80 % per step. Consequently, in a synthesis involving 20 steps, the final yield of uniform material is only about 1 %.

*Merrifield*[37] therefore linked the carboxyl group of the first amino acid of the peptide to an insoluble carrier, *e.g.* a cross-linked polymer

BOC–NH–R–COO-carrier.

All reagents can then be used in excess, so that yields of approximately 100 % per step are obtained. After each reaction, the cross-linked polymer bearing the peptide chains can be filtered off and washed if necessary. When the synthesis is complete, the peptide chains are carefully released from the cross-linked polymer. Other polycondensates can, in principle, also be prepared in this way. The main problem is to find a suitable cross-linked polymer.

A question that arises here is how Nature produces uniform polypeptides and proteins, many of which have

[33] *R. Fordyce, E. L. Lovell,* and *H. Hibbert,* J. Amer. chem. Soc. *61,* 1905 (1939); *W. Kern* and *W. Thoma,* Makromolekulare Chem. *16,* 89 (1955); *W. Kern,* Angew. Chem. *71,* 585 (1959); *W. Kern, H. Kalsch, K. J. Rauterkus,* and *H. Sutter,* Makromolekulare Chem. *44–46,* 78 (1961).

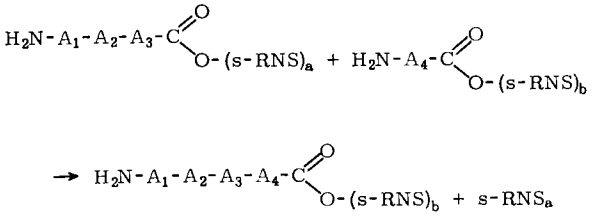
[34] Cf. *H. Zahn, C. Borstlap,* and *G. Valk,* Makromolekulare Chem. *64,* 18 (1963).

[35] For example, see *S. A. Narang, T. M. Jacob,* and *H. G. Khorana,* J. Amer. chem. Soc. *87,* 2988 (1965).

[36] *K. Hofmann* and *P. G. Katsoyannis* in *H. Neurath*: The Proteins. 2nd Ed., Vol. 1, p. 53, Academic Press, New York-London 1963; *Th. Wieland* and *H. Determann,* Angew. Chem. 75, 539 (1963); Angew. Chem. internat. Edit. *2,* 358 (1963); *R. Schwyzer, W. Rittel, H. Kappeler,* and *B. Iselin,* Angew. Chem. *72,* 915 (1960); *H. Zahn, J. Meienhofer,* and *H. Klostermeyer,* Z. Naturforsch. *19b,* 110 (1964).

[37] *R. B. Merrifield,* Biochemistry *3,* 1385 (1964); Science *150,* 178 (1965); *R. B. Merrifield* and *J. M. Stewart,* Nature (London) *207,* 522 (1965).

extremely high molecular weights. The syntheses themselves take place in the cell cytoplasm, and exhibit certain similarities to "stepwise" laboratory syntheses. However, one fundamental difference is that the peptide chains are produced in special centers of synthesis, the ribosomes, one chain being synthesized per ribosome. The information concerning the synthesis, *i.e.* the synthesis program, is carried from the cell nuclei to the ribosomes by nucleic acids, the messenger RNA's (m-RNA). Other nucleic acids, the transfer (soluble) RNA's (s-RNA), are linked by their carboxyl groups to the monomeric amino acids. Special s-RNA's correspond to the various amino acids. The synthesis program is fixed in the m-RNA by the sequence of the nucleotide units, a sequence code (the "genetic code") consisting of a combination of three out of four fundamental units ("codons") being assigned to the amino acids [38]. In accordance with this key system, the amino acids are carried to the growing peptide chains by their s-RNA, which becomes attached for a short time to the m-RNA. The linkage itself is brought about by enzymes, and proceeds in accordance with the following scheme:



$A_1$, $A_2$, *etc.*: amino-acid residues.

## 3. Syntheses on Templates

In the syntheses described so far, the contact of a substance with the active polymer ends favors certain reaction steps, and so leads to a more controlled synthesis. Contact of this nature can be extended to include the whole of the polymer molecule being formed. Such processes are known as syntheses on templates.

A t mplate may be described as a polymeric substance or a crystal of a low molecular weight compound, which exerts a contact effect on the polymer being formed; under favorable conditions, the latter assumes the dimensions of the available contact area. The polymer formed may be related or unrelated to the template substance, and in the extreme case the two are interchangeable or even identical, so that replication of polymers becomes possible. The contact effect is exerted by bonding of the entire polymer being formed to the matrix for a limited time; all types of bonds are possible, and they may differ widely in strength. It must be possible for the polymer molecule to be released intact from the template. Thus a template is simply a catalyst, though this does not mean that no other catalysts and (for chain reactions) initiators are required.

[38] See, *e.g.*, *S. Ochoa*, Ber. Bunsenges. physik. Chem. *68*, 707 (1964).

### a) Crystals of Low Molecular Weight Compounds as Templates

Many studies have been carried out in recent years on polymerizations of crystalline monomers. The monomer molecules rearrange in the crystal lattice and form the polymer. The polymer occupies a smaller volume than its monomers. If the contraction on polymerization is not too great, the crystal lattice of the monomer should impose order on the polymer, *i.e.* it should act as a template.

However, only a few examples of this nature are known: Solid methyl methacrylate (mixed with magnesium) undergoes free-radical polymerization at −100 °C to form isotactic polymethyl methacrylate, though it normally gives a syndiotactic polymer at low temperatures [39]. This observation can only be explained by the influence of the solid monomer. Solid trioxane gives a crystalline polymer whose chains are arranged parallel to the trigonal axis of the monomer crystal [40]. Crystalline polymers of high structural uniformity are also formed in the crystalline monomers diketene, β-propiolactone, and 3,3-bis(chloromethyl)oxetane [41].

Whereas the templates in these cases are the crystalline monomers themselves, this function can also be taken over by foreign substances. *Clasen* [42] made use of the fact that crystalline urea and thiourea, when powdered with many low molecular weight compounds (in the presence of a little methanol) and shaken, change their crystal structure. They form tubular tunnels, in which the added compounds are deposited. *Clasen*, and later other authors, prepared tunnel inclusion compounds of polymerizable substances such as 2,3-dimethylbutadiene, 1,3-cyclohexadiene, and vinylidene chloride [43]. These monomers could be converted into polymers of high structural uniformity by heating or by irradiation with electrons, γ rays or X rays. The space available in the tunnels forces the monomers into an arrangement that is reproduced in the polymers (Fig. 2).

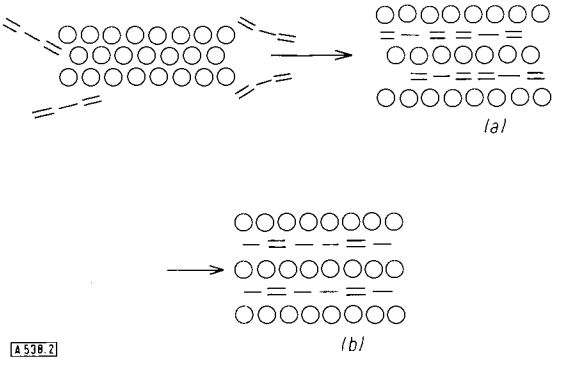



Fig. 2. Channel inclusion (a) and channel polymerization (b), schematic (after [42]).

[39] *V. A. Kargin*, *V. A. Kabanov*, and *V. P. Zubov*, Vysokomolekuljarnye Soedinenija *2*, 303 (1960).

[40] *J. Lando*, *N. Morosoff*, *H. Morawetz*, and *B. Post*, J. Polymer Sci. *60*, S 24 (1962).

[41] *K. Hayashi*, *Y. Kitanishi*, *M. Nishii*, and *S. Okamura*, Makromolekulare Chem. *47*, 237 (1961).

[42] *H. Clasen*, Z. Elektrochem. Ber. Bunsenges. physik. Chem. *60*, 982 (1956).

[43] *J. F. Brown jr.* and *D. M. White*, J. Amer. chem. Soc. *82*, 5671 (1960); *O. L. Glavati* and *L. S. Polak*, Petroleum Chem. 2, 201 (1963).

The template effects of urea and of thiourea can be seen from the fact that only monomers of suitable dimensions can be used in this method. However, the degrees of polymerization are not uniform. To obtain uniformity in size, the lengths of the tunnels would have to be the same and chain-terminating reactions would have to be excluded, and neither of these conditions has so far been achieved. It should also be noted that in all the cases described, the only forces between the templates and the polymers being formed were physical forces.

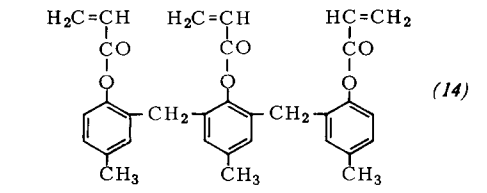
### b) Polymers as Templates

Polymers as templates for the formation of polymers are found in Nature in the replication of deoxyribonucleic acids (DNA), the genetic material of living organisms. The nucleic acids differ only in their bases. There are normally only four bases present, and two of these, a purine and a pyrimidine base, form very strong hydrogen bonds. The result is that two DNA chains of equal length in which the corresponding bases are situated opposite to each other are "complementary" and fit closely together. The double chains are wound into right-handed helices. In replication, the hydrogen bonds are broken, starting at one end. Activated nucleotides can act as the substrate, and are linked with the aid of enzymes and in contact with the individual chains in such a way that they again complete the double chains. Thus the existing polymers have acted as templates for the polymers being formed, which will in turn act as templates in the next replication, and so on. In this way, identical polymer molecules are built up in pairs (ultimately from a single molecule). These processes are not confined to living cells. Artificial polynucleotides have been prepared enzymatically *in vitro*, and these replicated by the same mechanism [44].

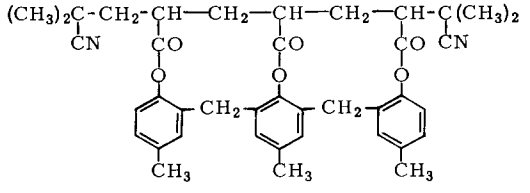
According to *Marx-Figini* and *G. V. Schulz*, another type of template evidently occurs in Nature [45]. These authors found that the secondary-wall cellulose of cotton is uniform, not only in its structure, but also in its degree of polymerization (*ca.* 14000). This degree of polymerization is reached after only a short period of growth, and subsequently remains constant. The templates may be tubular proteins from which the cellulose grows.

The preparation of identical polymer molecules on templates without the aid of enzymes has not yet been accomplished. However, a point of departure for such syntheses is found in the range of low degrees of polymerization.

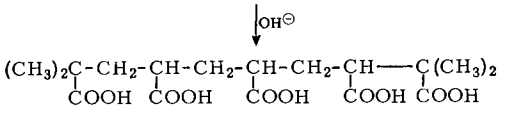
*Kämmerer* and his co-workers started with a monodisperse 4-methylphenol-formaldehyde condensate [4-methyl-2,6-bis-(2-hydroxy-5-methylbenzyl)phenol], obtained by "stepwise" and "stagewise" synthesis [46], and from which they prepared the triacrylate *(14)* [47].



*(14)*



*(15)*



*(16)*

A dilute solution of *(14)* in benzene was polymerized with about four equivalents of azobisisobutyronitrile as a free-radical initiator and chain-terminating agent. Owing to the high dilution and the large quantity of primary radicals present, the oligomers were largely isolated from one another during the reaction, and the dinitrile *(15)* was formed in 70 % yield. Alkaline hydrolysis of *(15)* leads to the pentacarboxylic acid *(16)*, which is uniform in its molecular weight, though it is a mixture of various stereoisomers.

## 4. Other Synthetic Routes

### a) Defined Conversions of Existing Uniform Polymers

It is not always necessary to prepare a desired uniform polymer directly from the monomers. It is sometimes better to convert an existing uniform polymer chemically into the desired polymer. Since polymers generally contain a large number of reactive sites, the reactions may be either complete or incomplete with respect to the individual molecules, but they must take place in the same positions in all the molecules. If the reactions are incomplete with respect to all the molecules of a polymer, it is still possible to isolate the uniformly transformed components.

In practice, one aims at complete reaction without degradation of the polymer. It is necessary to use dissolved or at least solvent-swollen polymers, since the reagents cannot otherwise reach all the reactive sites. The classical example is the hydrolysis of polyvinyl acetate to polyvinyl alcohol [48]. Most of the reactions carried out so far also have taken place on functional

[44] *H. K. Schachman, J. Adler, C. M. Radding, I. R. Lehman,* and *A. Kornberg*, J. biol. Chemistry *235*, 3242 (1960); *C. M. Radding, J. Josse,* and *A. Kornberg, ibid. 237*, 2869 (1962); *C. M. Radding* and *A. Kornberg, ibid. 237*, 2877 (1962).

[45] *M. Marx-Figini* and *G. V. Schulz*, Makromolekulare Chem. *62*, 49 (1963); *M. Marx-Figini, ibid. 68*, 227 (1963); *80*, 235 (1964), *M. Marx-Figini* and *E. Penzel, ibid. 87*, 307 (1965); cf. also *G. V. Schulz*, IUPAC Symposium on Macromolecular Chemistry, Prague 1965.

[46] *H. Kämmerer* and *H.-G. Haub*, Makromolekulare Chem. *59*, 150 (1963).

[47] *H. Kämmerer* and *Sh. Ozaki*, Makromolekulare Chem. *91*, 1 (1966).

[48] *W. O. Herrmann* and *W. Haehnel*, Ber. dtsch. chem. Ges. *60*, 1658 (1927); *H. Staudinger, K. Frey,* and *W. Starck, ibid. 60*, 1782 (1927).

groups. Since these are generally close together they influence one another, and even their steric position can be of some importance [49], particularly so when the reactions involve *two* adjacent groups (bifunctional reactions). The influence of the chain conformation of a polymer is shown by the difference in the reactivities of proteins before and after denaturation [50]. Specific reactions can be brought about with the aid of enzymes.

### b) Transformation of Replicating Polymers

If replicative polymers are modified in such a way that the power of replication is retained, only one polymer molecule need, in principle, be changed. Identical molecules will then be formed by replication, provided the correct substrate is present. The only replicative polymers known at present are nucleic acids and polynucleotides. Detailed studies have been carried out on changes by mutation in the genetic matter of bacteria, bacteriophages, and viruses. However, these nucleic acids usually suffer lethal lesions during chemical changes. Nevertheless, changes that do not prevent replication occasionally occur in the bases of the nucleotides (premutations). The modified bases are "read" in the same way as a natural, but different base. This leads to the incorporation of these wrongly "read" bases into the resulting polymer, and into the complementary polymer of the latter. Reactions of this type are brought about by X-rays and ultraviolet radiation, as well as by chemical agents (mutagens) such as nitrous acid, mustard gas, nitrogen mustards, diazomethane, ethylene oxide, formaldehyde, and hydroxylamine.

[49] See, *e.g.*, *G. Smets*, Angew. Chem. *74*, 337 (1962); Angew. Chem. internat. Edit. *1*, 306 (1962); *H. Morawetz* and *J. Oreskes*, J. Amer. chem. Soc. *80*, 2591 (1958).

[50] *C. B. Anfinsen*, J. Polymer Sci. *49*, 31 (1961); *G. H. Gundlach*, *W. H. Stein*, and *S. Moore*, J. biol. Chemistry *234*, 1754 (1959).

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# Syntheses of Carboxylic Acids from 1,1-Dichloroethylene [1]

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FORSCHUNGSLABORATORIEN DER CHEMISCHE WERKE HÜLS AG., MARL (GERMANY)

*Dedicated to Professor F. Broich on his 60th birthday*

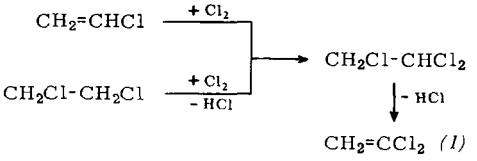
*Many β-alkyl- and β-arylpropionic acids are readily obtainable by the reaction of secondary or tertiary alcohols, esters of these, or olefins with the inexpensive 1,1-dichloroethylene in sulfuric acid. The success of the synthesis depends on the bulk and energy of the carbonium ion intermediate formed from the alcohols or olefins. With carbonium ions having one H atom attached to the carbonium C atom, electrophilic substitution of the 1,1-dichloroethylene takes place to a small extent. Dicarboxylic acids and carboxylic acids with higher molecular weights are sometimes formed as a result of side reactions.*

## 1. Introduction

β-Alkyl- and β-arylpropionic acids generally are prepared by syntheses involving several steps. In the course of attempts to find a convenient route to β,β-dimethylbutyric acid, we discovered a synthesis that can be used for the preparation of a series of carboxylic acids of the above type in a one-stage process using 1,1-dichloroethylene (vinylidene chloride) *(1)*.

Two processes are available for the industrial production of 1,1-dichloroethylene [2, 3].

The action of an equimolar amount of chlorine on vinyl chloride or on 1,2-dichloroethane yields 1,1,2-trichloroethane. Subsequent dehydrochlorination with aqueous sodium hydroxide [4] or calcium hydroxide [5] leads almost exclusively to 1,1-dichloroethylene *(1)*. This dichloroolefin is a colorless liquid boiling at 37 °C; it is stable on storage in the monomeric state only after the addition of polymerization inhibitors such as triethylamine and 4-t-butylcatechol.




[1] *K. Bott*, Angew. Chem. *77*, 967 (1965); Angew. Chem. internat. Edit. *4*, 956 (1965); Chem. Ber., in press.

[2] French Pat. 804491 (1936), Compagnie de Produits Chimiques et Electrometallurgiques Alais, Froges & Camargue, Chem. Abstr. *31*, 3509 (1937).

[3] Brit. Pat. 627263 (1946), B. F. Goodrich; Chem. Abstr. *44*, 2542 (1950).

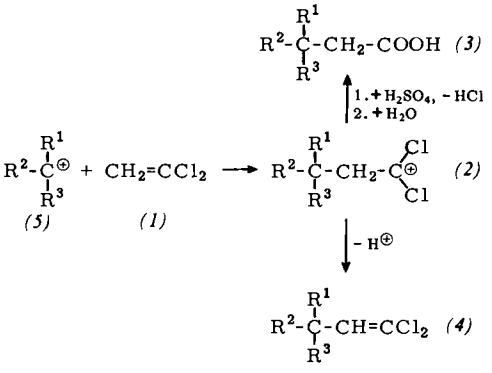
[4] *C. J. Strosacker* and *F. C. Amstutz*, US.-Pat. 2322258 (1938), Dow Chem. Co.

[5] *C. Jung* and *A. Zimmermann*, Ger. Pat. 529604 (1929), I.G.-Farben.

## 2. General Notes on the Course of the Reaction

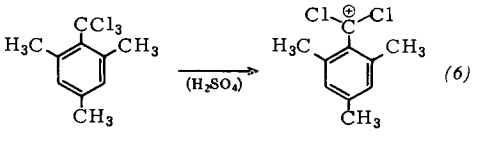
It is well known that trichloromethyl compounds can be hydrolysed to form carboxylic acids; however, the preparation of aliphatic carboxylic acids by hydrolysis of 1,1,1-trichloroalkanes with sulfuric acid requires temperatures between 90 and 100 °C [6]. The rate-determining step may be assumed to be the proton-catalysed removal of a chloride ion, which results in the formation of a dichlorocarbonium ion [*e.g. (2)*].

The principal feature of the new carboxylic acid synthesis is that ions of structure *(2)* can be produced under much milder conditions by the addition of carbonium ions *(5)* to 1,1-dichloroethylene.



Suitable reaction partners for 1,1-dichloroethylene are secondary or tertiary alcohols, esters of these, and olefins, which readily form carbonium ions in 90 to 100% sulfuric acid. The adduct-ion *(2)* cannot be isolated, but reacts very rapidly with the sulfuric acid. Subsequent treatment with water yields the carboxylic acid *(3)*. The rate of reaction at 0 to 15 °C is generally sufficiently high, but it can be considerably increased by the addition of Lewis acids such as boron trifluoride. The low reaction temperature permits also the synthesis of aliphatic carboxylic acids containing aryl groups.

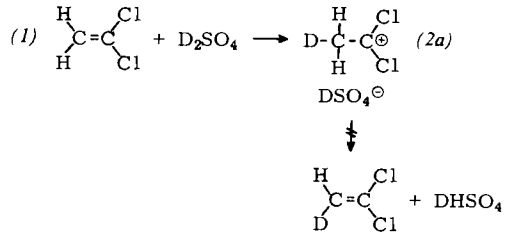
The cation *(6)* resulting from the dissolution of 2,4,6-trimethylbenzotrichloride in sulfuric acid evidently is stabilized by the trimethylphenyl group [7].



The intermediate *(2)* formed by secondary carbonium ions ($R^1$ = H; $R^2$, $R^3$ = alkyl) and dichloroethylene *(1)* can also lose a proton to give substitution products *(4)* of 1,1-dichloroethylene. 1,1-Dichloroolefins having a secondary alkyl group on C-2 are converted into carboxylic acids by sulfuric acid only at temperatures above 60 °C.

If the carbon chain in *(2)* is more highly branched ($R^1$, $R^2$, $R^3$ = alkyl), the elimination of the hydrogen from C-2 is suppressed by steric hindrance.

Instead of the carbonium ion *(5)*, 1,1-dichloroethane itself can take up a proton and forms acetic acid on hydrolysis. This "blank hydrolysis" predominates only when the formation of the carbonium ion *(5)* or the subsequent conversion into *(2)* is not sufficiently fast.



In order to study the formation of acetic acid, dichloroethylene *(1)* was treated with $D_2SO_4$. If the solvolysis is interrupted at an early stage, no deuterium can be detected in the remaining vinylidene chloride by infrared and mass-spectrometric examination. This shows that the protonation of *(1)* is the rate-determining step in the formation of acetic acid.

## 3. Application of the Carboxylic Acid Synthesis

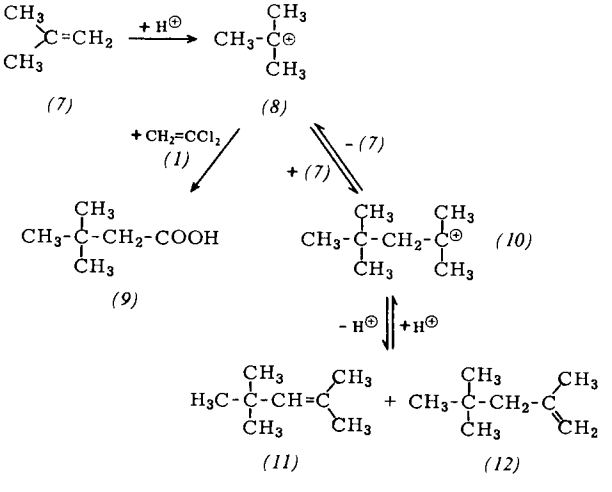
### a) t-Alkylacetic Acids

Several substances (Table 1) can be used as sources of the carbonium ion required for the preparation of β,β-dimethylbutyric acid *(9)*, the simplest t-alkylacetic acid.

Table 1. Starting materials for the synthesis of β,β-dimethylbutyric acid *(9)*.

| $CH_2=CCl_2$ + starting material | Yield (%) |
|---|---|
| $(CH_3)_3COH$ | 80 |
| $(CH_3)_3CCl$ | 79 |
| $CH_3-COOC(CH_3)_3$ | 78 |
| $(CH_3)_2C=CH_2$ *(7)* | 75 |
| *(11)* + *(12)* | 33 |
| $(CH_3)_2CH-CH_2OH$ | 15 |

Isobutene *(7)* first adds a proton to form the t-butyl cation *(8)*, which then reacts with vinylidene chloride *(1)*.



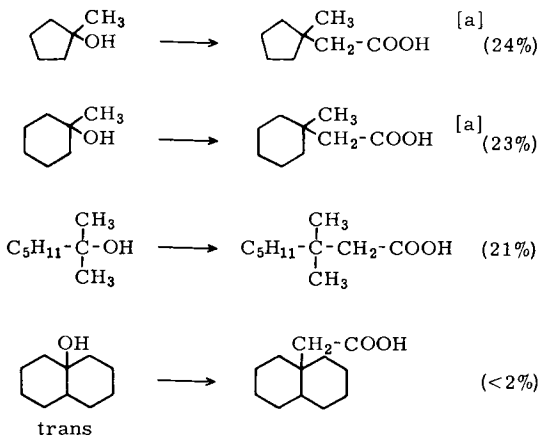
The kinetically preferred addition of *(8)* to isobutene *(7)* to form *(10)* is reversible. Consequently, the formation of t-butylacetic acid from "diisobutylene", a mixture of the olefins *(11)* and *(12)*, is not surprising. The reluctance of the

[6] *R. M. Joyce*, US.-Pat. 2398430 (1942), du Pont; Chem. Abstr. *40*, 3768 (1946).

[7] *R. J. Gillespie* and *E. A. Robinson*, J. Amer. chem. Soc. *86*, 5676 (1964).

cation *(10)* to add to dichloroethylene probably is due to steric hindrance.

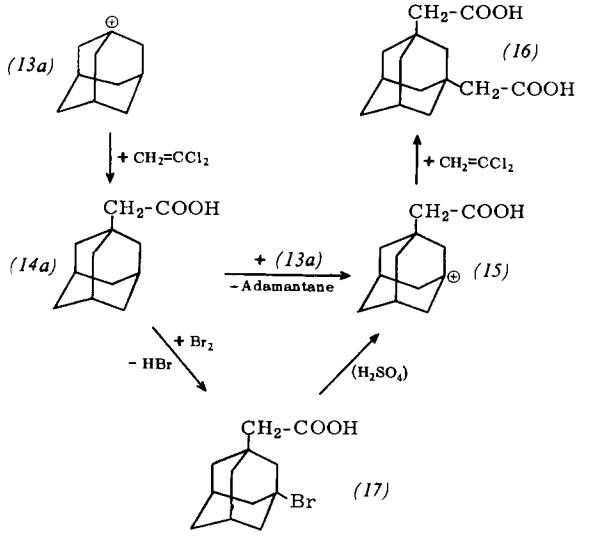
The yields of carboxylic acid decrease rapidly when the number of carbon atoms in the tertiary alcohols increases. This is true both of open-chain and of cyclic alcohols (Scheme 1).




Scheme 1

[a] It was shown by gas-chromatographic analysis of the methyl ester that no isomeric carboxylic acids were present.

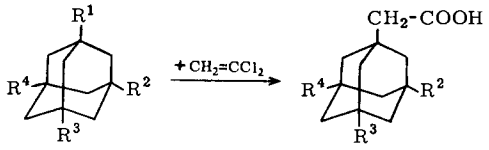
The only exceptions to this rule are carbonium ions of the adamantane series, in which the charge is situated on a bridgehead C atom. The carbon skeleton of the 1-adamantyl cation *(13a)* is so rigid that the steric hindrance is even weaker than in the planar t-butyl cation *(8)*.




The ion *(13a)* is, in addition, stable in concentrated sulfuric acid. Since the conversion of the adamantane system into an olefin and into secondary products of the latter is not possible, the preparation of adamantane-1-acetic acids from adamantane derivatives and vinylidene chloride *(1)* gives particularly high yields (Table 2).

When the reaction of 1-bromoadamantane is carried out at high carbonium ion concentrations, *i.e.* in a small volume of pure sulfuric acid in the presence of boron trifluoride, the resulting adamantaneacetic acid *(14a)* can exchange a hydride ion with the adamantyl cation. The resulting carbonium ion *(15)* undergoes a second synthesis step to form adamantane-1,3-diacetic acid *(16)*. The diacid *(16)* is best prepared from 3-bromoadamantaneacetic acid *(17)*.

Table 2. Preparation of adamantane-1-acetic acid *(14a)* and methylated derivatives.




| R1 | R2 | R3 | R4 | M.p. (°C) | Yield (%) |
|---|---|---|---|---|---|
| Br | H | H | H | | 92 |
| OH | H | H | H | 135–136 | 93 |
| $OCOCH_3$ | H | H | H | | 94 |
| Br | $CH_3$ | H | H | 107–108 | 89 |
| $OCOCH_3$ | $CH_3$ | H | H | | 94 |
| Br | $CH_3$ | $CH_3$ | H | 113–114 | 89 |
| $OCOCH_3$ | $CH_3$ | $CH_3$ | H | 113–114 | 94 |
| $OCOCH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | 139–140 | 80 [a] |

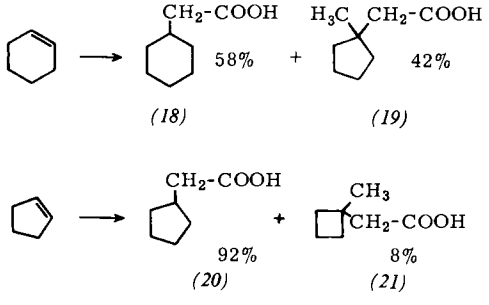
[a] Approximately 15% of the compound used is converted into 1-chloro-3,5,7-trimethyladamantane.

Unlike adamantanecarboxylic acid [8], adamantaneacetic acid *(14a)* and 3-methyladamantaneacetic acid, in which the carboxyl groups are further from the bridgehead C atom, can be brominated as easily as adamantane and its methyl derivatives [9–11].

If the methyl groups in the t-butyl cation are progressively replaced by phenyl groups, the resulting ions no longer add to 1,1-dichloroethylene, owing to their resonance stabilization and their large bulk.

### b) sec-Alkylacetic Acids

The ease of formation of carbonium ions is considerably smaller in secondary alcohols than in tertiary alcohols. The same relationship is found for the olefins on which the alcohols are based. Thus, yields of between 4 and 8% of carboxylic acid are obtained when cyclohexene and cyclopentene are used as the starting materials.




The formation of 1-methylcyclopentylacetic acid *(19)* in addition to cyclohexylacetic acid *(18)* must be regarded as evidence that the cyclohexyl cation has rearranged to form the more stable 1-methylcyclopentyl cation. Further ring contraction is largely suppressed in the cyclopentyl system, owing to the strain of the cyclobutane ring.

The remarkable stability of the norbornyl cation *(22)* in strong acids is due to the rapid establishment of an equilibrium between identical non-classical ions, which change into one another by hydride shifts and Wagner-Meerwein rearrangements [12].


[8] *H. Stetter* and *P. Goebel*, Chem. Ber. *96*, 550 (1963).

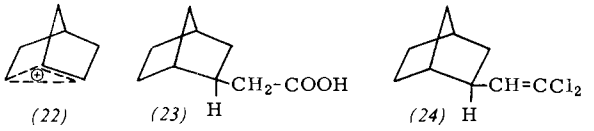
[9] *H. Stetter* and *C. Wulff*, Chem. Ber. *93*, 1366 (1960).

[10] *K. Gerzon, E. V. Krumkalns, R. L. Brindle, F. J. Marshall,* and *M. A. Root*, J. med. Chem. *6*, 760 (1963).

[11] *H. Koch* and *J. Franken*, Chem. Ber. *96*, 213 (1963).

[12] *M. Saunders, P. v. Schleyer,* and *G. A. Olah*, J. Amer. chem. Soc. *86*, 5680 (1964).

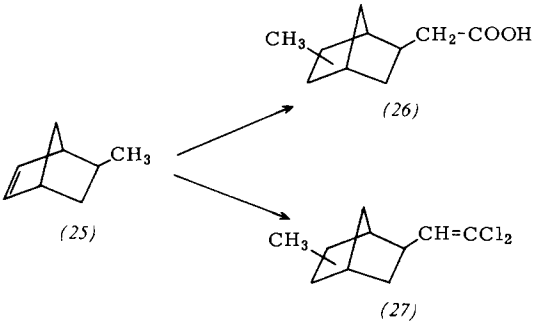
As expected, the reaction of norbornene with vinylidene chloride yields *exo*-2-norbornylacetic acid *(23)* (77% yield), the anilide of which melts at 124–125 °C, *i.e.* 14 °C below *endo*-norbornylacetanilide, which was described by *Alder* and *Windemuth* [13]. The use of *exo*-norborneol or *exo*-norbornyl acetate instead of norbornene results in a lower yield of *exo*-norbornylacetic acid (62 and 46%, respectively).



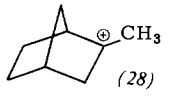

*(22)* *(23)* *(24)*

This shows the smaller ionization tendency of norborneol and its esters as compared with tertiary alcohols. The reaction in 90% sulfuric acid yields not only *(23)*, but also 2-(2-norbornyl)-1,1-dichloroethylene *(24)*, which is formed by electrophilic substitution of dichloroethylene with norbornene. The hydrolysis of *(24)* to *exo*-norbornylacetic acid is possible only above 60 °C. Owing to the presence of the H atom on C-2', *(24)* is readily autoxidized with liberation of hydrogen chloride and small quantities of phosgene.

The alkyl substituent in the norbornyl system has an interesting effect on the course of the reaction. 5-Methylnorbornene *(25)* gives a mixture of methylnorbornylacetic acids *(26)*, the three principal components being present in the proportions 64, 21, and 9%. The position of the methyl group in these compounds is not yet known. It is reasonable to assume that *(26)* consists entirely of *exo*-norbornylacetic acids. The

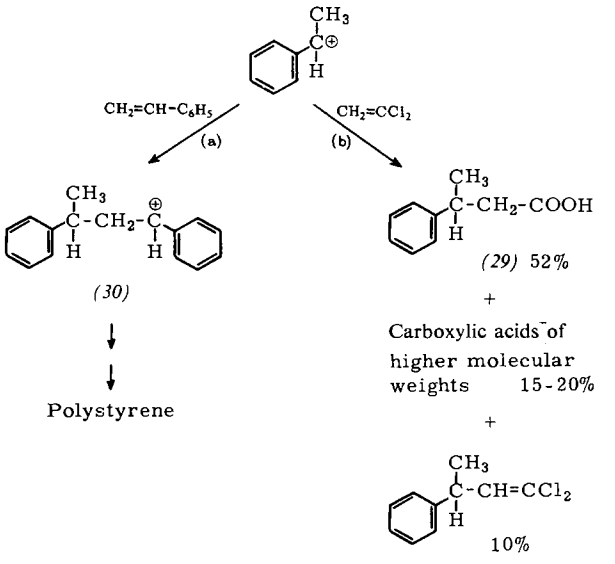



methylnorbornyldichloroethylene *(27)* isolated as a by-product does not contain appreciable quantities of an isomer derived, as suggested by the classical formulation, from the energetically favored 2-methylnorbornyl cation *(28)*. Thus *(27)* is autoxidized and converted into the carboxylic acid at almost the same rate as *(24)* [14].




### c) Hydrocinnamic Acids

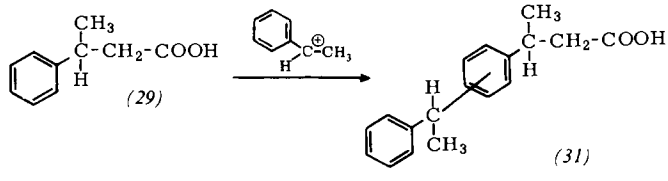
β-Methylhydrocinnamic acid *(29)* is the first aryl-substituted aliphatic carboxylic acid to become readily obtainable through the new synthesis. The recommended starting material is 1-phenylethanol, which is formed by the addition of water to styrene.



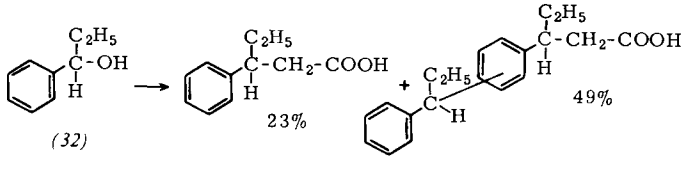

Styrene itself undergoes proton-catalysed polymerization, since step (a) leading to *(30)* is much faster than (b), and is irreversible.

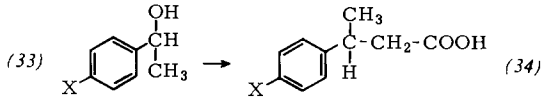
In addition to the acid *(29)* and the dichloroolefin, carboxylic acids with higher molecular weights, *e.g. (31)*, are also formed.

These acids could be formed by the addition of *(30)* to vinylidene chloride or by alkylation of methylhydrocinnamic acid *(29)* in the nucleus to form *(31)*. The following experimental evidence clearly supports the second of these possibilities.




No carboxylic acid is formed by linear distyrene [15], which initially is converted into *(30)* by the action of acids. On the other hand, the reaction of 1-phenylpropanol *(32)*, whose precursor β-methylstyrene exhibits little tendency to polymerize, leads preferentially to carboxylic acids with high molecular weights.




| | Yield |
|---|---|
| *(a)*: X = Cl | 82% |
| *(b)*: X = t-Butyl | 76% |
| *(c)*: X = 1-Methylcyclohexyl | 65% |

The reactions of the *p*-halogeno- and *p*-t-alkylphenylethanols *(33a)–(33c)* are particularly revealing. These reactions lead almost exclusively to the formation of the expected β-methylhydrocinnamic acids *(34a)–(34c)*. The bulky or electro-

[13] *K. Alder* and *E. Windemuth*, Ber. dtsch. chem. Ges. *71*, 1954 (1938).

[14] t-Alkyl derivatives of 1,1-dichloroethylene, on the other hand, are stable towards sulfuric acid up to 90 °C.

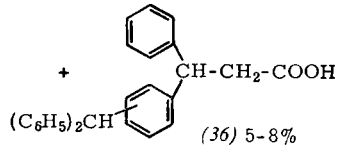
[15] *B. B. Corson, W. J. Heintzelmann, H. Moe*, and *C. R. Rousseau*, J. org. Chemistry *27*, 1636 (1962).

negative substituents in the benzene nucleus prevent the entry of phenylethyl groups into *(34)*, and so increase the yield of the uniform carboxylic acid.

It may seem surprising that the reactivity of the 1-phenylethyl cation is not greater than that of the more stable benzhydryl cation. Benzhydrol, benzhydryl chloride, and benzhydryl acetate all can be used for the preparation of β-phenylhydrocinnamic acid.

$$(C_6H_5)_2CHX \longrightarrow (C_6H_5)_2CH\text{-}CH_2\text{-}COOH$$

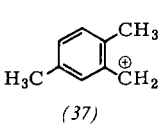
X = OH, Cl, $OCOCH_3$ *(35)* 72-76%



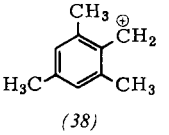
*(36)* 5-8%

Benzhydrylation of *(35)* to *(36)* takes place only to a small extent. The influence of substitution in the nucleus on the composition of the product has so far been studied in only one example. *p,p'*-Dichlorobenzhydryl acetate gives pure 3,3-bis-(*p*-chlorophenyl)propionic acid in 78% yield.

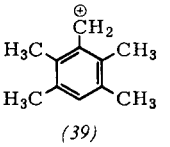
Mention should also be made of the action of primary carbonium ions on 1,1-dichloroethylene. Carbonium ions with a primary carbon atom as the charge carrier are sufficiently stable in strong sulfuric acid only if the positive charge can distribute itself over the molecule by resonance. In our experience the only ions of this type that are suitable for the synthesis of carboxylic acids are the polymethylated benzyl cations *(37)–(39)*.



*(37)*



*(38)*



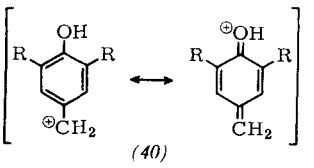
*(39)*

The ions *(37)–(39)* were produced from the products obtained on chloromethylation of *p*-xylene, mesitylene, and durene [16–18].

The reactions of the polymethylbenzyl cations with $CH_2{=}CCl_2$ follow a complex course. The formation of the phenylhydrocinnamic acids is followed by secondary reactions that have already been mentioned. Hydride exchange on the methyl groups leads to dicarboxylic acids; the molecular weight of the carboxylic acids is greatly increased by benzylation in the nucleus.

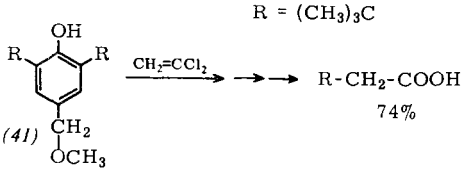
Nevertheless, in the reaction of the 2,3,5,6-tetramethylbenzyl cation *(39)*, pure 2,3,5,6-tetramethylphenylhydrocinnamic acid can be isolated in 5% yield.

A much more stable ion than *(37)–(39)* should be one having the structure *(40)*, the substitution of which with t-butyl groups would prevent any hydride migration in the resulting carboxylic acid. However, 3,5-di-t-butyl-4-hydroxybenzyl methyl ether *(41)*, the precursor of *(40)*, transfers a t-butyl cation *(8)* to the vinylidene chloride, and is itself converted into β,β-dimethylbutyric acid *(9)*.



*(40)*

R = $(CH_3)_3C$



*(41)*

## 4. Procedures

### a) *β,β-Dimethylbutyric acid (9)*

A mixture of 92.5 g (1 mole) of t-butyl chloride and 146 g (1.5 mole) of 1,1-dichloroethylene [19] is added dropwise during 2 hours to 200 ml of 90% sulfuric acid containing 35 g of boron trifluoride, with vigorous stirring at 5 °C. Stirring is continued for a further two hours at 15 °C. The reaction mixture is poured on ice, and the resulting carboxylic acid is taken up in ether and distilled under reduced pressure. Yield 92 g (79% based on the t-butyl chloride); b.p. 80–82 °C/12 mm, m.p. 6–7 °C (lit. [20] 6 °C).

### b) *exo-2-Norbornylacetic acid (23)*

A solution of 188 g (2 moles) of norbornene in 388 g (4 moles) of 1,1-dichloroethylene is added dropwise during 4 hours to 800 ml of 98% sulfuric acid containing 120 g of boron trifluoride at 14 to 16 °C. The mixture is then stirred for 1 hour. On decomposition with ice and dissolution in ether, vacuum distillation yields 237 g of *exo*-2-norbornylacetic acid (77% based on norbornene); b.p. 117–118 °C/1.5 mm, $n_D^{20} = 1.4820$.

### c) *p-Chloro-β-methylhydrocinnamic acid (34a)*

50 g (0.32 mole) of 1-(*p*-chlorophenyl)ethanol and 95 g (0.98 mole) of 1,1-dichloroethylene are allowed to react in 100 ml of 90% sulfuric acid containing 18 g of boron trifluoride, as described in procedure (a). On hydrolysis the crude *p*-chloro-β-methylhydrocinnamic acid separates in crystalline form. This material is further purified by dissolution in sodium hydroxide solution, separation of the neutral product, and precipitation with dilute hydrochloric acid. Yield 53 g (83% based on the alcohol); m.p. 89–92 °C. On recrystallization from cyclohexane, the melting point rises to 92–93 °C.

### d) *3,5-Dimethyladamantaneacetic acid*

A solution of 25 g (0.113 mole) of 1-bromo-3,5-dimethyladamantane and 100 g (1.03 mole) of 1,1-dichloroethylene is added dropwise during 2 hours to 100 ml of 90% sulfuric acid containing 18 g of boron trifluoride at 10 °C. After stirring for a further 2 hours, the solution is decomposed with ice. The crystalline product is purified as in example (c). Yield 20.5 g (90% based on dimethylbromoadamantane); m.p. 110–112 °C. Pure 3,5-dimethyladamantaneacetic acid (from ethanol/water) melts at 113–114 °C.

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Translated by Express Translation Service, London

[16] *C. D. Shacklett* and *H. A. Smith*, J. Amer. chem. Soc. *73*, 766 (1951).

[17] *R. C. Fuson* and *N. Rabjohn*, Org. Syntheses *3*, 557 (1955).

[18] *R. R. Aitken, G. M. Badger*, and *J. W. Cook*, J. chem. Soc. (London) *1950*, 331.

[19] In the examples described here we used 1,1-dichloroethylene stabilized with 0.3% of triethylamine.

[20] *L. Schmerling*, J. Amer. chem. Soc. *71*, 701 (1949).

# Recent Syntheses and Reactions of Cyclic Imidic Esters

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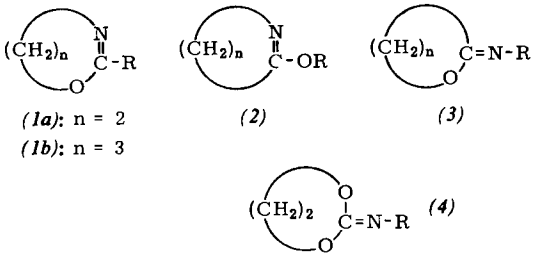
FORSCHUNGSLABORATORIEN DER CHEMISCHE WERKE HÜLS AG., MARL (GERMANY)

*Dedicated to Professor F. Broich on the occasion of his 60th birthday*

*$\Delta^2$-Oxazolines and 4H-5,6-dihydrooxazines are readily obtainable from carboxylic acids and 2- or 3-amino alcohols by gas-phase dehydration, and 4H-dihydrooxazines can also be obtained by condensation of N-(hydroxymethyl)carboxamides with olefins. These cyclic imidic esters undergo reactions in which the ring is cleaved; these reactions include a new type of polymerization. The behavior of alkyl groups in position 2 and the cycloadditions in the 2,3-position also have been studied. Reactions in side chains on position 2 and addition experiments on the sulfur analogues of the cyclic imidic esters are also reported. A table shows the principal infrared bands of substituted $\Delta^2$-oxazolines.*

## 1. Introduction

Since *Pinner*'s pioneering work on the chemistry of imidic esters [1], this class of compounds has excited steadily growing interest [2]. One need only mention the numerous publications dealing with the conversion of these compounds into *N*-substituted amides [2–4]. Cyclic imidic esters generally react like the acyclic derivatives [5] but there are a number of differences, which depend on the constitution. Of the three types of cyclic imidic esters *(1)*–*(3)*, *i.e.* compounds containing the grouping



*(1a)*: n = 2
*(1b)*: n = 3

*(2)*

*(3)*

*(4)*

–O–C=N–, the lactim ethers *(2)* can readily be converted into *N*-substituted lactams [6]. In the iminolactone series *(3)* [7], the rearrangement of the iminocarbonates *(4)* to *N*-substituted 2-oxazolidones has been described [7c,8]. No corresponding rearrangement of the compounds *(1a)* or *(1b)*, which would give *N*-acylaziridines and -azetidines respectively, is known. However, owing to the ring strain in these cyclic imines, the reverse reactions leading to $\Delta^2$-oxazolines [9] and 4*H*-5,6-dihydro-1,3-oxazines [10] can easily be brought about.

## 2. Preparation of Cyclic Imidic Esters

The $\Delta^2$-oxazolines *(1a)* [5,11] and 4*H*-dihydrooxazines *(1b)* [12,13] can be obtained in many ways. From the literature data it can be deduced that the ease of cyclization generally increases with the number of substituents on the heterocycle *(1)* to be formed. Unfortunately the starting materials generally also become more difficult to prepare with increasing substitution.

Particularly suitable derivatives for the study of the reactions of $\Delta^2$-oxazolines *(1a)* and 4*H*-dihydrooxazines *(1b)* are those with substituents only in position 2. An obvious synthesis of these compounds is the reaction of acyclic imidic esters or their hydrochlorides with 2-aminoethanol [5,11a,14] and with 3-aminopropa-

[1] *A. Pinner*: Die Imidoäther und ihre Derivate. R. Oppenheim-Verlag, Berlin 1892.

[2] *R. Roger* and *D. G. Neilson*, Chem. Reviews *61*, 179 (1961).

[3] *F. Möller* in Houben-Weyl: Methoden der organ. Chemie. 4th Edit., Vol. XI/1, p. 910, Georg Thieme, Stuttgart 1957.

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[8] *K. Gulbins* and *K. Hamann*, Angew. Chem. *73*, 434 (1961).

[9] *S. Gabriel* and *R. Stelzner*, Ber. dtsch. chem. Ges. *28*, 2929 (1895).

[10] *Y. Iwakura, A. Nabeya, T. Nishiguchi*, and *Y. Ichikawa*, J. org. Chemistry *30*, 3410 (1965).

[11] a) *J. W. Cornforth* in *R. C. Elderfield*: Heterocyclic Compounds. Vol. 5, p. 377, Wiley, New York 1957; b) *R. Oda, M. Okano, S. Tokiura*, and *F. Misumi*, Bull. chem. Soc. Japan *35*, 1219 (1962); Chem. Abstr. *57*, 12453 (1962); c) *D. F. Loder*, US.-Pat. 2402198 (1946), E. I. du Pont de Nemours, Chem. Abstr. *40*, 5457 (1946).

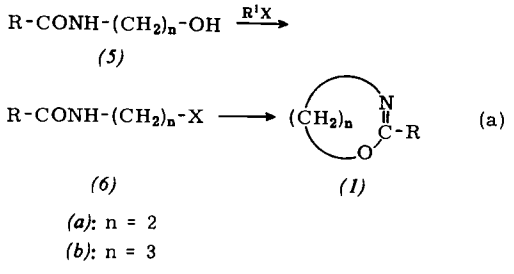
[12] a) *R. L. McKee* in *A. Weissberger*: The Chemistry of Heterocyclic Compounds. Vol. XVII, p. 341, Wiley, New York-London 1962; b) *N. H. Cromwell*, see [11a], Vol. 6, p. 534; c) *G. Drefahl* and *H. H. Hörhold*, Chem. Ber. *94*, 1641 (1961); d) Belg. Pat. 623714 (1963), Shell Research Ltd., Chem. Abstr. *60*, 9299 (1964).

[13] *C. Zioudrou* and *G. L. Schmir*, J. Amer. chem. Soc. *85*, 3258 (1963).

[14] *H. J. Barber, P. Z. Gregory, R. Slack, C. E. Stickings*, and *A. M. Woolman*, Report 66 of Comittee for Penicillin Synthesis (1944).

nol [12c, 13]. In our experience these reactions proceed particularly well when equimolar amounts of the imidic ester and the amino alcohol are heated with a catalytic quantity of a strong acid and the resulting heterocycle *(1)* is distilled off.

Most of the syntheses of the compounds *(1)* are based on *N*-2- and *N*-(3-hydroxyalkyl)amides *(5)*, which are readily obtained by treatment of carboxylic acids [15] or their esters [16] with the amino alcohols at 150–200 °C. One molecule of water must formally be eliminated from *(5)*. Usually, however, *(5)* is first treated with reagents such as $SOCl_2$ [5], $RSO_2Cl$ [17], $COCl_2$ [18], or $PO(OR_2)Cl$ [13] in order to replace the hydroxyl group by a group X that can be eliminated more readily.



*(5)*

*(6)* *(1)*

*(a)*: n = 2
*(b)*: n = 3

The cyclization is greatly facilitated if the carbon atom adjacent to either the nitrogen or the substituent X is disubstituted [17, 19].

Particularly ready conversion of *(5)* into *(6)*, X = Cl, is achieved with only slightly more than the equivalent amount of $SOCl_2$ at about 80 °C. The cyclization of *(6)*, X = Cl, containing aromatic groups R proceeds in very good yields in aqueous alkali solutions at 50–70 °C, if necessary in the presence of solubilizing additives such as methanol or dioxane.

### 2.1. Dehydration of *N*-(2-Hydroxyethyl)carboxamides in the Gas Phase

The simplest method of synthesis is obviously the direct dehydration of the *N*-(hydroxyalkyl)amides *(5)*, which can be achieved by heating of the derivative *(5a)* containing the aliphatic group R to 250–300 °C [15, 20]. However, the aliphatically substituted $\Delta^2$-oxazolines are obtained only in modest yields. Aromatic derivatives have not so far been obtained by this reaction [15].

A number of substances have been tested for possible catalysis of the dehydration of *N*-(2-hydroxyethyl)-benzamide. In the presence of granulated alumina, the slow distillation of this compound at 220 °C/25 mm Hg leads to the desired 2-phenyl-$\Delta^2$-oxazoline in a yield of about 50 % (based on a conversion of 70 %). Under similar conditions, the methyl derivative can be prepared in 56 % yield [22a].

From these results one may conclude that the cyclization step is based on an equilibrium

$$(5a) \rightleftharpoons (1a) + H_2O \qquad (b)$$

which normally lies well to the left [21], but which is displaced towards the right at high temperatures, and is established so rapidly on alumina that side reactions cannot interfere. We therefore extended the reaction to the gas phase. However, the thermal stability of the cyclic imidic esters *(1)* was dubious. For example, 2-methyl-$\Delta^2$-oxazoline is completely fragmented in an autoclave at 275 °C/20–120 atm under nitrogen; it was found by mass spectrometry that in addition to ammonia and a tarry residue, the products contained $H_2$, CO, and hydrocarbons.

#### 2.1.1. Apparatus and Method

The gas-phase dehydration is carried out in a contact tube packed with a granulated dehydration catalyst and equipped with a temperature-sensing device [22a]. The pressure in the reaction chamber should be 0.5 to 20 mm Hg. Starting materials *(5a)* which are volatile under these conditions are passed over the catalyst as vapors, while high-boiling or unstable substances are preferably applied in the form of drops. On leaving the contact tube, the dehydration mixture is quenched and condensed in cooled vessels in order to freeze the reverse reaction of equation (b), which takes place slowly already at room temperature [21]. The activity of the catalyst decreases with time, depending on the reaction temperature, contact time, and purity of the starting material; however, the original activity is restored by the usual treatment with steam and air.

#### 2.1.2. Recovery of Products

High-boiling $\Delta^2$-oxazolines that are not very sensitive to hydrolysis can be isolated by direct vacuum fractionation of the reaction mixture. $\Delta^2$-Oxazolines that are sensitive to hydrolysis are separated from the remaining *N*-(2-hydroxyethyl)amide (which has an appreciably higher boiling point), together with the water formed, at the lowest temperature possible (vacuum distillation or thin-film evaporation). The pure $\Delta^2$-oxazolines can be isolated from the distillate by addition of solid KOH and/or extraction with ether, followed by drying with KOH or sodium. Larger quantities are better freed from water by azeotropic distillation [22b]. The residues, which consist of impure *N*-(2-hydroxyethyl)amides, may be mixed with fresh starting material without prior purification, and used again in the dehydration.

[15] *H. Wenker*, J. Amer. chem. Soc. *57*, 1079 (1935).
[16] *G. F. D'Alelio* and *E. E. Reid*, J. Amer. chem. Soc. *59*, 111 (1937).
[17] *R. N. Boyd* and *R. H. Hansen*, J. Amer. chem. Soc. *75*, 5896 (1953).
[18] *D. Ben-Ishai*, J. Amer. chem. Soc. *78*, 4962 (1956).
[19] *H. Dersin*, Ber. dtsch. chem. Ges. *54*, 3158 (1921).
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[21] *R. Greenhalgh*, *R. M. Heggie*, and *M. A. Weinberger*, Canad. J. Chem. *41*, 1662 (1963).
[22] a) *W. Seeliger* and *W. Thier*, Liebigs Ann. Chem., in press; b) *W. Seeliger* and *M. Lütke-Daldrup*, French Pat. 1436297 (1965), Chem. Werke Hüls.

### 2.1.3. Results

Table 1 shows that the substituted oxazolines *(1a)* can be obtained in satisfactory purity and in good yields ultimately from carboxylic acids and 2-amino alcohols.

Table 1. $\Delta^2$-Oxazolines *(1a)* obtained by gas-phase dehydration of *N*-(2-hydroxyethyl)amides *(5a)* on alumina contact HO 412 [a].

| *(1a)* | Conditions (°C/mm Hg) | Yield (%) [b] | % conversion | B.p. (°C/mm Hg) | Lit. b.p. (°C/mm Hg) | $n_D^{20}$ | M.p. °(C) |
|---|---|---|---|---|---|---|---|
| 2-Methyl- | 550/16–18 | 92.3 | 77.8 | 110–111 | 110–111 [20] | 1.4341 | – |
| 2,5-Dimethyl- | 390/10–20 | 54.1 | 54.3 | 114–115 | 116–118 [20] | 1.4268 | – |
| 2-Ethyl- | 320/10–20 | 62.8 | 73.3 | 129–130 | 126–128 [20] | 1.4369 | – |
| 2-n-Propyl- | 575/10–20 | 84.2 | 66.2 | 148–149 | – | 1.4410 | – |
| 2-iso-Propyl- | 350/10–20 | 62.2 | 64.5 | 136 | 136–139 [20] | 1.4362 | – |
| 2-n-Undecyl- | 365/3 | 66.6 | 75.3 | 82/0.04 | – | 1.4521 [c] | 22–24 |
| 2-Cyclohexyl [d] | 400/5–10 | – | – | 104–105/17 | – | 1.4810 | – |
| 2-Phenyl- | 400/0.5 | 84.3 | 79.1 | 60/0.2 | 90–100/2 [23] | 1.5674 [f] | 27–28 |
| 2-*p*-Toluyl- | 500/14 | 64.1 | 58.6 | 94–97/1.3 | 264–265 [24] | – | 67–68 [e] |

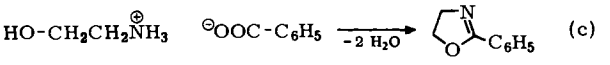
[a] Katalysatorenwerke Houdry-Hüls GmbH.
[b] Based on *(5a)* reacted.
[c] Measured at 30 °C.
[d] Alumina contact HO 417 [a].
[e] Ref. [24]: 66 °C.
[f] Measured on the supercooled melt.

By-products formed, particularly above 400 °C, include small quantities of nitriles, as well as a little diethyl ketone and $CO_2$ in the case of *N*-(2-hydroxyethyl)-propionamide.

The reaction temperatures given in Table 1 are the highest temperatures measured in the contact tube. Because of the endothermic reaction, these are generally reached only in the last quarter of the tube.

Figure 1 shows the relationship between the reaction temperature, conversion, and yield. A surprising feature is the steep rise of the yield curve with rising temperature up to a maximum at about 350 °C.

Interestingly, 2-hydroxyethylammonium benzoate also can be dehydrated to 2-phenyl-$\Delta^2$-oxazoline if its melt is allowed to drop onto the hot contact.



(c)

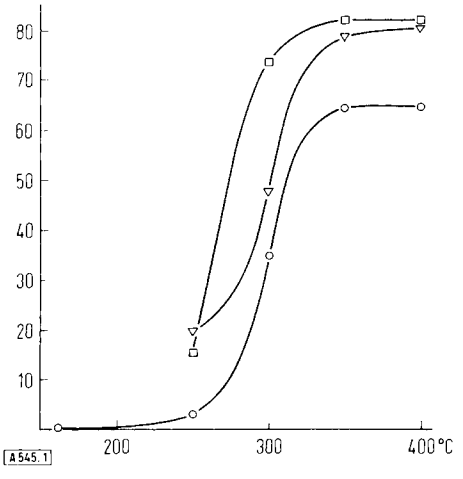



Fig. 1. Conversion of *N*-(2-hydroxyethyl)acetamide and yield of 2-methyl-$\Delta^2$-oxazoline as functions of the dehydration temperature. ▽: conversion; □: yield based on conversion; ○: yield based on amount of starting material.
Ordinate: mole-%; abscissa: reaction temperature.

### 2.2. Dehydration of *N*-(3-Hydroxypropyl)amides in the Gas Phase

The gas-phase dehydration of *N*-(3-hydroxypropyl)-carboxamides *(5b)*, including separation of the products, is carried out as described in Section 2.1. The 4*H*-5,6-dihydrooxazines *(1b)* shown in Table 2 have been obtained in this way.

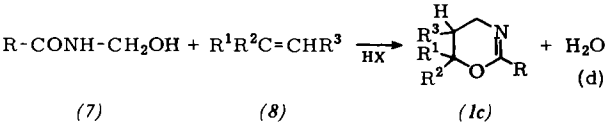
Table 2. 4*H*-5,6-dihydrooxazines *(1b)* obtained by gas-phase dehydration of *N*-(3-hydroxypropyl)amides on alumina contact HO 412 [a].

| *(1b)* | Conditions (°C/mm Hg) | Yield (%) [b] | % conversion | B.p. (°C/mm Hg) | Lit. b.p. (°C/mm Hg) | $n_D^{20}$ |
|---|---|---|---|---|---|---|
| 2-Methyl- | 380/4–10 | 50 | 66 | 132–134 | 133–133.5 [25] | 1.4507 |
| 2-n-Propyl- [c] | 400/3–5 | 51 | 57 | 63–65/14 | – | 1.4565 |
| 2-Phenyl- [d] | 350/3–5 | 72 | 31 | 78–80/0.5 | 115/1.5 [26] | – |

[a] Katalysatorenwerke Houdry-Hüls GmbH.
[b] Based on converted *N*-(3-hydroxypropyl)amide.
[c] Alumina contact HO 403 [a].
[d] Alumina contact HO 417 [a].

### 2.3. Cyclizing Amidomethylation of Olefins [27]

As shown above, the cyclic imidic esters *(1a)* and *(1b)* are conveniently obtained from 2-aminoethanols and 3-aminopropanols, respectively. However, the substituted 3-aminopropanols required for a similar preparation of substituted 4*H*-5,6-dihydrooxazines *(1c)* generally are accessible only with difficulty. Substituted 4*H*-dihydrooxazines *(1c)* are more simply prepared from olefins *(8)* and *N*-hydroxymethylamides *(7)*, which are readily obtainable from amides and formaldehyde [27].



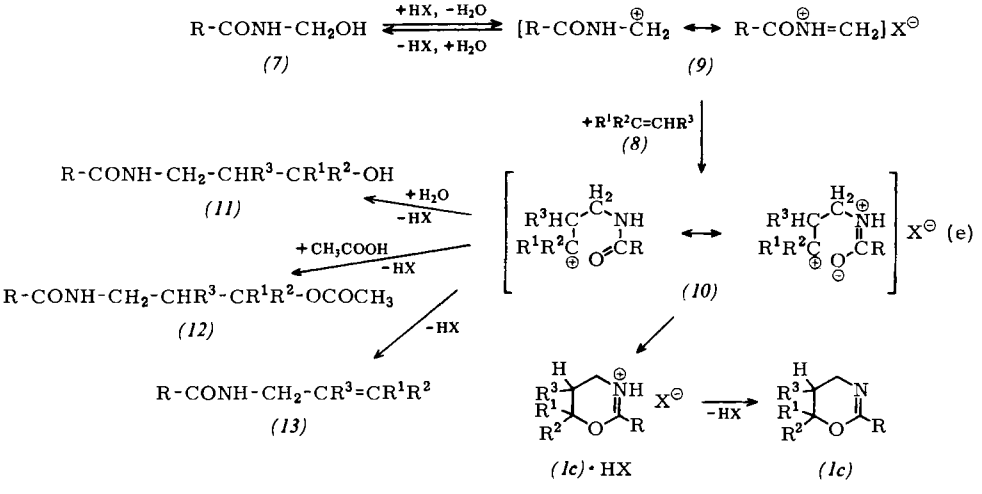
(d)

*(7)* *(8)* *(1c)*


[23] *R. N. Boyd* and *R. C. Rittner*, J. Amer. chem. Soc. *82*, 2032 (1960).
[24] *A. Salomon*, Ber. dtsch. chem. Ges. *26*, 1321 (1893).
[25] *J. F. Arens*, US.-Pat. 2813862 (1957), Organon Inc.; Chem. Abstr. *52*, 8212 (1958).
[26] *J.H.Boyer* and *J.Hamer*, J. Amer. chem. Soc. *77*, 951 (1955).
[27] *W. Seeliger* and *W. Diepers*, Liebigs Ann. Chem., in press.

This reaction, which proceeds in the presence of stoichiometric amounts of a strong acid under otherwise mild conditions, bears a certain resemblance to the amidomethylation [28] and ureidoalkylation [29] of olefins, though these lead to different products. The great versatility of the reaction (d) and the ease with which it can be carried out, together with the ease of hydrolysis of the compounds *(1c)*, permit the convenient preparation of substituted 3-aminopropanols that are otherwise difficult to obtain, or of acyl derivatives of these.

Corresponding to the mechanisms for the amidomethylation proposed by *Hellmann* [30] and the electrophilic addition to olefins, *e.g.* in the Prins reaction [31], reaction (d) may be assumed to proceed in accordance with Scheme (e). The *N*-(hydroxymethyl)amide *(7)* and the acid HX first react to form the resonance-stabilized ion *(9)*, which adds electrophilically to the more nucleophilic carbon atom of the olefin *(8)* to give the intermediate *(10)*. The main reaction under the conditions used is cyclization by intramolecular *O*-alkylation of *(10)* to the HX salt of the 4*H*-dihydrooxazine, while the competing reactions leading to *(11)*, *(12)*, and *(13)* proceed only to a small extent, which varies according to the substituents and reaction conditions.




The salts *(1c)*·HX can be readily converted into the free bases, *e.g.* by treatment with aqueous alkalis.

The reaction (d) is carried out as follows. Roughly equimolar quantities of the olefin *(8)* and the *N*-(hydroxymethyl)amide *(7)* [30] are dissolved in a polar solvent such as glacial acetic acid, and an equimolar quantity of the strong acid (preferably diluted with the same solvent) is gradually added at about 10 °C. Sulfuric acid is particularly suitable. The 4*H*-dihydrooxazinium hydrogen sulfate formed under these conditions can be precipitated by addition of ether and isolated or converted into *(1c)* [27]. The pure 4*H*-dihydrooxazines can be obtained by distillation and characterized as the picrates.

Table 3 shows a number of substituted 4*H*-5,6-dihydrooxazines *(1c)* that have been prepared in this way, most of which were formerly unknown.

Table 3. Substituted 4*H*-5,6-dihydrooxazines *(1c)* prepared by cyclizing amidomethylation of olefins [27].

| | *(1c)* | | | B.p. | $n_D^{20}$ | Yield |
|---|---|---|---|---|---|---|
| R | $R^1$ | $R^2$ | $R^3$ | (°C/mm Hg) | | % |
| $C_6H_5$ | H | $C_6H_5$ | H | 155–156/0.05 | 1.6008 | 79 |
| $C_6H_5$ | H | $C_2H_5$ | H | 93–95/0.02 | 1.5427 | 37 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | H | 107–108/2.0[a] | – | 66 |
| $C_6H_5$ | H | $CH_2$=CH | H | 83–84/0.1 | 1.5597 | 40 |
| $C_6H_5$ | H | $CH_3CO$–O | H | 147–153/2.0 | 1.5432 | 22 |
| $C_6H_5$ | H | $-(CH_2)_4-$ | | 119–120/0.3 | 1.5630 | 69 |
| $CH_3$ | H | $C_6H_5$ | H | 93–94/0.04 | 1.5383 | 61 |
| $CH_3$ | $CH_3$ | $CH_3$ | H | 74–77/60 [32] | 1.4416 | 31 |
| $CH_3$ | H | $CH_2$=CH | H | 99/85 | 1.4646 | 30 |
| $CH_3(CH_2)_{10}$ | H | $C_6H_5$ | H | 140–145/0.005 | 1.5020 | 60 |
| $CH_2$=CH | $CH_3$ | $CH_3$ | H | 101–102/80 | 1.4702 | 26 |
| $CH_2$=CH | H | $C_6H_5$ | H | 103–113/0.005 | 1.5575 | 44 |
| $CH_2$=CH | H | $-(CH_2)_4-$ | | 67–69/0.01 | 1.5071 | 37 |
| H | $CH_3$ | $CH_3$ | H | 86–87/100 | 1.4455 | 15 |
| H | H | $C_6H_5$ | H | 87/0.005 | 1.5654 | 25 |

[a] M.p. 48.5–49 °C.

## 3. Reactions of Cyclic Imidic Esters Involving Ring Cleavage

The reactions of the cyclic imidic esters *(1a)* and *(1b)* with water [33, 21], halogen acids, acyl chlorides [34a], anhydrides [33], and phenols [34b] proceed with ring cleavage and formation of 2- or 3-substituted *N*-alkylamide derivatives, and less frequently of 2-aminoethyl- or 3-aminopropyl esters of carboxylic acids [22, 33], or compounds derived from these. Sections 3.1 to 3.4 contain further examples of the strong tendency of the cyclic imidic esters to undergo ring cleavage, the driving force of which is probably the formation of the more stable amide structure.

Whereas the hydrohalides of the heterocycles *(1a)* and *(1b)* are converted into the 2- or 3-halogenoalkylamides *(6)*, X = halogen, below 100 °C, and often even at room temperature, their *p*-toluenesulfonates (at 140 °C) and methiodides (1 hour at 180 °C) are thermally very stable and react only very slowly.

[28] *W. D. Schaeffer*, US.-Pat. 3190882 (1965), Union Oil Comp. of California; Chem. Abstr. *63*, 9821h (1965).

[29] *H. Petersen*, Angew. Chem. *76*, 909 (1964).

[30] a) *H. Hellmann*, Angew. Chem. *69*, 463 (1957); b) *H. E. Zaugg* and *W. B. Martin*, Org. Reactions *14*, 52 (1965).

[31] *V. Franzen*: Reaktionsmechanismen. Erste Folge. Hüthig, Heidelberg 1958, p. 135.

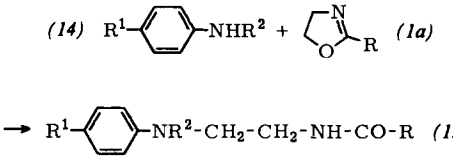
[32] *C. A. Grob*, *F. Ostermayer*, and *W. Raudenbusch*, Helv. chim. Acta *45*, 1672 (1962).

[33] See the collective reviews [5, 11a, 12a, 12b].

[34] *E. M. Fry*, J. org. Chemistry *15*, 802 (1950); b) *A. Jäger*, Ger. Pat. 1062253 (1959), Farbwerke Hoechst; Chem. Abstr. *55*, 13380i (1961).

### 3.1. Reaction with Aromatic Amines

Acyclic imidic esters react with ammonia [35] or amines to form amidines [36]. Oxazolines *(1a)* and aromatic amines *(14)* react at high temperatures in the presence of small quantities of strong acids to form *N*-(2-arylaminoethyl)amides *(15)*.



*(14)* $R^1$-C$_6$H$_4$-$NHR^2$ + *(1a)* → $R^1$-C$_6$H$_4$-$NR^2$-$CH_2$-$CH_2$-NH-CO-R *(15)* (f)

The product obtained by *Kormendy et al.* [37a] from 2-phenyl-$\Delta^2$-oxazoline and anilinium chloride at room temperature also has the structure *(15)* (R = $C_6H_5$, $R^1$ = $R^2$ = H), although it was formulated as the product of addition of aniline to the ring double bond.

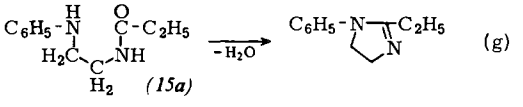
Table 4 shows the success of the reaction (f) with 2-ethyl- and 2-phenyl-$\Delta^2$-oxazoline.

Table 4. *N*-(2-arylaminoethyl)amides *(15)* prepared by the reaction of $\Delta^2$-oxazolines *(1a)* with aromatic amines.

| *(3)* R | $R^1$ | $R^2$ | Yield (%) | B.p. (°C/mm Hg) |
|---|---|---|---|---|
| $C_2H_5$ | H | H | 50 | 185/0.4 |
| $C_2H_5$ | $CH_3$ | H | 84 | 190/0.4 |
| $C_2H_5$ | H | $CH_3$ | 66 | 155–156/0.1 |
| $C_6H_5$ | H | H | 76 | [a] |

[a] M.p. 123–124 °C, Lit. [37a] 123–124 °C, [37b] 127 °C.

The compounds *(15)* can readily be converted into imidazolines.



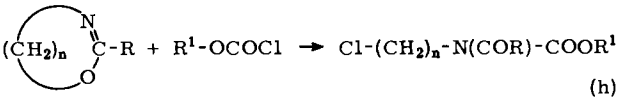
$C_6H_5$-NH-CO-$C_2H_5$ (*15a*) $\xrightarrow{-H_2O}$ $C_6H_5$-N=C($C_2H_5$)-N (g)

#### Procedure

*1-Phenyl-2-ethyl-$\Delta^2$-imidazoline*: 192 g (1.0 mole) of *N*-(2-anilinoethyl)propionamide *(15a)* is mixed in portions with 250 g (1.75 mole) of $P_2O_5$ and heated for 2.5 hr in a bath kept at 150 °C. The solid product is crushed and dissolved in 500 ml of water, and 500 g of KOH in 500 ml of water is added with cooling in ice. After extraction with a total of 600 ml of ether, the ether extract is washed with water, dried over $K_2CO_3$, and fractionated. 1-Phenyl-2-ethyl-$\Delta^2$-imidazoline (133.5 g, 78 %) is obtained as a colorless liquid, b.p. 85–86 °C/0.15 mm Hg.

### 3.2. Reaction with Derivatives of Chloroformic Acid

The addition of aromatic acyl chlorides to oxazolines *(1a)* leads to *N*-2-chloroethyl-*N*-aroylamides [34a]. Acyl chlorides and esters of chloroformic acid react differently with tertiary amines. Whereas the acyl chlorides can form relatively stable salts [38], the esters of chloroformic acid decompose to $CO_2$ and chloroalkanes in the presence of tertiary amines, even under mild conditions [39]. It was therefore of interest to study the behavior of esters of chloroformic acid towards the "tertiary amines" *(1)*. The study showed that in this case the esters of chloroformic acid react in the same manner as acyl chlorides, adding smoothly to oxazolines *(1a)* and 4*H*-dihydrooxazines *(1b)* under mild conditions, sometimes in practically quantitative yields, to give esters *(16)* of *N*-2-chloroethyl- and *N*-3-chloropropyl-*N*-acylcarbamic acids.



*(1a)*: n = 2; *(1b)*: n = 3 + $R^1$-OCOCl → Cl-$(CH_2)_n$-N(COR)-$COOR^1$ (h)

*(16a)*: n = 2; *(16b)*: n = 3

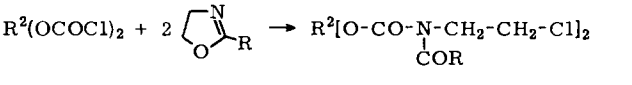
The reaction of esters of chloroformic acid with imidic esters *(1)* in accordance with equation (h) generally is carried out in an inert solvent; after separation the liquid esters *(16)* of *N*-acylcarbamic acids can be purified by distillation, and the crystalline esters by recrystallization. The results are shown in Table 5.

Table 5. Ethyl *N*-ω-chloroalkyl-*N*-acylcarbamates *(16)*, $R^1$ = $C_2H_5$, prepared from $\Delta^2$-oxazolines *(1a)* and 4*H*-5,6-dihydrooxazines *(1b)* with esters of chloroformic acid.

| *(16)* R | n | Temp. (°C) | Yield (%) | B.p. (°C/mm Hg) | $n_D^{20}$ |
|---|---|---|---|---|---|
| $CH_3$ | 2 | 35 [a] | 80 | 115–117/12 | 1.4594 |
| $C_2H_5$ | 2 | 80 [b] | 98 | 120–123/12 | 1.4595 |
| n-$C_3H_7$ | 2 | 80 [b] | 97 | 128–131/10 | 1.4585 |
| n-$C_{11}H_{23}$ | 2 | 80 [b] | 76 | 161–163/0.2 | 1.4622 |
| $C_6H_5$ | 2 | 25 [a] | 84 | 124–126/0.3 | 1.5267 |
| $CH_3$ | 3 | 45 [b] | 42 | 134–135/12 | 1.4618 |
| $C_6H_5$ | 3 | 35 [a] | 77 | 147–150/0.4 | 1.5229 |

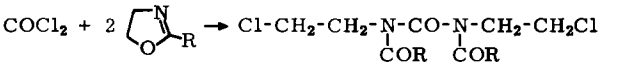
[a] Solvent: ether. [b] Solvent: benzene.

The $\Delta^2$-oxazolines react similarly with diol diesters of chloroformic acid, *e.g.* with the ethylene glycol ester or the cyclohexane-1,4-dimethanol ester; the reaction



$R^2(OCOCl)_2$ + 2 oxazoline → $R^2$[O-CO-N(COR)-$CH_2$-$CH_2$-Cl]$_2$

of $\Delta^2$-oxazolines with phosgene leads to symmetrical bis(2-chloroethyl)diacylureas.



$COCl_2$ + 2 oxazoline → Cl-$CH_2$-$CH_2$-N(COR)-CO-N(COR)-$CH_2$-$CH_2$Cl

### 3.3. Halogenation of 2-Aryl-$\Delta^2$-oxazolines

Chlorine and bromine react with 2-aryl-$\Delta^2$-oxazolines to give different types of products. Tertiary amines such

[35] *A. Pinner* and *F. Klein*, Ber. dtsch. chem. Ges *10*, 1889 (1877)

[36] *H. Hennecka* and *P. Kurtz* in [3], Vol. VIII, p. 703 (1952).

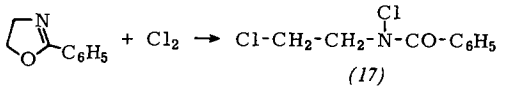
[37] a) *K. Kormendy*, *P. Sohar*, and *J. Volford*, Ann. Univ. Sci. Budapest. Rolando Eötvös nominatae, Sect. Chim. *4*, 61 (1962); Chem. Abstr. *59*, 12805e (1963); b) *K. Kormendy* and *J. Volford*, Acta chim. Acad. Sci. hung. *32*, 121 (1962); Chem. Abstr. *58*, 1444f (1963).

[38] a) *V. Prey*, Ber. dtsch. chem. Ges. *75*, 537 (1942); b) *N. O. V. Sonntag*, Chem. Reviews *52*, 237 (1953).

[39] *M. Matzner*, *R. P. Kurkjy*, and *R. J. Cotter*, Chem. Reviews *64*, 645 (1964).

as pyridine or triethylamine form adducts with bromine [40]. In acyclic imidic esters, the hydrogen atom attached to the nitrogen is replaced by bromine [41].

2-Phenyl-$\Delta^2$-oxazoline smoothly adds chlorine, with ring cleavage, to form the *N*-chloroamide *(17)*.



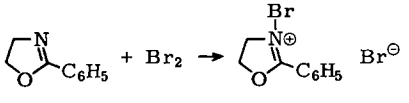
*(17)*

Procedure

*N-chloro-N-2-chloroethylbenzamide (17)*: A mixture of 75.0 g (*ca.* 0.5 mole) of 2-phenyl-$\Delta^2$-oxazoline with 250 ml of $CCl_4$ is saturated with chlorine at 20 °C during $2^1/_2$ hr, and the reaction mixture is then allowed to stand for 60 hr. The excess of chlorine is driven out of the clear solution by a current of nitrogen. The product crystallizes on cooling with ice-water and scratching; it is collected by suction filtration, washed with a little cold $CCl_4$, and dried in air. A second fraction can be obtained from the filtrate by concentration and cooling. A yield of 76.5 g (69 %) of crude, colorless crystals is obtained, and after recrystallization from $CCl_4$ (the temperature not exceeding 30 °C), the product melts at 59–61 °C.

This reaction evidently proceeds *via* an *N*-chlorooxazolinium chloride, which undergoes the ring cleavage characteristic of oxazolinium chlorides.

On the other hand, when bromine is allowed to act on 2-phenyl-$\Delta^2$-oxazoline, the addition stops at the first stage. A crystalline, orange substance is obtained, which analysis and spectra indicate to be *N*-bromo-2-phenyloxazolinium bromide *(18)*.



*(18)*

However, it appears that not all bromine adducts of 2-aryloxazolines have an ionic structure similar to that of *(18)*. The investigations are complicated by the fact that other 2-aryloxazolines often give addition products that do not contain stoichiometric quantities of bromine.

Substitution in the phenyl nucleus can be ruled out, since 2-phenyloxazoline is obtained from *(17)* and *(18)* by treatment with aqueous alkalis. From 2-(4-methoxyphenyl) $\Delta^2$-oxazoline, on the other hand, products brominated also in the phenyl nucleus have been obtained.

Depending on the method of preparation, the bromine adduct *(18)* may be an unstable substance melting at 40 °C and smelling faintly of bromine, even after purification, or a stable substance melting at 85–87 °C and having no smell of bromine, but having the same IR spectrum as the other product [*]. The lower-melting form is obtained by dropwise addition of the calculated quantity of undiluted bromine to the phenyloxazoline (with slight cooling); the higher-melting form is obtained in the presence of a solvent.

Procedure

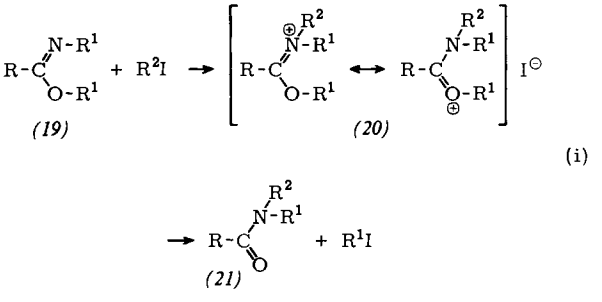
*N-Bromo-2-phenyloxazolinium Bromide (18)*: 32 g (0.2 mole) of bromine is added to a solution of 37 g (0.25 mole) of 2-phenyl-$\Delta^2$-oxazoline in 200 ml of anhydrous ether over 15 min at room temperature. The mixture is stirred for three hr and then refluxed for 1 hr. On standing for 2 days the addition compound, which is sparingly soluble in ether, separates as orange leaflets, m.p. 85–87 °C, yield 60 g (97 %).

To determine the content of "active" bromine, 1.000 g of this adduct is dissolved in 10 ml of acetone and the solution is added to a mixture of 30 ml of 10 % KI solution and 30 ml of acetone. Concentrated HCl (5 ml) is added; this does not lead to any intensification of the iodine color. Solutions of pure samples titrated with 0.1 N thiosulfate solution give the calculated titer of 32.5 ml, corresponding to 26.0 % of "active" bromine.

The compounds *(18)* can be used for the bromination of many substances, *e.g.* olefins, from which dibromo adducts have been obtained.

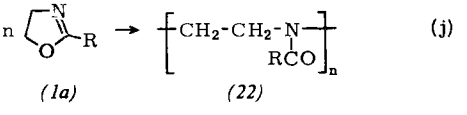
### 3.4. Polymerization of $\Delta^2$-Oxazolines [42]

*N*-Substituted imidic esters *(19)* are converted into *N,N*-disubstituted amides *(21)* by alkylating agents, a compound *(20)* occurring as an intermediate [4].



*(19)* *(20)* *(21)* (i)

The question arose whether this reaction (as described for the cyclic iminolactones *(3)* and cyclic iminocarbonates *(4)* [7c]) can lead to polymerization when the two groups $R^1$ in the imidic ester *(19)* form a ring. The oxazolines *(1a)* can in fact be converted into high polymers *(22)* containing *N*-acylethylenimine units with the aid of cationic catalysts [43].



*(1a)* *(22)* (j)

The preparation of *N*-vinylcarboxamides by dehydrochlorination of *N*-2-chloroethylamides with alkali and the polymerization of these *N*-vinyl compounds with peroxides or Friedel-Crafts catalysts have been described by *Bácskai*

[40] *A. Roedig* in [3], Vol. V/4, p. 34 (1960).

[41] a) *H. L. Wheeler* and *P. T. Walden*, Amer. chem. J. *19*, 129 (1897); b) *J. Stieglitz*, *ibid. 18*, 751 (1896).

[*] This is true of the spectra of the melts; the spectra of the crystalline compounds show slight shifts of individual bands, which can be attributed to differences in crystal structure.

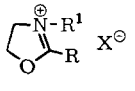
[42] *W. Seeliger* and *W. Thier*, Angew. Chem. *78*, 613 (1966); Angew. Chem. internat. Edit. *5*, 612 (1966).

[43] *W. Seeliger*, German published Pat. appl. 1206585 (1965), Chem. Werke Hüls.

and *Halmos*[44]. It was later found that the dehydrochlorination leads predominantly to 2-alkyl-$\Delta^2$-oxazolines[45], so that one might conclude that these authors had already obtained polyalkyloxazolines *(22)*. However, this cannot be so, since the properties of the polymers and peculiarities of the polymerization reported by *Bácskai* and *Halmos* disagree in essential points with the results obtained in the polymerization of pure 2-alkyl-$\Delta^2$-oxazolines.

### 3.4.1. Catalysts

Compounds of the type *(23)*, where $R^1$ is hydrogen, an alkyl group, or an acyl group and $X^\ominus$ is the weakly nucleophilic anion of a strong acid, generally are suitable as catalysts. These catalysts may be used as such,



*(23)*

or may be generated in the reaction medium by the addition of strong acids or their esters or anhydrides. Complexing agents of the Friedel-Crafts type are also effective. For example, sulfuric acid, dialkyl sulfates, sulfonic acids and their alkyl esters, alkyl iodides, iodine (for 2-alkyloxazolines), the mixed *p*-toluenesulfonic-benzoic anhydride[46a], $BF_3$-ether adduct, *p*-nitrophenyldiazonium fluoroborate, or the crystalline salts *(23)*, R = phenyl, $R^1$ = H, and $X^\ominus$ = *p*-toluenesulfonate or perchlorate[46b], have been found suitable.

Simple carboxylic acids and their anhydrides are not suitable as catalysts for the preparation of polyoxazolines *(22)* of high molecular weight; the corresponding anions are presumably too strongly nucleophilic and become irreversibly attached to the chain ends. Peroxides are also unsuitable.

### 3.4.2. Conditions

In the presence of sufficiently large quantities of catalyst, the reaction (j) proceeds already at room temperature, even though only slowly. The polymerization of the oxazolines *(1a)* (*e.g.* R = ethyl or phenyl) begins rapidly between 120 and 130 °C; the reaction stops when the temperature is reduced to less than 120 °C, and starts again between 120 and 130 °C.

To obtain very high molecular weights, the polymerization should be carried out for several hours in the absence of solvent to as high a conversion as possible.

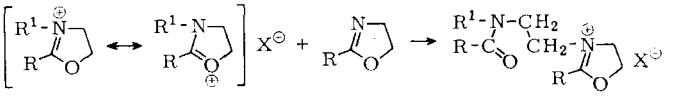
[44] a) *R. Bácskai* and *L. Halmos*, Magyar Chem. Folyóirat *60*, 8, 43 (1954); Chem. Abstr. *52*, 3396 (1958); b) *R. Bácskai*, Acta chim. Acad. Sci. hung. *19*, 1 (1959); Chem. Abstr. *54*, 13097 (1960).

[45] a) *A. A. Vansheidt, S. S. Skorokhodov, S. G. Ershova*, and *N. V. Mikhailova*, Vysokomolekul. Soedin. *3*, 320 (1961), Chem. Abstr. *61*, 3084 (1964); b) *S. S. Skorokhodov, S. G. Ershova, N. V. Mikhailova*, and *A. A. Vansheidt*, Zh. Obshch. Khim. *31*, 3626 (1961); Chem. Abstr. *57*, 8555 (1962).

[46] a) *C. G. Overberger* and *E. Sarlo*, J. Amer. chem. Soc. *85*, 2446 (1963); b) *S. Hünig* and *L. Geldern*, Chem. Ber. *96*, 3110 (1963).

### 3.4.3. Reaction Mechanism

The polymerization of oxazolines may be interpreted analogously to the rearrangement of imidic esters formulated in equation (i):



*(23)* *(1a)* (k)

The initiation, which consists in alkylation of the basic $\Delta^2$-oxazoline by the oxazolinium cation, can be repeated [$R^1$ in *(23)* then denotes the growing polymer chain] as long as monomer molecules are available. Prerequisite for completion of the reaction is that $X^\ominus$ should not be capable of being alkylated or that the alkylation product $R^1$–N(COR)–$CH_2$–$CH_2$–X can again quaternize *(1a)*, as is the case when X = I.

### 3.4.4. Purification of the Monomer

Like most cationic polymerizations, that of oxazolines *(1a)* is very sensitive towards impurities. Though even crude monomers *(1a)* containing water can be polymerized at sufficiently high catalyst concentrations, the viscosities of the resulting products are low. If the reduced viscosities $\eta_{red}$ (measured in 0.5 % chloroform solution at 20 °C) of polymers obtained from samples of 2-phenyloxazoline purified in various ways are plotted against the catalyst concentrations used, viscosity maxima whose positions depend on the pretreatment of the monomer are obtained (Fig. 2). No direct dependence of the viscosity on the purity (up to 99.99 %) as found by gas chromatography could be established. It was therefore necessary to develop suitable purification methods on an empirical basis.

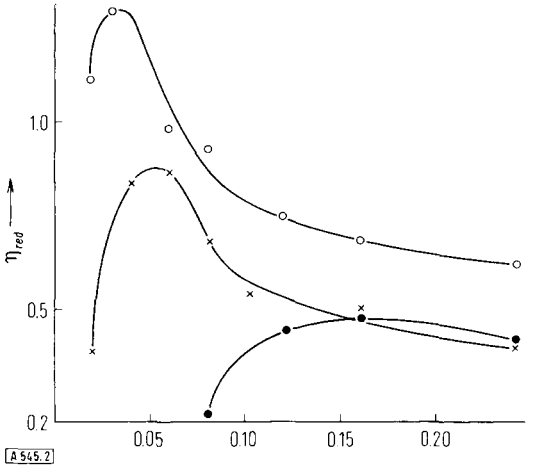



Fig. 2. Polymerization of 2-phenyl-$\Delta^2$-oxazoline; viscosity maxima for monomers purified in various ways; catalyst: 2-phenyl-$\Delta^2$-oxazolinium *p*-toluenesulfonate.

●: monomer distilled once with 1 wt.-% of benzoyl chloride; ×: monomer preteated with powdered KOH (50 °C, 4 hr), filtered and distilled once with 1 wt.-% of benzoyl chloride; ○: monomer rectified after pretreatment with powdered KOH.

Ordinate: Reduced viscosity $\eta_{red} = (\eta_{rel}-1)/c$ (dl/g).

Abscissa: Quantity of catalyst added (mole-%).

The oxazolines can be purified adequately for polymerization purposes by careful fractionation. For laboratory experiments,a two-stage purification is preferable. Most of the interfering impurities are first bound by pretreatment with KOH powder, sodium, small quantities of benzoyl chloride, or diisocyanates, or by polymerization of a small proportion of the monomer. Subsequent column distillation then gives a very pure monomer.

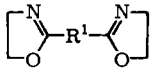
### 3.4.5. Molecular Weights of Polyoxazolines

Theoretically, all the catalyst molecules present should almost simultaneously initiate polymer chains in accordance with equation (k), so that, on statistical grounds, the lengths of all the polymer chains should be approximately the same, and should depend only on the catalyst concentration. The investigation of the polymers obtained at various catalyst concentrations is not yet complete, but it may be concluded from light-scattering measurements that the maxima in Figure 2 correspond to weight-average molecular weights $\overline{M}_w$ of about 300000, 200000, and 100000, respectively. The Zimm diagrams suggest that the polymers *(22)* generally are linear.

### 3.4.6. Copolymerizations

Polyoxazolines *(22)* with different groups R, which may contain halogen, can be prepared by copolymerization of differently substituted oxazolines *(1a)*.

Alkylene- or arylene-bisoxazolines *(24)* give (depending



*(24)*

on the quantity used) viscous, soluble, evidently branched, or even completely cross-linked products. 4*H*-5,6-Dihydrooxazines *(1b)* and *(1c)* also can be polymerized or copolymerized with oxazolines *(1a)* in the same manner the resulting polymers containing (sometimes substituted) poly-*N*-acyltrimethylenimine units.

### 3.4.7. Properties of the Polymers

Polyoxazolines having degrees of polymerization above about 100 are solid and when first obtained more or less yellow. Their properties are strongly dependent on the substituents. Polymers *(22)* in which R is methyl or ethyl dissolve readily in water, in which the derivatives with higher alkyl groups are practically insoluble. All polyoxazolines, however, dissolve very easily in chloroform.

## 4. Reactions at the Alkyl Group of 2-Alkyl-$\Delta^2$-oxazolines

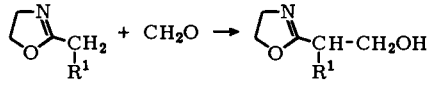
It has already been pointed out that the reactions of $\Delta^2$-oxazolines studied so far are mainly those leading to open-chain amide derivatives. The only known reactions of the alkyl group in position 2 are additions and condensations with aldehydes.

### 4.1. 2-Alkyl-$\Delta^2$-oxazolines and Aldehydes

A reaction that has no parallel in acyclic imidic esters [11a] is the condensation of quaternized 2-alkyl-oxazolines with aromatic aldehydes [47]. Another unusual reaction is the addition of aromatic aldehydes to 2-dichloromethyloxazoline, which proceeds under mild conditions [48]. 4-Disubstituted derivatives of $\Delta^2$-oxazolines *(1a)*, which are much more stable (particularly towards acid hydrolysis) than the unsubstituted compounds, condense with aromatic aldehydes [49] and undergo addition and condensation with any aldehydes [50]. However, the literature [50] does not contain characteristic data or yields for the products obtained from alkyloxazolines substituted only in position 2.

#### 4.1.1. 2-(2-Hydroxyalkyl)-$\Delta^2$-oxazolines

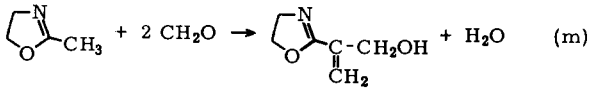
2 Alkyloxazolines *(25)* react with paraformaldehyde in the presence of catalytic amounts of strong bases (*e.g.* triethylamine) to form the compounds *(26)*.



(1)

*(25a)*: $R^1 = H$ *(26a)*: $R^1 = H$
*(25b)*: $R^1 = CH_3$ *(26b)*: $R^1 = CH_3$

The reaction with 2-methyloxazoline *(25a)* proceeds differently when formaldehyde is present in excess: 2-(2-oxazolinyl)-2-propen-1-ol *(27)* is formed in good



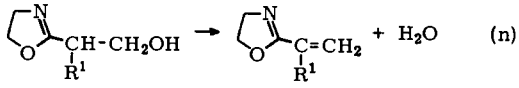
(m)

*(25a)* *(27)*

yield. The reaction of 2-vinyloxazoline *(28a)* with formaldehyde also leads to *(27)*.

#### 4.1.2. 2-Alkenyl-$\Delta^2$-oxazolines

Water can be eliminated readily and in high yield from the hydroxyethyl derivatives *(26)* at elevated temperatures when alkali metal alkoxides or other strongly



(n)

*(26)* *(28a)*: $R^1 = H$
*(28b)*: $R^1 = CH_3$

alkaline substances are used as catalysts. For the compounds *(26)* with no substituents on the ring, the usual

[47] *F. M. Hamer* and *R. J. Rathbone*, Brit. Pat. 541330 (1941), Kodak Ltd.; Chem. Abstr. *36*, 4767 (1942).

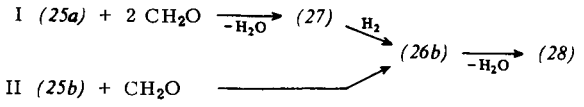
[48] *H. Bretschneider*, *G. Piekarski*, and *K. Biemann*, Mh. Chem. *85*, 882 (1954).

[49] *H. L. Wehrmeister*, J. org. Chemistry *27*, 4418 (1962).

[50] *H. L. Wehrmeister*, French Pat. 1385727 (1965), Commercial Solvents Corp.; Chem. Abstr. *63*, 610c (1965).

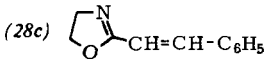
acidic calatysts cannot be used owing to the tendency of these compounds to polymerize.

The vinyl derivatives *(28)* can be polymerized by a free-radical mechanism [51]. The interesting 2-isopropenyloxazoline *(28b)* can be prepared by two routes (I and II), in yields of 41 % and 54 % respectively.




Compound *(27)* can be selectively reduced to *(26b)* in a yield of more than 80 % with Raney nickel at normal pressure and room temperature.

Other aldehydes also can be condensed with the oxazolines *(25)*. However, it is recommended that stoichiometric quantities of acidic catalysts should be used with these compounds, since the condensation is otherwise accompanied by polymerization. Condensation of *(25a)* with benzaldehyde by elimination of water in the presence of equimolar quantities of zinc chloride or *p*-toluenesulfonic acid leads to 2-styryl-$\Delta^2$-oxazoline *(28c)* in 44 % yield. When zinc chloride is used, the

*(28c)* 

reaction proceeds *via* a stable, crystalline complex intermediate containing 2 molecules of 2-styryloxazoline per molecule $ZnCl_2$, in which the UV absorption of the former [$\lambda_{max}$ = 280 mμ (ε = 24200)] is retained unchanged, and which is decomposed by alkali solutions.

### 4.1.3. Compounds Prepared

Some of the compounds discussed in Section 4.1 are listed in Table 6.

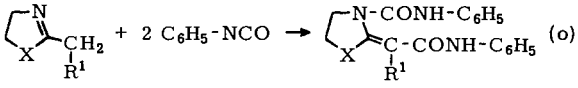
Table 6. 2-Alkenyl- and 2-(2-hydroxyalkyl)-$\Delta^2$-oxazolines.

| Cpd. | Prepn. | Yield (%) | B.p. (°C/mm Hg) (M.p., °C) | $n_D^{20}$ |
|---|---|---|---|---|
| *(28a)* | Eq. (n) | 64.5 | 75/93 | 1.4780 |
| *(28b)* | Eq. (n) | 76.5 | 90/98 | 1.4768 |
| *(27)* | Eq. (m) | 66 | 97—99/1 (44—46) | — |
| *(26a)* | Eq. (l) | 23 | 58/0.1 | 1.4830 |
| *(26b)* | Eq. (l) | 73 | 62/0.1 | 1.4770 |
| *(28c)* | 4.1.2. | 44 | 100—105/0.05 (54) | — |

## 4.2. 2-Alkyl-$\Delta^2$-oxazolines and Isocyanates [52]

### 4.2.1. Results

The 2-alkyloxazolines *(25)* are surprisingly reactive towards phenyl isocyanate. A mixture of 1 mole of *(25a)* and 2 moles of phenyl isocyanate prepared at room temperature yields a crystalline 1:2 adduct, 3-(phenylcarbamoyl)-2-oxazolidinylideneacetanilide *(30a)*, in a strongly exothermic reaction.




*(25a)*: X = O; $R^1$ = H
*(25b)*: X = O; $R^1$ = $CH_3$
*(29)*: X = S; $R^1$ = H

*(30a)*: X = O; $R^1$ = H
*(30b)*: X = O; $R^1$ = $CH_3$
*(30c)*: X = S; $R^1$ = H

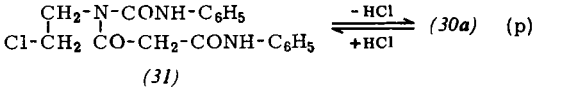
2-Ethyl-, 2-propyl-, and 2-n-undecyl-$\Delta^2$-oxazoline and 2-methyl-$\Delta^2$-thiazoline *(29)* also form adducts of the type *(30)*. 2-Isopropyl- and 2-cyclohexyloxazoline, on the other hand, do not react with phenyl isocyanate. Further, no reaction occurs when isothiocyanates are used in equation (o) instead of phenyl isocyanate.

The structure of the compounds *(30)* was confirmed by an independent synthesis of *(30a)* and by comparison of the IR spectra. The products obtained in accordance with equation (o) are shown in Table 7.

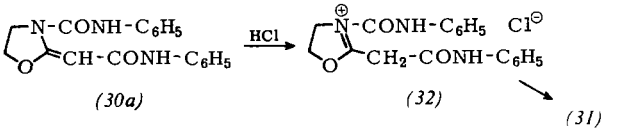
Table 7. Adducts obtained from 2-alkyl-$\Delta^2$-oxazolines and 2-methyl-$\Delta^2$-thiazoline with phenyl isocyanate.

| | *(30)* $R^1$ | X | Yield (%) | M.p. (°C) |
|---|---|---|---|---|
| *(30a)* | H | O | 81 | 153—156 |
| *(30b)* | $CH_3$ | O | 59 | 126—127 |
| | $C_2H_5$ | O | 43 | 100—102 |
| | n-$C_{10}H_{21}$ | O | 42 | 104—105 |
| *(30c)* | H | S | 60 | 169—174 |

The last step in the independent synthesis of *(30a)* is the dehydrochlorination of *(31)* with cyclization, which

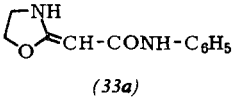



leads to an interesting intramolecular *O*-alkylation of the malonamide derivative *(31)*, though a 5-membered ring would also result from *C*-alkylation. Remarkably, the reaction (p) is reversible, and *(30a)* is smoothly converted into *(31)* with HCl in dioxane at room temperature. The reaction may be assumed to proceed *via* the oxazolinium chloride *(32)*, which rearranges to *(31)*, in analogy to equation (h).

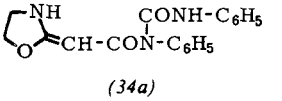



### 4.2.2. Intermediates and Reaction Mechanism

In reaction (o) with 2-methyloxazoline *(25a)*, two intermediates were isolated. On the basis of their spectra these compounds are assigned the structures



*(33a)*



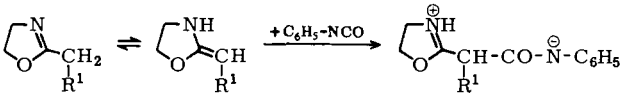
*(34a)*

[51] *L. S. Luskin* and *P. L. De Benneville*, Ger. Pat. 1067437 (1959); Röhm and Haas; Chem. Abstr. *55*, 19960a (1961).

[52] *R. Nehring* and *W. Seeliger*, Liebigs Ann. Chem., in press.

*(33a)* and *(34a)*. Compound *(30a)* is formed from *(34a)* by rearrangement on heating, and from *(33a)* by the uptake of a further molecule of phenyl isocyanate.

On the basis of these observations and of the known [53] reactions of compounds such as cyclopentanone anil, the oxazoline *(25)* [and analogously the thiazoline *(29)*] is assumed to contain a small equilibrium concentration of the "enamine form" *(35)* (possibly induced by phenyl isocyanate), which then adds phenyl isocyanate to form the intermediate *(36)*.




*(25)* *(35)* *(36)*

Compound *(36)* can form the anilide *(33)* by proton shift and the unstable diadduct *(34)* by addition of phenyl isocyanate with proton shift, both *(33)* and *(34)* being converted into the dianilide *(30)* under the conditions of the reaction.

### 4.2.3. Reaction with Diisocyanates

2-Alkyloxazolines *(25)* react with diisocyanates to form polymers; *(25a)* reacts with aromatic diisocyanates vigorously and with considerable evolution of heat when the reactants are undiluted. If the temperature is kept below about 120 °C, the polymers are linear; they can be cross-linked by heating. Since the IR spectra of the linear polymers correspond to those of the compounds *(30a)* and *(30b)*, the structures are assumed to be analogous. 2-Alkyl-4*H*-5,6-dihydrooxazines *(1b)* also form polyadducts with diisocyanates.

## 4.3. Halogenation of 2-Alkyl-$\Delta^2$-oxazolines [54]

In Section 3.3 it was shown that chlorine and bromine can add to 2-aryloxazolines. It was of interest to determine whether the 2-alkyl derivatives *(25)* behave analogously or undergo substitutions similar to those of alkyl groups activated by an adjacent C=N double bond. For example, 2- or 4-methylpyridine derivatives undergo unusually fast halogenation in the methyl group [55], whereas methylaryl compounds generally require free-radical initiators for halogenation of the alkyl group.

The halogenation of 2-alkyloxazolines *(25)* leads mainly to substitution products, *i.e.* *N*-2-halogenoethylamides of carboxylic acids that are partially or completely halogenated in the α position, and $\Delta^2$-oxazolines with halogenoalkyl substituents.

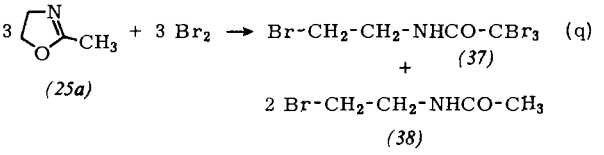
[53] *R. Huisgen, R. Grashey, J. M. Vernon*, and *R. Kunz*, Tetrahedron *21*, 3311 (1965).

[54] *E. Aufderhaar* and *W. Seeliger*, Liebigs Ann. Chem., in press.

[55] a) *B. R. Brown, D. L. Hammick, B. H. Thewlis*, and *D. J. Walbridge*, J. chem. Soc. (London) *1953*, 1369, and literature cited there; b) *W. Koenigs*, Ber. dtsch. chem. Ges. *31*, 2364 (1898).

### 4.3.1. Bromination

When an equimolar amount of bromine is added dropwise to methyloxazoline *(25a)*, a vigorous reaction takes place even in the cold, leading to a mixture of *N*-2-bromoethyltribromoacetamide *(37)* and *N*-2-bromoethylacetamide *(38)*.




*(25a)*

Similarly, other 2-alkyloxazolines give *N*-2-bromoethylamides of α-dibrominated carboxylic acids. No partially α-brominated products could be isolated, even when less than one equivalent of bromine was used. The compounds *(37)* and *(38)* undoubtedly are formed by rearrangement of the corresponding oxazolinium bromides.

Surprisingly, *N*-2-bromoethylamides of α-perbrominated carboxylic acids, which are very sensitive to alkalis, can be cyclized smoothly to 2-(α-perbromoalkyl)oxazolines when the treatment with strong alkali is carried out at room temperature in a heterogeneous mixture, *e.g.* with caustic alkali powder in inert solvents. Thus the interesting 2-tribromomethyloxazoline is formed in 78 % yield in the form of colorless crystals from *(37)*, which can be obtained in 72 % yield in accordance with equation (q).

2- or 4-Methylpyridines (see Section 4.3.) are brominated in glacial acetic acid in the presence of a base, *e.g.* sodium acetate [55]. On the other hand, the 2-alkyl-$\Delta^2$-oxazolines can be halogenated in the undiluted form or in an inert solvent, and it is not even necessary that unchanged oxazoline should be present to act as a base. The same products are obtained in comparable yields even when *e.g.* 2-methyloxazoline is added dropwise to an excess of bromine diluted with ether. In this case an orange salt mixture is first formed, and the IR spectrum shows that this contains bromine adducts of the type *(18)* as well as the hydrobromides of the brominated and the unbrominated oxazolines.

### 4.3.2. Chlorination

In contrast to bromination, chlorination of 2-alkyloxazolines *(25)* leads to partially halogenated products as well. 2-(1-Monochloroalkyl)oxazolines can be prepared directly by the use of an excess of the oxazoline.

2-Ethyloxazoline and an equimolar amount of chlorine give a mixture containing the compounds *(39a)*–*(39c)*, which are difficult to separate; the $^1$H-NMR spectra give values of 1:1:1 to 1.7:1:1.5 for the ratio *(39a)*: *(39b)*: *(39c)*.

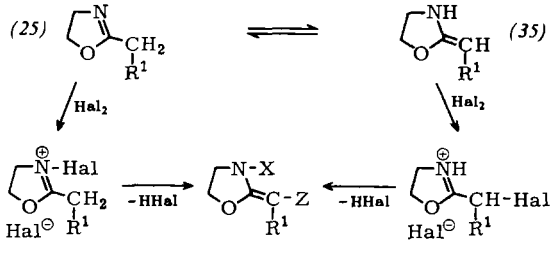
Cl–$CH_2$–$CH_2$–NH–CO–R

*(39a)*: R = $CH_2$–$CH_3$
*(39b)*: R = CHCl–$CH_3$
*(39c)*: R = $CCl_2$–$CH_3$

The chlorination of 2-methyloxazoline leads to a corresponding mixture of chlorinated amides. Conversion

into the mixture of the corresponding oxazolines by treatment with alkali, followed by further chlorination and repetition of this process several times, ultimately leads to pure 2-trichloromethyloxazoline.

On the basis of the existing experimental results, it may be concluded that the halogenation of 2-alkyloxazolines *(25)* proceeds *via* one of the enamine structures *(41)*; *(41a)* could be formed from the oxazoline *(25)* *via* an *N*-halogenooxazolinium halide *(40)*, and *(41b)* from the "enamine form" *(35)* that may exist in equilibrium with *(25)*, *via* the halogen adduct *(42)*.



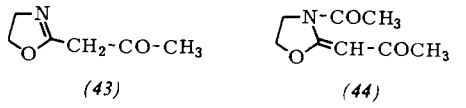
*(40)* *(41a)*: X = Hal; Z = H *(42)*
*(41b)*: X = H; Z = Hal

The data are not sufficient to permit a decision as to whether *(41a)* or *(41b)* occurs as an intermediate. An alkyloxazoline would act as hydrogen halide acceptor in both cases. The difference in degrees of halogenation of the final products obtained with bromine and with chlorine probably is due to the fact that amides *(39)* that under the conditions of the reaction cannot be halogenated further are formed more rapidly with chlorine than with bromine, as was shown in the halogenation of 2-aryl-$\Delta^2$-oxazolines.

### 4.4. 2-Alkyl-$\Delta^2$-oxazolines and Ketene

The reaction of 2-alkyloxazolines *(25)* with ketene is complicated, since the ketene not only enters into addition reactions, but is also polymerized by the base *(25)*.

The principal modes of reaction can be seen in the reaction with 2-methyloxazoline *(25a)*, which can lead to the addition of one or two molecules of ketene, depending on the conditions. The monoaddition product, the *C*-acetyl compound *(43)*, melts at 115–116 °C, can be distilled, and exists as the enol, as expected.



*(43)* *(44)*

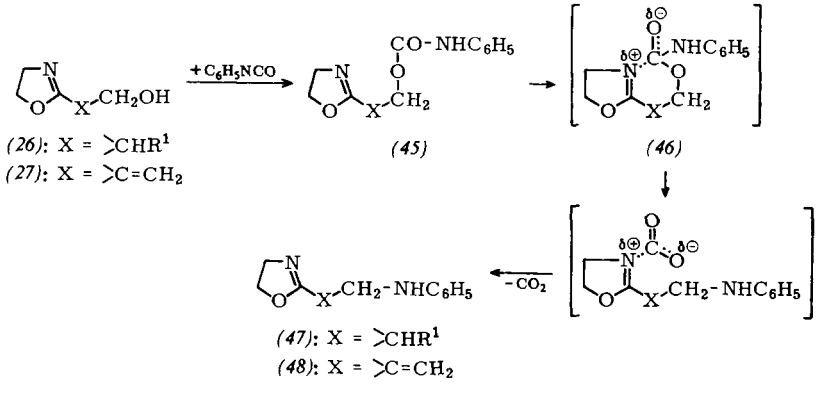
Compound *(43)* is sparingly soluble in cold ether, exhibits the reactions of enols, and forms stable complexes with heavy metal salts.

The structure proposed for the diadduct is that of (3-acetyl-2-oxazolidinylidene)acetone *(44)*.

## 5. Reactions with Other Substituents in Position 2 of $\Delta^2$-Oxazolines

### 5.1. 2-(2-Phenylcarbamoyloxyalkyl)-$\Delta^2$-oxazolines and their Decarboxylation

The ready attack of phenyl isocyanate on 2-alkyloxazolines *(25)* was discussed in Section 4.2. If the hydroxyethyloxazolines *(26)* or *(27)* are used in this reaction, urethanes *(45)* are formed. These can be decarboxylated readily by heating to about 150 °C, giving 2-(2-anilinoethyl)-$\Delta^2$-oxazolines *(47)* or 2-(2-oxazolinyl)-*N*-phenylallylamine *(48)*.



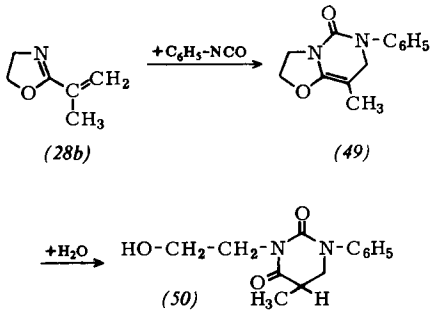
*(26)*: X = $>CHR^1$
*(27)*: X = $>C=CH_2$
*(45)* *(46)*
*(47)*: X = $>CHR^1$
*(48)*: X = $>C=CH_2$

The decarboxylation probably involves the approach of the carbonyl group to the basic ring nitrogen, as shown in *(46)*; this would explain the ease with which this reaction proceeds.

The decarboxylation of 2-(2-phenylcarbamoyloxyethyl)-pyridine leads analogously, though less smoothly, to 2-(2-anilinoethyl)pyridine.

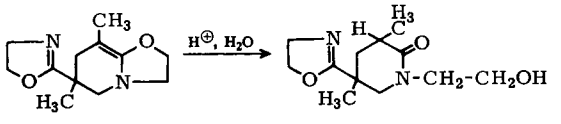
### 5.2. 2-Alkenyl-$\Delta^2$-oxazolines as "Dienes"

The reaction of 2-isopropenyl-$\Delta^2$-oxazoline *(28b)* with phenyl isocyanate leads to an unstable 1:1 adduct which tends to polymerize, and whose characteristic double bond absorption in the IR spectrum at 1760 $cm^{-1}$ is compatible with the structure *(49)*. This compound, which must result from a 1,4-addition to the "diene" system of *(28b)*, very rapidly takes up 1 mole of water in acidic solution to form a hydrolysis product to which structure *(50)* can be assigned.



(28b) (49) (r)

Equation (r) suggests that the possibility of other 1,4-additions should be investigated. Attempts were therefore made to bring about reaction of *(28b)* with dienophiles such as acrylonitrile, maleic anhydride, and hexachlorocyclopentadiene. The only product that could be isolated was a dimer of isopropenyl-$\Delta^2$-oxazoline, to which the structure *(51)* is assigned on the basis of analysis and IR spectra.



*(51)* *(52)*

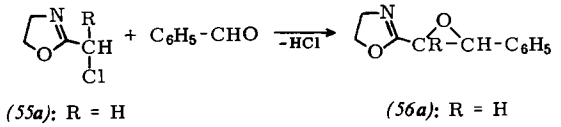
As expected, *(51)* is hydrolysed exothermally in aqueous acid with formation of *(52)*.

### 5.3. 2-(1,2-Epoxyalkyl)-$\Delta^2$-oxazolines

In the preparation of epoxides by the Darzens method (condensation of α-chloro esters with carbonyl compounds in the presence of strongly alkaline substances such as sodamide or potassium t-butoxide), the first step is assumed to be the formation of a carbanion *(53)* [56], to which the carbonyl compound can add. Similarly, *(54)* could be formed as an intermediate from 2-(α-chloroalkyl)oxazolines.

*(53)* *(54)*

It was actually found that α-chloroalkyloxazolines *(55)* can react in the same manner with benzaldehyde in the presence of potassium t-butoxide to give good yields of the 2-(1,2-epoxyalkyl)-$\Delta^2$-oxazolines *(56)*.



*(55a)*: R = H *(56a)*: R = H
*(55b)*: R = $CH_3$ *(56b)*: R = $CH_3$

### Procedure

*2-(2-Phenyl-1,2-epoxyethyl)-$\Delta^2$-oxazoline (56a)*: A solution of 7.8 g (0.2 g-atom) of potassium in 200 ml of anhydrous tert-butyl alcohol is added over a period of 1.5 hr to a mixture of 24 g (0.2 mole) of 2-chloromethyl-$\Delta^2$-oxazoline and 63 g (0.6 mole) of benzaldehyde at 20 °C. The reaction mixture is then stirred for 2 hr at room temperature and refluxed for 3 hr. The mixture is allowed to stand overnight, and the precipitated KCl (15 g, 100 %) is centrifuged off; the solvent is evaporated from the clear dark-red supernatant and the residue is distilled. 23 g (61 %) of the condensation product is obtained in the boiling range 135–138 °C/0.5 mm Hg. The pure compound is a colorless oil, b.p. 102 °C/0.01 mm Hg, which rapidly turns brown in air.

[56] *S. Winstein* and *R. B. Henderson* in [11a], Vol. 1, p. 14 (1950).

## 6. 2,3-Cycloadditions to Cyclic Imidic Esters

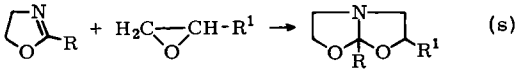
Apart from the additions with ring cleavage described in Section 3, cyclic imidic esters have also been observed to undergo additions with retention of the ring.

By reaction of the imidic ester *(1)* with epoxides, 2,3-cycloadducts [57] can be isolated.

Epoxides undergo a number of additions to C=O or C=N bonds leading to 1,3-dioxolanes [58], 2-oxazolidinones [59], or 1,3-oxazolidines [60]. No reactions with imidic esters are known as yet.

### 6.1. 4,6-Dioxa-1-azabicyclo[3.3.0]octanes

When a $\Delta^2$-oxazoline is heated with equimolar amounts of an epoxide at 120–200 °C in the absence of air and moisture, the epoxide adds to the double bond of the oxazoline to give the 4,6-dioxa-1-azabicyclo[3.3.0]-octane *(57)*.

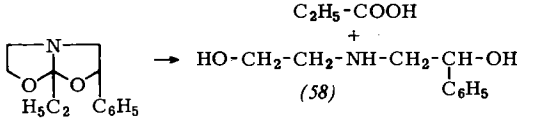


(s)

*(57)*

Instead of epoxides, substances that yield epoxides under the conditions of the reaction may be used, *e.g.* cyclic carbonates of 1,2-diols [57]. The addition of catalysts such as lithium chloride can accelerate the reaction, but is generally unnecessary; presumably the base *(57)* formed has an autocatalytic effect.

The compounds *(57)* are high-boiling but distillable strong bases, the cyclic structure of which has been shown by molecular-weight determinations and by IR spectra, which contain no absorption in the region of the O–H, N–H, C=O, and C=N vibrations [57], as well as by acid hydrolysis, which leads to the carboxylic acids R–COOH. The position of the substituent $R^1$ in *(57)* was proved in one case by hydrolysis to the known ethanolamine derivative *(58)*.



*(58)*

[57] *R. Feinauer* and *W. Seeliger*, Liebigs Ann. Chem., in press.

[58] *M. T. Bogert* and *R. O. Roblin*, J. Amer. chem. Soc. *55*, 3741 (1933).

[59] *K. Gulbins*, *G. Benzing*, *R. Maysenhölder*, and *K. Hamann*, Chem. Ber. *93*, 1975 (1960).

[60] *R. Oda*, *M. Okano*, *Sh. Tokiura*, and *A. Miyasu*, Bull. Chem. Soc. Japan *35*, 1216 (1962); Chem. Abstr. *57*, 12453e (1962).

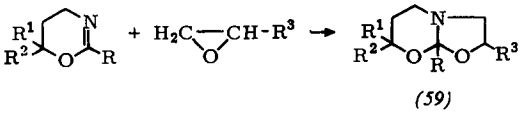
The parent compound *(57)* (R = $R^1$ = H) was prepared recently from dimethylformamide dimethyl acetal and bis-(2-hydroxyethyl)amine [61]. Bases *(57)* prepared in accordance with equation (s) are listed in Table 8.

Table 8. 4,6-dioxa-1-azabicyclo[3.3.0]octanes *(57)* obtained from $\Delta^2$-oxazolines and epoxides.

| *(57)* R | $R^1$ | Yield (%) | B.p. (°C/mm Hg) | M.p. (°C) |
|---|---|---|---|---|
| $CH_3$ | $CH_2-OC_6H_5$ | 48 | 116–120/0.1 | 74.5–75.5 |
| $C_2H_5$ | $CH_2-OC_6H_5$ | 69 | 121/0.1 | 64.5 |
| $C_2H_5$ | $C_6H_5$ | 62 | 90–92/0.05 | — |
| $C_2H_5$ | $CH_2-OCH_2-CH=CH_2$ | 36 | 65–67/0.03 | — |
| $C_2H_5$ | $CH_2-OC_{12}H_{25}$ | 20 | 148/0.05 | — |
| n-$C_3H_7$ | $CH_2-OC_6H_5$ | 57 | 145–147/0.6 | 53–54 |
| $C_6H_5$ | $CH_2-OC_6H_5$ | 37 | 196/0.6 | 82.5 |
| $C_6H_5$ | $CH_3$ | 17 | 85–87/0.05 | — |
| $C_6H_5$ | H | 17 | 79–80/0.03 | — |

### 6.2. 5,7-Dioxa-1-azabicyclo[4.3.0]nonanes

Like $\Delta^2$-oxazolines, 4*H*-5,6-dihydrooxazines react with epoxides, with formation of the bicyclic ring homologues *(59)* of *(57)*.



*(59)*

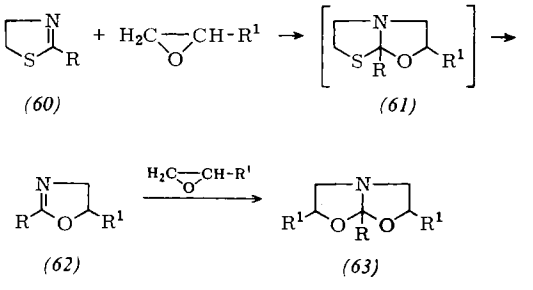
The preparation conditions and general properties are similar to those of the compounds *(57)*. Some examples are given in Table 9.

Table 9. 5,7-Dioxa-1-aza[4.3.0]nonanes *(59)* obtained from 4*H*-5,6-dihydrooxazines and epoxides.

| *(59)* R | $R^1$ | $R^2$ | $R^3$ | Yield (%) | B.p. (°C/mm Hg) (M.p., °C) |
|---|---|---|---|---|---|
| $C_6H_5$ | H | $C_2H_5$ | $CH_2-OC_6H_5$ | 68 | 162–164/0.05 |
| $C_6H_5$ | $CH_3$ | $CH_3$ | $CH_2-OC_6H_5$ | 61 | 175/0.05 (106.5) |
| $CH_3$ | H | H | $C_6H_5$ | 27 | 107/0.05 |
| $(CH_2)_{10}CH_3$ | H | $C_6H_5$ | $CH_2-OCH_2-CH=CH_2$ | 61 | 190–196/0.05 |

### 6.3. $\Delta^2$-Thiazolines and Epoxides [62]

When the reaction (s) is extended to $\Delta^2$-thiazolines *(60)*, the only pure compounds obtained by distillation are sulfur-free. The principal product is always the oxazoline *(62)*; in one case the 4,6-dioxa-1-azabicyclo[3.3.0]-octane *(63)* (R = $CH_3$, $R^1$ = $CH_2-O-CH=CH_2$) was also isolated. This reaction may be represented by scheme (t) if it is assumed that a bicyclus *(61)*, analogous to *(57)*, is formed as an intermediate, and decomposes with elimination of thiirane (or its polymer) to give the oxazoline *(62)*. This can react further in accordance with equation (s) with the epoxide still present to form the trisubstituted bicyclus *(63)*.



*(60)* *(61)* (t)

*(62)* *(63)*

Table 10. Characteristic IR bands of 2-substituted $\Delta^2$-oxazolines (wave numbers in $cm^{-1}$)

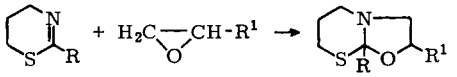
| *(1a)* R | −C=N stretching | −C−O−C= | $\Delta^2$-Oxazoline skeletal | Substituent bands Subst. | ($cm^{-1}$) |
|---|---|---|---|---|---|
| n-(iso-)Alkyl | 1670 | 1143–1230 | 900–1000 | — | — |
| Cyclohexyl | 1660 | 1191, 1170 | 980, 955, 915 | — | — |
| $HO-CH_2-CH_2$ | 1655 | 1238, 1170 | 990, 960, 938 | OH | 1050 |
| $HO-CH_2-CH(CH_3)$ | 1665 | 1250, 1182 | 988, 960, 923 | OH | 1050 |
| $C_6H_5-NH-CH_2-CH(CH_3)$ | 1655 | 1252, 1238, 1210 | 979, 945, 920 | $C_6H_5-NH$ | 3270,1595 |
| $C_6H_5-CH-CH$ (O) | 1660 | 1255, 1180 | 955, 910 | — | — |
| $Cl-CH_2$ | 1665 | 1243 | 981, 961, 921 | — | — |
| $Cl_3C$ | 1650 | 1225 | 1003, 975, 918 | — | — |
| $CH_3-CHCl$ | 1662 | 1247, 1182 | 980, 947, 908 | — | — |
| $Br_3C$ | 1668 | 1245, 1170 | 982, 952, 911 | — | — |
| $CH_3CBr_2$ | 1650 | 1245 | 970, 950, 911 | — | — |
| $CH_2=CH$ | 1670 | 1257, 1190 | 1041,995,961, 910 | −C=C− | 1600 |
| $CH_2=C(CH_3)$ | 1650 | 1280, 1135 | 988, 958, 928 | −C=C− | 1602 |
| $C_6H_5-CH=CH$ | 1655 | 1250, 1203 | 988, 957, 909 | $C_6H_5-CH=CH$ | 1610,1600 |
| $HO-CH_2-C(=CH_2)-$ | 1646 | 1275, 1200 | 998, 958, 919 | −C=C−/OH | 1603/1055 |
| $C_6H_5-NH-CH_2-C(=CH_2)-$ | 1643 | 1263 | 977, 958, 918 | $C_6H_5-NH$ | 3305, 1592 |
| $C_6H_5-NH-COO-CH_2-C(=CH_2)-$ | 1648 | 1210 | 990, 935 | $C_6H_5-NH$ | 1590 |
| | | | | −O−CO−NH− | 1710 |
| $C_6H_5$ | 1650 | 1262 | 975, 945, 897 | — | — |
| *p*-$CH_3-C_6H_4$ | 1650 | 1260, 1182 | 973, 940, 896 | — | — |
| *p*-$CH_3O-CO-C_6H_4$ | 1650 | 1170 | 975, 945, 895 | $OCOCH_3$ | 1725 |
| *p*-$CH_3O-C_6H_4$ | 1652 | 1200 | 1015, 970, 940 | -*p*-O−$C_6H_4$− | 1605/1260 |

[61] *Z. Arnold* and *M. Kornilov*, Collect. czechoslov. chem. Commun. *29*, 645 (1964).

[62] *R. Feinauer*, Angew. Chem. *78*, 938 (1966); Angew. Chem. internat. Edit. *5*, 894 (1966).

### 6.4. 4*H*-5,6-Dihydro-1,3-thiazines and Epoxides [62]

The experiments described above left unanswered the question of what products are obtained in the reaction of 4*H*-5,6-dihydro-1,3-thiazines *(64)* with epoxides.The 7-oxa-5-thia-1-azabicyclo[4.3.0]nonanes *(65)* obtained by the cycloaddition of epoxides to the 2,3 double bond are sufficiently stable for distillation from the reaction mixture (yields 25–30 %).



*(64)* *(65)*

### 7. IR Spectra of Cyclic Imidic Esters [63]

Table 10 shows the influence of the substituent R on the positions of the IR bands assigned to the $\Delta^2$-oxazoline ring. In this connection, reference should be made to the IR spectra of the simple compounds *(1a)* [64,65,22a].

The IR spectra of the 4*H*-5,6-dihydrooxazines *(1b)* and *(1c)* [66,67,22a,27] contain no surprising differences from those of the oxazolines *(1a)*. In particular, the positions of the C=N double-bond absorptions are practically the same. However, the compounds *(1a)* can be distinguished from *(1b)* and *(1c)* by the position of the skeletal vibrations, which generally give three characteristic bands between 890 and about 1000 $cm^{-1}$ in the case of the 5-membered ring *(1a)*, and between 1070 and 1160 $cm^{-1}$ in the case of the 6-membered rings *(1b)* and *(1c)* [22a,27].

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German version: Angew. Chem. *78*, 913 (1966)
Translated by Express Translation Service, London

[63] We are grateful to Dr. *T. Böhm-Gössl* and Ing. *G. Peitscher* for recording and discussing the IR spectra.

[64] *R. Greenhalgh*, Canad. J. Chem. *40*, 976 (1962).

[65] *R. Huisgen, L. Möbius, G. Müller, H. Stangl, G. Szeimies*, and *J. M. Vernon*, Chem. Ber. *98*, 3992 (1965).

[66] a) *Z. Eckstein, K. Majewski*, and *P. Gluzinski*, Roczniki Chem. *36*, 73 (1962); Chem. Abstr. *57*, 11192 (1962); b) *Z. Eckstein, P. Gluzinski, W. Hofmann*, and *T. Urbanski*, J. chem. Soc. (London) *1961*, 489.

[67] *A. I. Meyers*, J. org. Chemistry *26*, 218 (1961).

# Syntheses and Derivatives of Squaric Acid

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*Dedicated to Professor F. Broich on his 60th birthday*

*Squaric acid (dihydroxycyclobutenedione), the dianion of which may be regarded as a novel aromatic system, has recently become readily accessible by simple syntheses. The acidic character of squaric acid manifests itself in the formation of salts and of lower alkyl esters, which can be converted into the amides. Squaric acid dichloride shows in its reactions typical acyl chloride behavior. Condensation of squaric acid with pyrrole, phenol, and azulene derivatives yields cyclotrimethine dyes.*

### 1. Introduction

Dihydroxycyclobutenedione *(1)* ("squaric acid") was first synthesized in 1959 by *Cohen, Lacher*, and *Park* [1].

*(1)* *(2)*

*West* suggested that the dianion *(2)* of squaric acid should be regarded as a member of a series of novel aromatic compounds [2]. The formal similarity of the dianion to cyclobutadiene (all the carbon atoms have $sp^2$ hybridization), together with the interest in aromaticity [3] and the increasing study of small rings, have placed squaric acid in a prominent position. As a result of simplified syntheses, it can now be produced in unlimited quantities [*].

### 2. The Structure of Squaric Acid

Squaric acid is a colorless, crystalline compound having a decomposition point of about 293 °C. The infrared spectrum contains a broad absorption band between 3 and 4 μ (maximum at 4.0 μ), indicating strong hydrogen bonding. Two carbonyl bands are present at 5.5 and

[1] *S. Cohen, J. R. Lacher*, and *J. D. Park*, J. Amer. chem. Soc. *81*, 3480 (1959).

[2] *R. West, H. Y. Niu, D. L. Powell*, and *M. V. Evans*, J. Amer. chem. Soc. *82*, 6204 (1960); *R. West* and *D. L. Powell, ibid. 85*, 2577 (1963); *M. Ito* and *R. West, ibid. 85*, 2580 (1963).

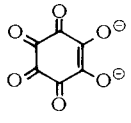
[3] See, *e.g., R. Breslow*, Chem. Engng. News *43*, No. 26, p. 90 (1965).

[*] Suppliers: see "Neues aus Hüls", Series 47, Nov. 1964.

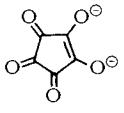
6.0 μ, while the C=C-conjugation band occurs at 6.5 μ. The hydrogen bonding explains the high decomposition point and the very low solubility, which is only about 2 % in water. The acid is insoluble in the usual organic solvents.

Squaric acid is dibasic, $pK_2 = 2.2$, $pK_1 \approx 1$. In the resonance-stabilized dianion *(2)*, all four oxygen atoms can accept the negative charge. The infrared spectrum of the dianion does not contain carbonyl bands at 5.5 μ, but has a broad absorption between 6.5 and 6.75 μ. LCAO calculations of the delocalization energy and the arrangement of the bonds show that the dianion is symmetrical and planar [2].

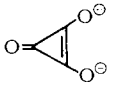
The dianion *(2)* belongs to a new class of compounds having the general formula $(C_nO_n)^{m-}$, the aromatic character of which was predicted and studied by *West et al.* [2]. Of the other members of this series, the dianions of rhodizonic acid *(3)* and of croconic acid *(4)* have been known for some time.



*(3)*



*(4)*

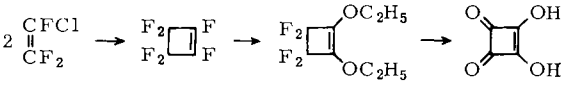


*(5)*

The dihydroxycyclopropenone dianion *(5)* has not yet been prepared [4].

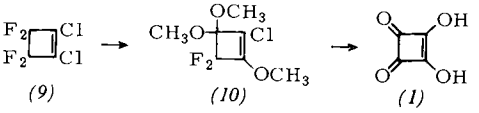
## 3. Syntheses of Squaric Acid

*Cohen et al.* [1] prepared squaric acid from chlorotrifluoroethylene *(6)*, which dimerizes on dechlorination with zinc to perfluorocyclobutene *(7)*. This is then converted into 1,2-diethoxytetrafluorocyclobutene *(8)*, which is finally hydrolysed with strong acid.



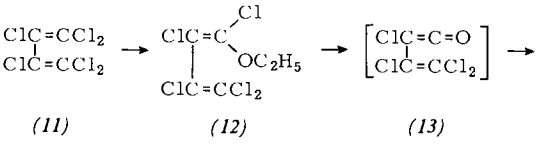
*(6)* *(7)* *(8)* *(1)*

It is more easily prepared [5,6] from the commercially available 1,2-dichlorotetrafluorocyclobutene *(9)*, which reacts with methanol to form 1-chloro-3,3-difluoro-2,4,4-trimethoxycyclobutene *(10)*. Treatment of *(10)* with hydrochloric acid leads to good yields of squaric acid.

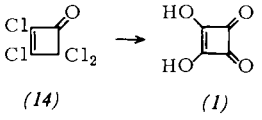


*(9)* *(10)* *(1)*

Other elegant syntheses are based on hexachlorobutadiene *(11)*, which is formed as an undesirable by-product in the manufacture of perchlorinated hydrocarbons or can be prepared by high-temperature chlorination of $C_4$ hydrocarbons [7]. Compound *(11)* generally is inert [8], but nucleophilic substitutions proceed relatively smoothly. Thus *Roedig* and *Bernemann* prepared 1-ethoxypentachloro-1,3-butadiene *(12)* from *(11)* [9]. Compound *(12)* can be thermally and catalytically cyclized, with elimination of ethyl chloride, to perchlorocyclobutenone *(14)*, probably *via* perchlorovinylketene *(13)* [10].



*(11)* *(12)* *(13)*

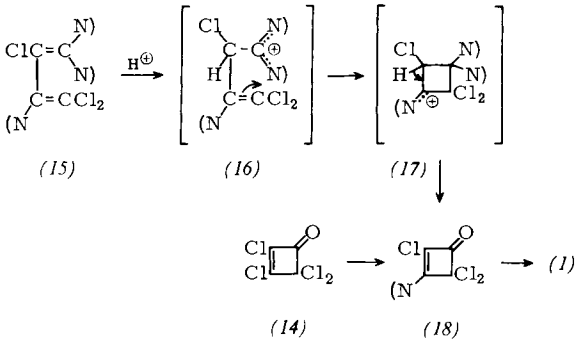


*(14)* *(1)*

Compound *(14)* is hydrolysed in neutral and alkaline media, mainly with simultaneous ring cleavage, whereas high yields of squaric acid can be obtained in acidic media. Compound *(14)* is also used in the preparation of reactive squaric acid derivatives (see Section 5).

Trichlorotrimorpholinobutadiene *(15)*, which can be prepared by the reaction of hexachlorobutadiene with an excess of morpholine [11], also can be used to prepare *(14)*.

When *(15)* is subjected to prolonged treatment with water at pH 5 to 7 at 55 °C, 3-morpholinotrichlorocyclobutenone *(18)* is formed; the structure of *(18)* was proved by the fact that perchlorocyclobutenone *(14)*, as a vinylogous acyl chloride, gives the same product with morpholine. As a vinylogous amide, *(18)* can be readily hydrolysed with acids to form squaric acid *(1)*.



*(15)* *(16)* *(17)* *(14)* *(18)*

N) denotes morpholino

The constitution of the trichlorotrimorpholinobutadiene *(15)* has not been definitely established, but the formation of 3-morpholinotrichloro-1-cyclobutenone *(18)* suggests that the arrangement of the morpholino groups is as shown. It can be seen that a proton can readily become attached to the ketene aminal to form a resonance-stabilized carbenium-imonium ion *(16)*, which can undergo ring closure to form another stabilized ion *(17)* and thence *(18)*.

[4] *S. W. Tobey* and *R. West*, Tetrahedron Letters *1963*, 1179.

[5] *J. D. Park*, *S. Cohen*, and *J. R. Lacher*, J. Amer. chem. Soc. *84*, 2919 (1962).

[6] *R. West*, *H. Y. Niu*, and *M. Ito*, J. Amer. chem. Soc. *85*, 2584 (1963).

[7] *L. M. Kogan*, Russ. chem. Reviews (transl. of Usp. Chim.) *33*, 176 (1964); Chem. Zbl. 39-0879, *1965*.

[8] *O. Fruhwirth*, Ber. dtsch. chem. Ges. *74*, 1700 (1941).

[9] *A. Roedig* and *P. Bernemann*, Liebigs Ann. Chem. *600*, 1 (1956).

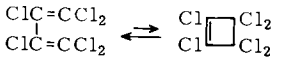
[10] *G. Maahs*, Liebigs Ann. Chem. *686*, 55 (1965).

[11] *P. Hegenberg* and *G. Maahs*, unpublished.

The preparation of squaric acid from hexachlorobutadiene by the route *(11)* → *(15)* → *(18)* → *(1)* can be carried out in a single step, without isolation of *(15)* and *(18)*; squaric acid is obtained in yields of up to 40 % based on hexachlorobutadiene. This process is therefore of interest for synthesis on the industrial or semi-industrial scale [11].

The tendency of the hexachlorobutadiene derivatives to undergo cyclization is in agreement with the general experience that the formation of four-membered rings is promoted by the introduction of fluorine or chlorine into a conjugated diene [12]. Thus perfluorocyclobutene *(7)* can be prepared in an equilibrium reaction at high temperatures from hexafluorobutadiene [13], the cyclic structure, according to *Haszeldine*, being the thermodynamically more stable one [14].

Hexachlorobutadiene itself shows a certain tendency towards ring formation, but in this case the open-chain structure is strongly favored. Hexachlorobutadiene that has been stored is found by IR analysis to contain 1–5 % (depending on the time of storage) of a product that is probably hexachlorocyclobutene *(19)* and which can be concentrated to *ca.* 20 % by vacuum fractionation and low-temperature crystallization. At higher temperatures, *e.g.* on distillation (b.p. 215 °C), *(19)* is reconverted into *(11)*.

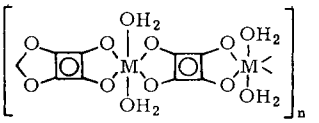


*(11)* *(19)*

A fraction of probable structure *(19)* and mass-spectrometric formula $C_4Cl_6$ was isolated by gas chromatography. The infrared spectrum did not contain the characteristic bands at 6.20 and 6.37 μ corresponding to the conjugated double bond of hexachlorobutadiene. On the other hand, it did contain a band at 6.11 μ, suggesting the presence of an isolated double bond. [Other absorption bands of *(19)*: 8.42, 11.1, 12.9, 14.90 μ]. Whereas the ultraviolet spectrum of *(11)* contains a broad absorption due to conjugation, that of *(19)* does not absorb up to 210 mμ [15].

## 4. Reactions of Squaric Acid

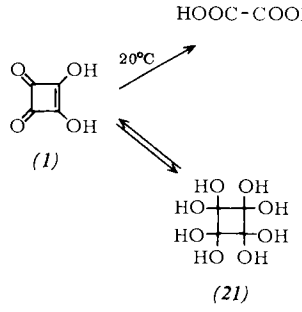
With univalent metals, *e.g.* potassium, squaric acid forms salts which are readily soluble in water, whereas the squarates (cyclobutenedionediolates) of bivalent and tervalent metals are insoluble. The salts of bivalent metals occur as dihydrates, those of tervalent metals as trihydrates. X-ray structure analysis showed that the salts of bivalent Mn, Fe, Co, Ni, Mg, and Zn have the same structure, small differences due to the different radii of the metal ions being observed only in the lattice parameters. *West* postulated a chain structure *(20)* for the salts of the general formula $M^{II}C_4O_4 \cdot 2H_4O$ [16]. The structure of the squarates of tervalent metals, $M^{III}(OH)C_4O_4 \cdot 3H_2O$, has not yet been established.



*(20)*

M = bivalent metal

With oxidizing agents, *e.g.* $HNO_3$ or $Br_2$, at room temperature, squaric acid undergoes oxidative ring cleavage to oxalic acid and carbon dioxide.



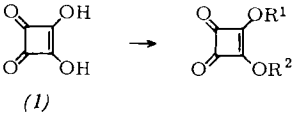

*(1)* *(21)*

Under mild conditions (0 °C, $HNO_3$ or $Br_2$), the four-membered ring remains intact [6], and the product obtained is cyclobutaneoctol *(21)*, the tetrahydrate of cyclobutanetetrone. On reduction with $SO_2$, *(21)* is converted into squaric acid.

Squaric acid reacts with acetic anhydride to form the strongly hygroscopic diacetoxycyclobutenedione *(22)*, which forms colorless crystals on sublimation in high vacuum [17]. This mixed anhydride is immediately decomposed by atmospheric moisture. Alcohols give acetates and free squaric acid, ammonia gives acetamide and diammonium squarate.

## 5. Esters and Amides of Squaric Acid

The diethyl *(23)* [11] and dibutyl *(24)* [10] esters can be prepared easily by the reaction of the acid with an excess of alcohol.



*(1)*

*(22)*, $R^1 = R^2 = COCH_3$
*(23)*, $R^1 = R^2 = C_2H_5$
*(24)*, $R^1 = R^2 = C_4H_9$
*(25)*, $R^1 = R^2 = CH_3$
*(26)*, $R^1 = H$; $R^2 = CH_3$

Dimethyl squarate *(25)* was recently synthesized [18] both by the action of diazomethane on *(1)* and by the reaction of the silver salt with methyl iodide. Transesterification of *(25)* with ethanol yields *(23)*. When squaric acid is heated with excess methanol it forms, not *(25)*, but the half-ester *(26)*, which has also been detected during the hydrolysis of *(25)* [18].

Dibutyl squarate *(24)* can also be prepared from perchlorocyclobutenone *(14)* [10, 19]. Depending on the temperature, the reaction of equimolar amounts of *(14)* and butanol leads either to substitution of a Cl atom and formation of 3-butoxytrichlorocyclobuten-1-one *(27)* or to ring cleavage to butyl

[12] See, *e.g.*, *E. Vogel*, Liebigs Ann. Chem. *615*, 1 (1958).

[13] *M. Prober* and *W.T. Miller jr.*, J. Amer. chem. Soc. *71*, 598 (1949).

[14] *R. N. Haszeldine* and *J. E. Osborne*, J. chem. Soc. (London) *1955*, 3880.

[15] *G. Peitscher* and *G. Maahs*, unpublished work.

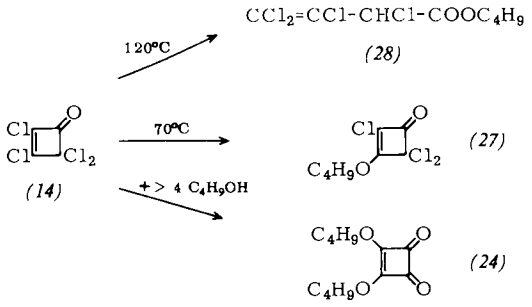
[16] *R. West* and *H. Y. Niu*, J. Amer. chem. Soc. *85*, 2589 (1963).

[17] *A. Treibs* and *K. Jakob*, Liebigs Ann. Chem., in press.

[18] *S. Cohen* and *S.G. Cohen*, J. Amer. chem. Soc. *88*, 1533 (1966).

[19] *G. Maahs*, Angew. Chem. *75*, 892 (1963); Angew. Chem. internat. Edit. *2*, 690 (1963).

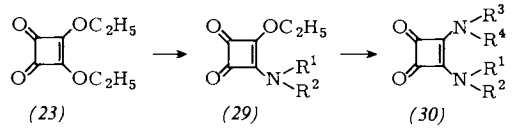
2,3,4,4-tetrachlorovinylacetate *(28)* (or butyl 3,4,4,4-tetrachlorocrotonate). At the boiling point and with a large excess of butanol, dibutyl squarate *(24)* is formed.




Other esters can be synthesized *via* squaryl chloride (see Section 6).

The alkoxy derivatives mentioned exhioit ester properties. They can be hydrolysed with water or alkali to squaric acid.

The diesters react readily with amines to give squaramides [11,18,20]. Equimolar amounts of amine give ester amides of squaric acid, such as *(29)*; excess of amine gives the diamides of squaric acid *(30)*.




Mixed diamides of squaric acid can also be prepared by reaction of the ester amides with other amines. Some examples are listed in Table 1.

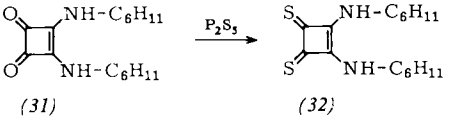
Table 1. Examples of ethyl ester amides *(29)* and diamides *(30)* of squaric acid [11,20].

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | *(29)* M.p. (°C) | *(29)* Yield (%) | *(30)* M.p. (°C) | *(30)* Yield (%) |
|---|---|---|---|---|---|---|---|
| H | H | H | H | 133–138 | 76 | 320 (decomp.) | 95 (87 [18]) |
| $C_4H_9$ | H | $C_4H_9$ | H | 44–47 | 65 | 252–255 | 96 |
| $-(CH_2)_2-O-(CH_2)_2-$ | | $-(CH_2)_2-O-(CH_2)_2-$ | | 154–157 | 79 | 272–275 | 66 |
| $-(CH_2)_5-$ | | $-(CH_2)_5-$ | | 79–79.5 | 94 | 158–160 | 81 |
| $-(CH_2)_4-$ | | $-(CH_2)_4-$ | | 89–90 | 98 | 278–280 | 97 |
| $(CH_2)_2OH$ | H | $(CH_2)_2OH$ | H | 205–208 | 91 | 223–226 | 98 |
| cyclo-$C_6H_{11}$ | H | cyclo-$C_6H_{11}$ | H | 108–110 | 84 | 314–323 | 99 |
| $C_{12}H_{25}$ | H | $C_{12}H_{25}$ | H | 73–75 | 94 | 174–177 | 95 |
| $C_6H_5$ | H | $C_6H_5$ | H | 114–118 | 89 | 270 (decomp.) | 75 |
| *p*-COOH–$C_6H_4$ | H | *p*-COOH–$C_6H_4$ | H | 252 (decomp.) | 95 | 320 (decomp.) | 90 |
| *p*-OH–$C_6H_4$ | H | *p*-OH–$C_6H_4$ | H | — | — | 320 (decomp.) | 85 |
| $C_{12}H_{25}$ | H | $(CH_2)_2OH$ | H | — | — | 201–202 | 92 |
| $-(CH_2)_2-O-(CH_2)-$ | | $-(CH_2)_5-$ | | — | — | 174–180 | 58 |

The methyl ester amide and the diamide of squaric acid have recently been described [18].

The ethyl ester amide can be hydrolysed to the monoamide [11].

Thio-analogues of squaramides are obtained by reaction of amides such as *N,N'*-dicyclohexylsquaramide *(31)*

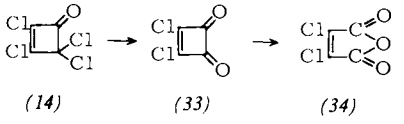



[20] *G. Maahs* and *P. Hegenberg*, German Pat. Appl. C 36340 IVb/120 (July 9th, 1965); Chemische Werke Hüls.

with phosphorus pentasulfide, the product in this case being bis(cyclohexylamino)cyclobutenedithione *(32)* [11].

## 6. Squaryl Dichloride

The dichloride of squaric acid, dichlorocyclobutenedione *(33)*, cannot be prepared from squaric acid. It is formed in the reaction of perchlorocyclobutenone *(14)* with oleum or $SO_3$ ($B_2O_3$ or $SbCl_5$ as catalyst) by the replacement of the geminal chlorine atoms with oxygen [10], a reaction that has already been used for the preparation of other cyclic ketones [21].

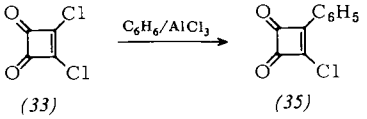



With excess of $SO_3$ at high temperatures *(33)* is oxidized to dichloromaleic anhydride *(34)*.

Compound *(33)* exhibits the typical properties of an acyl chloride. It is readily hydrolysed by water to squaric acid. It reacts with alcohols, *e.g.* with ethanol to give diethyl squarate *(23)*. Di-n-propyl squarate, which cannot be obtained directly from squaric acid, can also be prepared in this way [11].

Under Friedel-Crafts conditions (catalytic amounts of $AlCl_3$) in benzene, *(33)* can be converted into 1-chloro-2-phenylcyclobutenedione *(35)* [11], which also has been prepared from phenylcyclobutenedione [22].

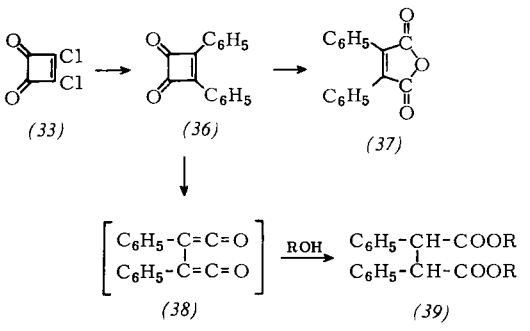
As a vinylogous acyl chloride, *(35)* can be converted into the known compounds 1-hydroxy-, 1-methoxy-, and 1-amino-2-phenylcyclobutenedione, which also exhibit the properties of an acid, an ester, and an amide, respectively [22].




[21] *A. Roedig* and *G. Märkl*, Liebigs Ann. Chem. *636*, 1 (1960).

[22] *E. J. Smutny*, *M. C. Caserio*, and *J. D. Roberts*, J. Amer. chem. Soc. *82*, 1793 (1960).

With stoichiometric amounts of $AlCl_3$ in benzene, *(33)* forms diphenylcyclobutenedione *(36)*[11], which has also been prepared by the hydrolysis of 1,2-diphenyl-3,3,4,4-tetrafluorocyclobutene[23].



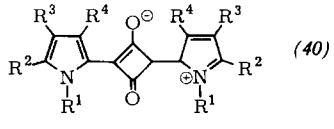
*(33)* *(36)* *(37)* *(38)* *(39)*

Compound *(36)* is very reactive, bright yellow, and crystallizes well. Mild oxidation with $H_2O_2$ yields diphenylmaleic anhydride *(37)*, while degradation to benzoic acid occurs under more vigorous conditions. The reaction of *(36)* with alcohols leads to ring cleavage; it probably proceeds *via* bis(phenylketene) *(38)*, which adds alcohol to form the 2,3-diphenylsuccinate *(39)*[23].

## 7. Condensations

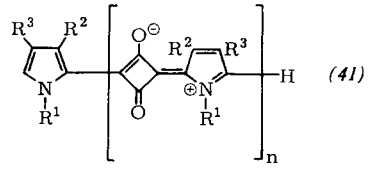
Cyclotrimethine dyes in which the cyclobutene ring is substituted in positions 1 and 3 are obtained from squaric acid itself, while esters of squaric acid in the presence of bases give disubstituted 1,2-cyclobutenediones.

The reaction of activated pyrroles with squaric acid in acetic acid leads to red-violet cyclotrimethine dyes of general formula *(40)*[24]. The pyrrole derivative used



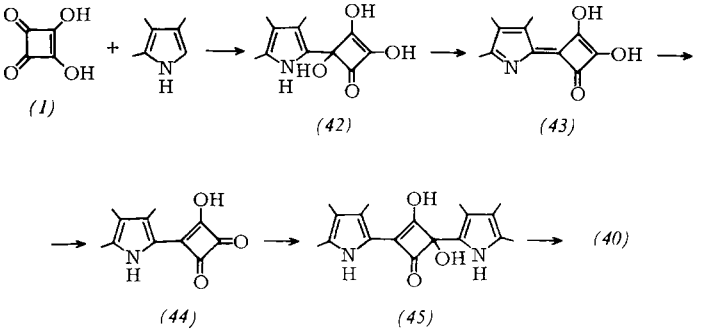
*(40)*

must be unsubstituted in position 2 and substituted in position 5. If positions 2 and 5 are both occupied, *e.g.* by alkyl groups, no reaction occurs. If, on the other hand, both positions are unoccupied, mixtures of readily variable blue to blue-green dyes, to which *Treib* and *Jakob* assign a polymeric structure *(41)*[17], are obtained.



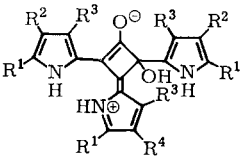
*(41)*

The reaction of pyrroles with squaric acid to form the dye *(40)* is thought to proceed *via* the intermediates *(42)–(45)*.



*(1)* *(42)* *(43)* *(44)* *(45)* *(40)*

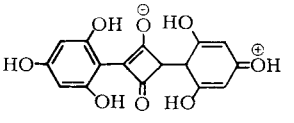
A further pyrrole group may be introduced to form compounds of structure *(46)*.



*(46)*

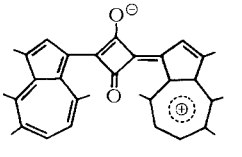
Indole condenses with squaric acid to form indole dyes having the same basic structure as *(40)*, but with the linkage in the indole 3-position.

Phenols have also been used as condensation components, but only the most active of these, *e.g.* phloroglucinol, react with formation of compounds *(47)* which are fundamentally similar to *(40)*.



*(47)*

*Sprenger* and *Ziegenbein* readily obtained condensation products of squaric acid with dialkylaniline. These authors used a butanol/benzene mixture instead of acetic acid as the solvent, and the water formed was removed by azeotropic distillation. The condensation could involve preliminary activation of the squaric acid by the formation of monobutyl squarate. Other interesting condensations have been obtained with azulenes, which give blue to green dyes having the structure *(48)*[25].



*(48)*

In contrast to these condensations, which lead to 1,3-derivatives of cyclobutene, squaric acid esters generally react with compounds containing active methylene groups, *e.g.* *N*-ethyl-2- or -4-methylpyridinium salts or *N*-ethyl-2-methylbenzothiazolium and -benzeneselen-

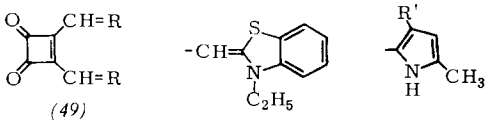
[23] *A. T. Blomquist* and *E. A. La Lancette*, J. Amer. chem. Soc. *83*, 1387 (1961); *84*, 220 (1962).

[24] *A. Treibs* and *K. Jacob*, Angew. Chem. *77*, 680 (1965); Angew. Chem. internat. Edit. *4*, 694 (1965).

[25] *H. E. Sprenger* and *W. Ziegenbein*, Angew. Chem. *78*, 937 (1966); Angew. Chem. internat. Edit. *5*, 894 (1966).

azolium salts, to form deeply colored 1,2-derivatives of cyclobutenedione of general formula *(49)*, such as that shown in example *(50)* [26].

*(50)*, -CH=R: *(51)*, -CH=R:



*(49)*

[26] *H. E. Sprenger*, personal communication.

Diacetoxycyclobutenedione *(22)* [17] also reacts with pyrroles to give yellow 1,2-dipyrrylcyclobutenediones *(51)*, as well as cyclotrimethine dyes of the type *(40)* [17].

*We are grateful to the management of Chemische Werke Hüls AG for permission to publish this report, and to Prof. H. Hellmann and Dr. A. Schmidt for their helpful interest.*

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Translated by Express Translation Service, London

# COMMUNICATIONS

## Oxidation of Sulfoxides with Hydroperoxides

By Dr. L. Kuhnen

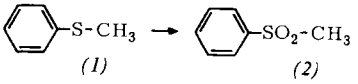
Forschungslaboratorien, Chemische Werke Hüls AG., Marl (Germany)

*Dedicated to Professor F. Broich on his 60th birthday*

Organic hydroperoxides oxidize sulfides to sulfoxides. Addition of excess of oxidizing agent does not lead to the formation of sulfones [1].

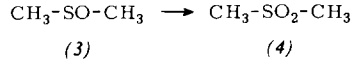
However, sulfides and sulfoxides can be oxidized by equimolar amounts of organic hydroperoxides in the presence of vanadium, molybdenum, or titanium compounds to sulfones in almost quantitative yields. The sulfides and sulfoxides – dissolved if convenient in benzene, ethyl acetate or ethanol – are mixed with the catalyst and heated to 50–70 °C, the organic hydroperoxide being then added slowly. The reaction, which is sometimes strongly exothermic, is complete as soon as only traces of peroxide can be detected with potassium iodide in the reaction mixture. The sulfones are then isolated by crystallization or distillation.

For example, oxidation of thioanisole *(1)* in benzene with t-butyl hydroperoxide in the presence of molybdenyl acetylacetonate produces methyl phenyl sulfone *(2)* in 98 % yield.



*(1)* *(2)*

Oxidation of dimethyl sulfoxide *(3)* with cumyl α-hydroperoxide in the presence of vanadium pentoxide gives dimethyl sulfone *(4)* in 91 % yield.



*(3)* *(4)*

Unsaturated sulfides such as allyl n-butyl sulfide or diallyl sulfide can be oxidized selectively to unsaturated sulfones.

In contrast to conventional oxidation procedures, these reactions proceed without the presence or formation of water or carboxylic acids.

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[1] *L. Bateman* and *K. R. Hargrave*, Proc. Roy. Soc. (London), Ser. A *224*, 389, 399 (1954); *K. R. Hargrave, ibid.*, Ser. A *235*, 55 (1956).

## Condensation Products of Squaric Acid and Azulenic Hydrocarbons

By Dr. W. Ziegenbein and Dr. H.-E. Sprenger

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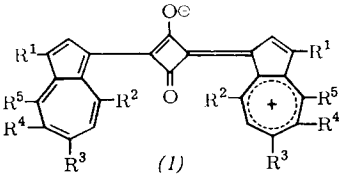
*Dedicated to Professor F. Broich on his 60th birthday*

On reaction of squaric acid (1,2-dihydroxycyclobutenedione) in, *e.g.*, butanol, with azulene or a homologue thereof [1] there is surprisingly smooth formation of condensation products, to which we assign the limiting structure *(1)* on the basis of elemental analysis and spectroscopic results [2] and in analogy with the products synthesized from squaric acid with pyrroles, resorcinol, and phloroglucinol [3].



*(1)*

*(a)*: $R^1 = R^2 = R^3 = R^4 = R^5 = H$
decomp. >240 °C

*(b)*: $R^1 = R^2 = CH_3$; $R^4 = (CH_3)_2CH$; $R^3 = R^5 = H$
decomp. >245 °C

*(c)*: $R^1 = R^4 = H$; $R^2 = R^3 = R^5 = CH_3$
does not melt below 350 °C

Compounds *(1a)–(1c)* are precipitated as sparingly soluble crystals with a green metallic luster. Their solutions in dimethylformamide are intensely blue to green.

*Preparation of 4-(1-azuleniumylidene)-2-(1-azulenyl)-3-oxo-1-cyclobutenolate (1a)*

A mixture of 1.92 g (0.015 mole) of azulene, 0.86 g (0.007 mole) of squaric acid, 60 ml of butanol, and 40 ml of benzene is refluxed for 5–7 hr with continuous removal of the water formed. After evaporation to one-third of the original volume the crystals that separate are filtered off and washed with methanol and light petroleum. Drying then affords 2.25 g (90 %) of material, which is purified by dissolution in hot benzonitrile and precipitation with ether; $\lambda_{max}$ = 680 mμ (ε = 110000), 460 (3440), 394 (7560), 366 (9500), 311 (17200), 284 (18500) (in chloroform).

Compounds *(1b)* and *(1c)* are obtained analogously. The last-mentioned can be purified by dissolution in warm,

concentrated sulfuric acid and precipitation with ethanol. *(1b)*: $\lambda_{max}$ = 770 mμ (ε = 132000), 440 (10400), 384 (7780), 316 (16400) (chloroform);

*(1c)*: $\lambda_{max}$ = *720*, 465, 405, 380, 316, 262 mμ (chloroform).

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[1] We thank Professor *K. Hafner*, Darmstadt, and Dr. *E. Klein* (Dragoco, Holzminden) for samples of azulene.

[2] We are indebted to Dr. *Th. Böhm-Gössl* and Mr. *G. Peitscher* for measurement and interpretation of the spectra.

[3] *A. Treibs* and *K. Jakob*, Angew. Chem. *77*, 680 (1965); Angew. Chem. internat. Edit. *4*, 694 (1965).

## Condensation Products of Squaric Acid and Tertiary Aromatic Amines

By Dr. H.-E. Sprenger and Dr. W. Ziegenbein

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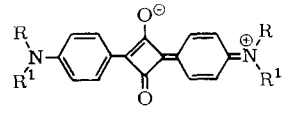
*Dedicated to Professor F. Broich on his 60th birthday*

Reaction of squaric acid (dihydroxycyclobutenedione) with phenols (resorcinol, phloroglucinol) and reactive pyrroles affords deeply colored condensation products to which respectively a *p*-quinonoid and a betaine structure[1] have been ascribed.

We have found that tertiary aromatic amines also condense smoothly as nucleophilic reagents with squaric acid, intensely blue to green, high-melting products being formed to which we assign the polar structures *(1a)* to *(1d)* on the basis of elemental analysis and spectroscopic findings[2] and in analogy with the condensation products from squaric acid and pyrroles. Structures *(1a)* to *(1d)* are to be regarded as limiting formulae.

The products are very slightly soluble in alcohol or ether, more soluble in dimethylformamide and dimethyl sulfoxide.



| | R | $R^1$ | M.p. [°C] |
|---|---|---|---|
| *(1a)* | $-CH_3$ | $-CH_3$ | 276 |
| *(1b)* | $-(CH_2)_2OH$ | $-(CH_2)_2OH$ | decomp. >230 |
| *(1c)* | $-CH_2-C_6H_5$ | $-CH_2-C_6H_5$ | 274–276 (decomp.) |
| *(1d)* | $-(CH_2)_2-O-(CH_2)_2-$ | | decomp. >250 |

*Preparation of 2-(p-dimethylaminophenyl)-4-(dimethylimonio-2,5-cyclohexadienylidene)-3-oxo-1-cyclobutenolate (1a)*

11.4 g (100 mmoles) of squaric acid and 24.2 g (200 mmoles) of *N,N*-dimethylaniline are heated with 150 ml of 1-butanol and 60 ml of benzene under reflux until a total of 3.6 ml of water has distilled off azeotropically. The mixture becomes deep blue. After cooling to 20 °C the condensation product, which is precipitated as small blue crystals, is filtered off and washed several times with light petroleum (boiling range 35–45 °C); yield 9.2 g (60 %); $\lambda_{max}$ = *628*, 414, 389, 366, 306, *263* mμ (chloroform).

Compounds *(1b)–(1d)* can be prepared analogously. Compound *(1d)* can be recrystallized from ethylene glycol.

*(1b)*, principal absorption band: 640 mμ (methanol)

*(1c)*, $\lambda_{max}$ = *624*, 417, 387, 367, 306, *261* mμ (chloroform)

*(1d)*, principal absorption band: 621 mμ (methanol).

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[1] *A. Treibs* and *K. Jacob*, Angew. Chem. *77*, 680 (1965); Angew. Chem. internat. Edit. *4*, 694 (1965).

[2] We thank Dr. *Böhm-Gössl* and Mr. *G. Peitscher* for measurement and interpretation of the spectra.

## Addition of Epoxides to 2-Imidazolines

By Dr. R. Feinauer

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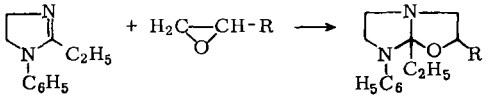
*Dedicated to Professor F. Broich on his 60th birthday*

Epoxides react with cyclic imidoic esters with formation of dioxaazabicycloalkanes[1]. Addition of epoxides to cyclic thioimidoyl esters takes place similarly; in the case of 2-thiazolines, however, a subsequent reaction leads to 2,5-disubstituted 2-oxazolines[2].

We have studied the reaction of epoxides with cyclic amidines and have found that 4-oxa-1,6-diazabicyclo[3.3.0]octanes *(2)* are formed smoothly from epoxides and 1-phenyl-2-imidazolines *(1)*.



*(1)* *(2)*

| R | Reaction temp. (°C) | Reaction time (hr) | Yield of *(2)* (%) | B.p. of *(2)* (°C) | B.p. of *(2)* (mm Hg) | $n_D^{20}$ |
|---|---|---|---|---|---|---|
| H | 140 | 7 | 18 | 107–108 | 0.2 | 1.5615 |
| $CH_3$ | 125 | 6 | 79 | 114–115 | 0.4 | 1.5519 |
| $C_6H_5$ | 150 | 5 | 92 | 171–172 | 0.2 | 1.5920 |
| $C_6H_5OCH_2$ | 150 | 6 | 86 | 174–176 | 0.05 | 1.5800 |
| Allyl-$OCH_2$ | 150 | 5 | 85 | 135–136 | 0.05 | 1.5428 |
| Lauryl-$OCH_2$ | 150 | 5 | 66 | 212–213 | 0.1 | 1.5071 |

The components are heated without a solvent to the temperatures given in the table, and the 4-oxa-1,6-diazabicyclo-[3.3.0]octanes formed are isolated by distillation. Cyclic carbonates of 1,2-diols may be used instead of the epoxides, since under the reaction conditions they lose $CO_2$ and are converted into epoxides. The products are viscous, usually yellow oils that are readily hydrolysed by aqueous acids or aqueous alkali. Their structures were proved by elemental analyses, IR spectra, and degradative reactions.

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[1] *R. Feinauer* and *W. Seeliger*, Liebigs Ann. Chem., in press.

[2] *R. Feinauer*, Angew. Chem. *78*, 938 (1966); Angew. Chem. internat. Edit. *5*, 894 (1966).

## Synthesis of $\Delta^2$-Oxazolines by Reaction of Epoxides with $\Delta^2$-Thiazolines

By Dr. R. Feinauer

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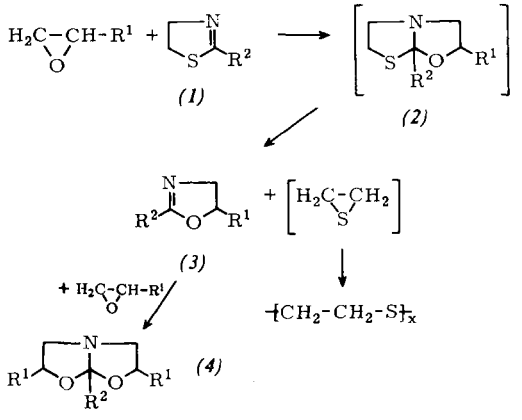
*Dedicated to Professor F. Broich on his 60th birthday*

Epoxides add to 2-oxazolines with formation of 4,6-dioxa-1-azabicyclo[3.3.0]octanes *(4)*[1]. However, by reaction of epoxides with 2-thiazolines *(1)* we obtained 2,5-disubsti-

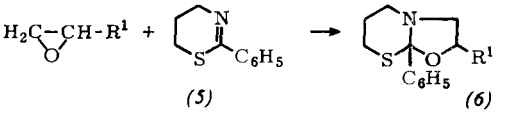
tuted 2-oxazolines *(3)* and products of their reaction with the excess of epoxide. We assume that the 1:1 addition products *(2)* are first formed and that these are then converted into the 2,5-disubstituted 2-oxazolines *(3)* by loss of ethylene sulfide (thiirane) (or its polymers). Depending on the reaction time and the amount of epoxide these products *(3)* may react further to give 4,6-dioxa-1-azabicyclo[3.3.0]octanes *(4)*.



| $R^1$ | $R^2$ | *(3)*, M.p. (°C) B.p. (°C/mm Hg) | $n_D^{20}$ | Yield (%) |
|---|---|---|---|---|
| $CH_2-O-C_6H_5$ | $CH_3$ | 60 | | 26.2 |
| $CH_2-O-C_6H_5$ | $C_2H_5$ | 39–40 | | 29.3 |
| $CH_2-O-C_6H_5$ | $C_3H_7$ | 47–48 | | 27 |
| $CH_2-O-C_6H_5$ | $C_6H_5$ | 75–77 | | 19.8 |
| $CH_2-O-CH_2-CH=CH_2$ | $CH_3$ | 56–58/0.2 | 1.4651 | 21.0 [a] |
| $CH_2-O-CH_2-CH=CH_2$ | $C_3H_7$ | 57–58/0.05 | 1.4663 | 10.4 |
| $CH_2-O-C_{12}H_{25}$ | $CH_3$ | 154–160/0.15 | 1.4539 | 8.8 |
| $C_6H_5$ | $C_2H_5$ | 77–80/0.07 | 1.5364 | 22.9 |

[a] This reaction gave also a 22.3 % yield (calculated on epoxide) of compound *(4)*, b.p. 126–127 °C/0.3 mm Hg, $n_D^{20}$ = 1.4768.

However, reaction of 5,6-dihydro-2-phenyl-4*H*-1,3-thiazine *(5)* with epoxides proceeded no further than the 1:1 adduct *(6)*, as did the reaction of the corresponding 1,3-oxazine[1].



*(6a)*, $R^1$ = $CH_2-O-C_6H_5$, m.p. 133–134 °C, yield 25.4 %

*(6b)*, $R^1$ = $CH_2-O-CH_2-CH=CH_2$, b.p. 133–134 °C/0.02 mm Hg, $n_D^{20}$ = 1.5786, yield 28.8 %

The reactions described above were carried out by heating the components at 140 to 150 °C. The products could be isolated by distillation of the reaction mixture. The structures of the products were proved by elemental analysis, molecular-weight determination, and IR spectra.

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German version: Angew. Chem. *78*, 938 (1966)

[1] *R. Feinauer* and *W. Seeliger*, Liebigs Ann. Chem., in press; *W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier*, and *H. Hellmann*, Angew. Chem. *78*, 913 (1966); Angew. Chem. internat. Edit. *5*, 875 (1966).

## Synthesis and Reactions of Perchlorodienamines

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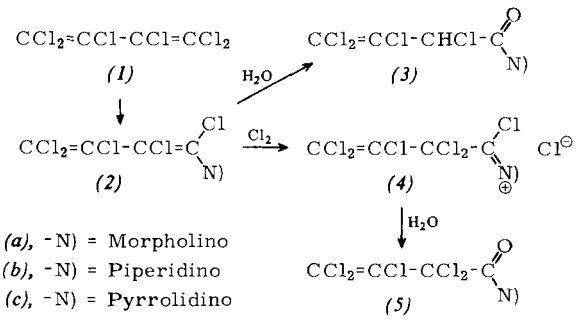
*Dedicated to Professor F. Broich on his 60th birthday*

In the series of perchlorinated enamines only the derivative from perchloroethylene is known[1], and no perhalogenated dienamine has been previously described. Such syntheses have now been achieved by replacement reactions of perchlorobutadiene *(1)* with cyclic secondary amines. The components are mixed in the molar ratio *(1)*: amine = 1:2, without a solvent, and are then distilled. In this way we isolated 4-(pentachloro-1,3-butadienyl)morpholine *(2a)* (66 %), b.p. 110–140 °C/0.7–2 mm (decomp.), $n_D^{20}$ = 1.5727, and 1-(pentachloro-1,3-butadienyl)piperidine *(2b)* (64 %), b.p. 125–129 °C/0.01 mm (decomp.), $n_D^{20}$ = 1.5700.



*(a)*, -N) = Morpholino
*(b)*, -N) = Piperidino
*(c)*, -N) = Pyrrolidino

Compound *(2a)* reacts readily with water, yielding 4-(2,3,4,4-tetrachloro-3-butenoyl)morpholine *(3a)* (97 %, m.p. 91 to 93 °C); however, the analogue *(2b)* is stable to water, although formic acid converts it smoothly into 1-(2,3,4,4-tetrachloro-3-butenoyl)piperidine (90 %, m.p. 94–96 °C).

The perchlorodienamine formed from hexachlorobutadiene and pyrrolidine cannot be isolated by distillation; if the reaction mixture is treated with water it yields 1-(2,3,4,4-tetrachloro-3-butenoyl)pyrrolidine *(3c)* (76 %, m.p. 106 °C). In inert solvents (*e.g.* perchlorinated hydrocarbons, petroleum ether), compound *(2a)* readily adds chlorine, with formation of 4-(hexachloro-3-butenylidene)morpholinium chloride *(4a)* [73 %, m.p. 81–83 ° (decomp.)], which is very sensitive to moisture, being smoothly hydrolysed by water to (4-(pentachloro-3-butenoyl)morpholine *(5a)* (92 %, m.p. 128 to 131 °C)[2]. The product *(4a)* is the first unsaturated perhalogenated amide chloride.

Received: July 12th, 1966 [Z 288 IE]
German version: Angew. Chem. *78*, 939 (1966)

[1] *A. J. Speziale* and *R. C. Freeman*, J. Amer. chem. Soc. *82*, 903 (1960); *A. J. Speziale* and *L. R. Smith*, *ibid. 84*, 1868 (1962).

[2] For the structure see *A. Roedig* and *P. Bernemann*, Liebigs Ann. Chem. *600*, 1 (1956).

## Alkyl Perchlorobutadienyl Sulfides and their Reactions

By Dr. G. Maahs and Dr. P. Hegenberg

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*Dedicated to Professor F. Broich on his 60th birthday*

Many attempts have been made[2] to find a use for hexachlorobutadiene *(1)*, which is a by-product of the large-scale manufacture of chlorinated hydrocarbons but is relatively inert[1]. Its reactions with alkoxides are rather unsatisfactory[3]. We have now found that it undergoes replacement reactions considerably more smoothly with thiolates. In boiling ethanolic solution equimolar amounts of *(1)*, a thiol, and 50 % NaOH afford high yields of alkyl perchlorobutadienyl sulfides *(2)*, together with disulfides *(3)* whose structures have not been determined unequivocally.

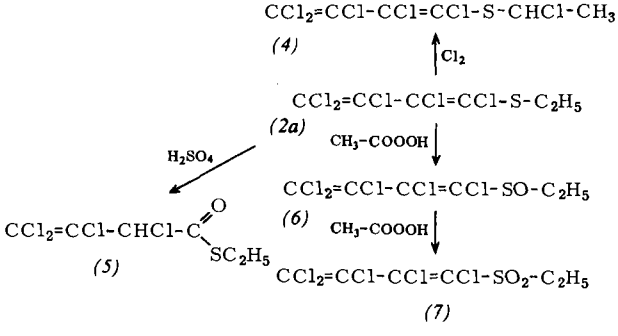
The sulfides *(2a)–(2f)* are much more inert than the corresponding ethers: *e.g.* perchlorocyclobutenethione could not be obtained from compound *(2)* in analogy with the catalytic thermolysis of ethyl pentachloro-1,3-butadienyl ether to perchlorocyclobutenone[4].

$$CCl_2{=}CCl\text{-}CCl{=}CCl_2 \xrightarrow[NaOH]{+\,RSH} CCl_2{=}CCl\text{-}CCl{=}CCl\text{-}SR$$
*(1)* *(2)*

$$+\ C_4Cl_4(SR)_2$$
*(3)*

| R | | Conversion of *(1)* (%) | Yield (%) | B.p. (°C/mm Hg) | $n_D^{20}$ |
|---|---|---|---|---|---|
| $-C_2H_5$ | *(2a)* | 97.5 | 70 | 92–93/0.8 | 1.5835 |
| | *(3a)* | | 18 | 116/0.5 | 1.5941 |
| $-C_4H_9$ | *(2b)* | 74 | 76 | 130/2 | 1.5640 |
| | *(3b)* | | 11 | 155/1 | 1.5645 |
| $-C_6H_5$ | *(2c)* | 70 | 59 | 125–126/0.3 | 1.6296 |
| | *(3c)* | | 11 | 190–200/0.4 | 1.6630 |
| $-CH_2-CHOH-CH_2OH$ | *(2d)* | 78 | 71 | m.p. 87–88 | – |
| | *(3d)* | | 18 | – | – |
| $-CH_2-CH_2OH$ | *(2e)* | 75 | 58 | 155/3 | 1.6004 |
| $-CH_2-COOC_2H_5$ | *(2f)* | 83 | 27 | 135–139/1 | 1.5624 |

Chlorination (at room temperature without solvent) of compound *(2a)* does not, like that of ethyl pentachloro-1,3-butadienyl ether, cause ether fission with formation of an acid chloride[3], but instead leads to α-chloroethyl pentachloro-1,3-butadienyl sulfide *(4)* (84 %, b.p. 119 °C/2.2 mm, $n_D^{20} = 1.5835$).




Reaction of the compound *(2a)* with sulfuric acid [conc. $H_2SO_4$: glacial acetic acid: *(1)* = 3.5:1.5:0.5; 60 °C; 45 hr] occurs with formation of *S*-ethyl 2,3,4,4-tetrachloro-3-butenethioate *(5)* (61 %, b.p. 92 °C/1 mm, $n_D^{20} = 1.5350$).

Oxidation of *(2a)* with 60 % peracetic acid leads to ethyl pentachloro-1,3-butadienyl sulfoxide *(6)* (83 %, m.p. 39 to 41 °C), from which the corresponding sulfone *(7)* (89 %, m.p. 43–45 °C) is obtained on further oxidation with peracetic acid.

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German version: Angew. Chem. *78*, 939 (1966)

[1] *O. Fruwirth*, Ber. dtsch. chem. Ges. *74*, 1701 (1941).

[2] *L. M. Kogan*, Uspekhii. Khim. *33*, 396 (1964); Chem. Zbl. *1965*, 39–0879.

[3] *A. Roedig* and *P. Bernemann*, Liebigs Ann. Chem. *600*, 1 (1956).

[4] *G. Maahs*, Angew. Chem. *75*, 982 (1963); Angew. Chem. internat. Edit. *2*, 690 (1963).

## Synthesis of Tellurophene and its 2,5-Disubstituted Derivatives

By Dr. W. Mack

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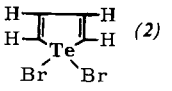
The ring system of tellurophene has so far been encountered only in the form of its tetraphenyl[1] and tetrachloro[2] derivatives. Attempts to prepare the parent compound were unsuccessful[3]. A method of broad scope for the preparation of tellurophene and its 2,5-disubstituted derivatives has now been found in the reaction of sodium telluride and diacetylenes.

$$R\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}R + Na_2Te \xrightarrow[CH_3OH]{20\,°C}$$



*(1)*, R: -H
*(3)*, R: $-CH_2OH$
*(4)*, R: $-C(CH_3)_2OH$



*(2)*

A solution of sodium telluride in methanol is treated with an equivalent quantity of the diacetylene. The reaction is complete when the violet color of the telluride has disappeared. The majority of the methanol is distilled off and a little water is added to the residue. The tellurophene is then extracted with ether and purified by distillation or recrystallization after evaporation of the ether from the extract.

Tellurophene *(1)* is obtained in this way in 69 % yield as a pale yellow liquid with a faint odor, b.p. 148 °C/714 mm, m.p. *ca.* −36 °C, $n_D^{20} = 1.6856$, $d_4^{22} = 2.13$.

The positions of the NMR multiplets[4] at 7.83 (protons on C-3 and C-4) and 8.94 ppm (protons on C-2 and C-5) indicate that *(1)* must have marked aromaticity. The infrared spectrum of *(1)* shows peaks at 3080 (m), 3030 (m), 1425 (s), 1310 (m), 1240 (s), 1220 (s), 1100 (m), 975 (m), 785 (m), and 665(s) $cm^{-1}$. In cyclohexane, *(1)* has $\lambda_{max}$ at 280 mμ (log ε = 3.62). Its mass spectrum contains the parent peak at m/e = 182 (relative intensity = 0.33) expected for $^{12}C_4{}^1H_4{}^{130}Te$. Other signals of high intensity are due to Te and $C_4$ fragments. Cryoscopic molecular-weight determinations indicate that the compound occurs in the form of its dimer in benzene.

A solution of bromine in methanol reacts with *(1)* to give an orange, insoluble precipitate of *(2)*, m.p. 125 °C (decomp.). Aqueous $HSO_3^-$ reduces *(2)* back to *(1)*.

2,5-Bis(hydroxymethyl)tellurophene *(3)* is obtained analogously in 25 % yield as water-soluble crystals, m.p. 107 °C. Its NMR signals occur at 7.43 (protons on C-3 and C-4), 4.85 (methylene protons), and 2.16 ppm (hydroxyl protons).

2,5-Bis(dimethylhydroxymethyl)tellurophene *(4)* is obtained in almost quantitative yield as colorless crystals, m.p. 94 °C, soluble in hot water. Its NMR signals occur at 7.29 (protons on C-3 and C-4), 1.63 (methyl protons), and 2.74 ppm (hydroxyl protons).

Both *(3)* and *(4)* have the molecular weights of the monomeric forms in benzene.

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[1] *E. A. Braye*, *W. Hübel*, and *J. Caplier*, J. Amer. chem. Soc. *83*, 4406 (1961).

[2] *W. Mack*, Angew. Chem. *77*, 260 (1965); Angew. Chem. internat. Edit. *4*, 245 (1965).

[3] *W. G. Zoellner*, Dissertations Abstr. *19*, 3139 (1959); Chem. Abstr. *53*, 17141i (1959); *F. A. McMahon*, *Th. G. Pearson*, and *P. L. Robinson*, J. chem. Soc. (London) *1933*, 1644.

[4] In $CDCl_3$ with tetramethylsilane as internal standard. We thank Dr. *Prigge* for the measurement and interpretation of the spectra.

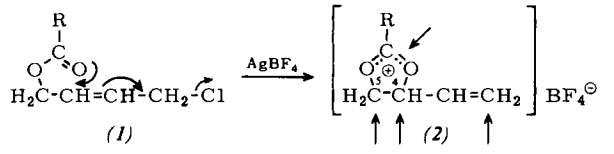
## 4-Vinyl-1,3-dioxolanylium Salts

By Dr. S. Kabuss

Chemisches Laboratorium, Universität Freiburg (Germany)

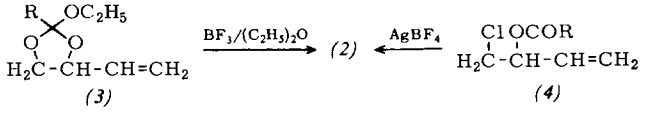
4-Chloro-2-butenyl carboxylates *(1)* react with $AgBF_4$ in nitromethane to yield 4-vinyl-1,3-dioxolanylium salts with allyl rearrangement and participation of the acyloxy group as a vinylogous neighboring group; *cis*- and *trans*-isomers of the esters *(1)* give the same cations *(2)*, as expected[1].

NMR spectra (in nitromethane, TMS as internal standard) of *(2)* include bands at $\tau$ = 3.5–5.0 (unseparated multiplet due to the ring protons at C-4 and C-5 and the vinyl protons), as well as for *(2)*, R = $CH_3$ (obtained as an oil; stable for only a few days) $\tau$ = 7.6 ($CH_3$ protons) and for *(2)*, R = $C_6H_5$ (m.p. 65–72 °C) $\tau$ = 1.5–2.5 (broad multiplet due to phenyl protons).



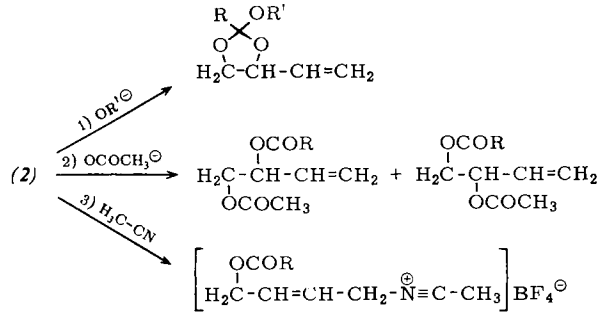
*(1)* *(2)*

The same cations *(2)* are obtained by *Meerwein*'s methods [2], namely, by the action of the $BF_3$-ether adduct on 2-alkoxy-4-vinyldioxolanes *(3)*, or by treatment of 1-(chloromethyl)-allyl esters *(4)* with $AgBF_4$.



*(3)* *(4)*

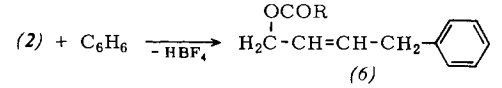
The vinyldioxolanylium ions *(2)* are ambident cations [3] with four different reactive centers [see arrows in formula *(2)*], which react 1) by addition with retention of the ring structure, 2) by alkylation with ring fission, or 3) by alkylation with allylic shift and ring fission, according to the nucleophilicity of the reagent:



*(5)*

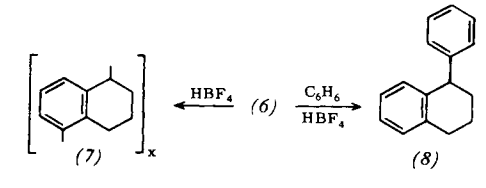
The nitrilium salts *(5)* were identified *via* the amides formed on hydrolysis.

The reactivity of the allylic $>O^{\oplus}-C$ bond results in the vinyldioxolanylium salts being even stronger alkylating agents than dialkoxycarbonium [4] or alkyldioxolanylium salts [5]. They even alkylate aromatic compounds such as benzene, toluene, and anisole at room temperature in *exothermic reactions*. In these reactions, attack is, as with nitriles (see reaction 3), on the terminal C atom of the vinyl group and involves an allyl shift and ring fission [6] (reversal of the reaction forming *(2)*).



*(6)*

The 4-aryl-2-butenyl esters, *e.g.* *(6)*, formed as primary products can be isolated if ethers are added to remove the $HBF_4$ formed. If an ether is not added, polymers of structure



*(7)* *(8)*

*(7)* are formed by alkylation, isomerization, and cyclization. Use of an excess of the aromatic compounds affords 1-aryltetralins, *e.g.* *(8)*.

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[1] According to preliminary experiments, cations *(2)* occur also as intermediates in the solvolysis of compounds of structure *(1)*.

[2] *H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert,* and *K. Wunderlich*, Liebigs Ann. Chem. *632*, 38 (1960).

[3] *S. Hünig*, Angew. Chem. *76*, 400 (1964); Angew. Chem. internat. Edit. *3*, 548 (1964).

[4] *S. Kabuss*, Angew. Chem. *78*, 714 (1966); Angew. Chem. internat. Edit. *5*, 675 (1966).

[5] *S. Kabuss*, unpublished work.

[6] It is not yet known whether these reactions occur by an $S_N2'$ mechanism or are preceded by a reversible valence isomerization of the dioxolanyl cation to the acyclic allyl cation.

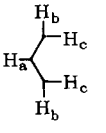
## π-Allylnickel Bromide under the Influence of Phosphines and Phosphites

By Dr. D. Walter and Prof. G. Wilke

Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany)

In the presence of Lewis acids π-allylnickel halides catalyse the dimerization of propylene. By the addition of various phosphines to the catalyst, the process can be directed at will so as to yield dimers of various structures [1]. In this connection, the influence of ligands containing phosphorus on π-allylnickel bromide was studied with the aid of the $^1H$–NMR spectra of 1:1 and 1:2 adducts. The crystalline adducts are obtained when π-allylnickel bromide, *e.g.* dissolved in ether, is treated with phosphines or phosphites in stoichiometric proportions.

The table shows the $\tau$ values (TMS as internal standard, Varian A 60, about 30 °C in chlorobenzene [*]) of $H_a$ (*meso*), $H_b$ (*syn*), and $H_c$ (*anti*) protons of the allyl group, as well as the coupling constants and the differences between the $\tau$ values of $H_c$ and $H_b$.



| Compound | $H_a$ | $H_b$ | $H_c$ | $J_{ab}$ | $J_{ac}$ | $H_c-H_b$ |
|---|---|---|---|---|---|---|
| π-$C_3H_5NiBr{\cdot}P(OC_6H_5)_3$ | 5.4 | 6.4 | 7.8 | 7 | 14 | 1.4 |
| π-$C_3H_5NiBr{\cdot}2P(OC_6H_5)_3$ | 5.7 | 6.42 | 7.46 | 7 | 14 | 1.04 |
| π-$C_3H_5NiBr{\cdot}P(C_6H_5)_3$ | 4.9 | 6.62 | 7.55 | 6.5 | 14.5 | 0.93 |
| π-$C_3H_5NiBr{\cdot}2P(C_6H_5)_3$ | 5.1 | 6.62 | 7.04 | 6.5 | 13.5 | 0.42 |
| π-$C_3H_5NiBr{\cdot}P(C_2H_5)_3$ | 5.1 | 6.7 | 7.8 | — | — | 1.1 |
| $C_3H_5NiBr{\cdot}2P(C_2H_5)_3$ | 5.04 | 6.76 | | 10 | | 0.0 |

The $H_a$, $H_b$, and $H_c$ signal intensities are in the ratio 1:2:2. As can be seen from the spectra, the 1:1 and 1:2 adducts of triphenyl phosphite and triphenylphosphine contain a π-allyl group ($H_b$ and $H_c$ are distinguishable). The difference between the $\tau$ values of $H_c$ and $H_b$ is smaller for the 1:2 adducts than for the 1:1 adducts. Whereas the spectrum of π-$C_3H_5NiBr{\cdot}P(C_2H_5)_3$ shows splitting of the $H_b$ and $H_c$ signals, $H_b$ and $H_c$ give only one signal in the spectrum of $C_3H_5NiBr{\cdot}2[P(C_2H_5)_3]$. This is typical of an allyl system in dynamic equilibrium $(CH_2{=}CH{-}CH_2) \rightleftharpoons (CH_2{-}CH{=}CH_2)$ [2]. π-$C_3H_5NiCN$, obtained from $(\pi\text{-}C_3H_5)_2Ni$ and HCN in ether or from π-$C_3H_5NiBr$ and KCN in methanol, behaves analogously. $C_3H_5NiCN{\cdot}2[P(C_2H_5)_3]$ gives the spectrum of the dynamic type ($H_a$: $\tau$ = 5.26; $H_{b/c}$: $\tau$ = 7.36; $J$ = 9.8 Hz, in $C_6D_6$, ratio 1:4).

The transition of the π-allyl system to a dynamic allyl system evidently is brought about by the strong electron donation to the nickel atom by two molecules of triethylphosphine. In π-$C_3H_5PdCl$, the same effect is achieved even with triphenylphosphine[3]. Transitions of this type are produced thermally in $Zr(C_3H_5)_4$ and $Th(C_3H_5)_4$[4].

Received: August 8th, 1966 [Z 308 IE]
German version: Angew. Chem. 78, 941 (1966)

[1] *G. Wilke* and *B. Bogdanović*, cited in *G. Wilke et al.*, Angew. Chem. *78*, 157 (1966), on p. 170; Angew. Chem. internat. Edit. *5*, 151 (1966), on p. 163.

[*] We thank Dr. *E. G. Hoffmann* for recording the $^1H$-NMR spectra.

[2] *I. E. Nordlander* and *J. D. Roberts*, J. Amer. chem. Soc. *81*, 1769 (1959).

[3] *J. Powell, S. D. Robinson*, and *B. L. Shaw*, Chem. Commun. *1965*, 78.

[4] *E. Steinrücke*, Dissertation, Technische Hochschule Aachen, 1966; *G. Wilke* and *E. Steinrücke*, cited in *G. Wilke et al.*, Angew. Chem. *78*, 157 (1966), on p. 162; Angew. Chem. internat. Edit. *5*, 151 (1966), on p. 156.

## Existence of Ternary Compounds of Phosphorus with Sulfur and Hydrogen

By Prof. P. W. Schenk and B. Leutner

Institut für Anorganische und Analytische Chemie, Technische Universität Berlin (Germany)

In this communication we report the first synthesis of volatile ternary compounds of phosphorus, sulfur, and hydrogen.

Equimolar mixtures of gaseous $H_2S$ and $PH_3$, or of $D_2S$ and $PD_3$, or of $CH_3SH$ and $PH_3$, were passed at 0.5 mmole/min and about 0.1 mm Hg through an electrodeless glow discharge (900 V at 90 mA and 27 MHz)[1]. The products were condensed at −196 °C; the conversion was 0.5–1.0 %.

For analysis the gases were passed directly from the glow discharge into a small mass spectrometer[2] or condensed at −180 °C in a low-temperature infrared absorption cell. The following products were indentified:

| Initial mixture | Main product | Subsidiary products |
|---|---|---|
| $H_2S + PH_3$ | $H_2PSH$ | $H_2S_2$, $P_2H_4$ |
| $D_2S + PD_3$ | $D_2PSH$ | $D_2S_2$, $P_2D_4$ |
| $CH_3SH + PH_3$ | $H_2PSCH_3$ | $P_2H_4$, $CH_3SSCH_3$ |

Mass-spectrometric identification of a product of molecular formula $H_3PS$ was complicated by the presence of $H_2S_2$ and $P_2H_4$ with the same nominal molecular weight ($m/e$ = 66). The following evidence is proof for a compound $H_3PS$:

1. The more frequent occurrence of a fragment of nominal mass 63 when a mixture of $H_2S$ and $PH_3$ is subjected to a discharge than with pure $P_2H_4$; this indicates the presence of $PS^+$ together with smaller amounts of $P_2H^+$.

2. The occurrence of the peak at $m/e$ = 63 in the reaction products of $PD_3 + D_2S$, which can be due to $PS^+$ only.

3. The formation of an analogous compound $H_2PSCH_3$ from $CH_3SH + PH_3$, the main peak of which at $m/e$ = 80 is not overlapped by that of any other compound.

A strong, sharp infrared band at 477 $cm^{-1}$, which can be assigned to a P–S single bond[3], of the gas mixture condensed at −180 °C supports the structure $H_2PSH$. It follows from the decrease in intensity of this band that the colorless compound decomposes already above −130 °C to an amorphous, nonvolatile, insoluble[4], yellow residue. The P:S ratio in this residue varies from 2:1 to 6:1 since, depending on the method of preparation, variable amounts of (also unstable) $P_2H_4$ and $H_2S_2$ are present.

$H_2PSCH_3$ is somewhat more stable. At −78 °C it still shows an infrared absorption with a P–S frequency of 480 $cm^{-1}$; at this temperature, however, slow decomposition is noticeable from the spectrum. This compound also leaves a yellow, non-volatile residue.

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German version: Angew. Chem. 78, 942 (1966)

[1] Telefunken high frequency generator HFG 120.

[2] Quadrupole mass spectrometer AMP 3, Fried. Krupp, Meß- und Analysentechnik, Bremen.

[3] Such an IR band is observed, *e.g.*, in the following compounds of known structure: $P_4S_3$; organophosphorus compounds [*R. A. Chittenden* and *L. C. Thomas*, Spectrochim. Acta *20*, 1690 (1964)].

[4] Solvents: benzene, $CS_2$, $H_2O$; aqueous solutions of bases such as NaOH dissolve the residue by decomposition.

## Di(cyclooctatetraene)titanium and Tri(cyclooctatetraene)dititanium [1]

By Dr. H. Breil and Prof. G. Wilke

Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr (Germany)

Di(cyclooctatetraene)titanium, $Ti[COT]_2$ *(1)*, is obtained as deep violet-red crystals in yields of over 80 % when $Ti(OC_4H_9)_4$ is heated at 80 °C in the presence of an excess of cyclooctatetraene (COT) and $Al(C_2H_5)_3$ in the molar ratio 0.2:2:2. The compound is sparingly soluble in aromatic hydrocarbons; the solutions are deep red. It can be recrystallized from hot toluene.

Similarly, tri(cyclooctatetraene)dititanium, $Ti_2[COT]_3$ *(2)*, is obtained as yellow crystals when the reactants are used in a molar ratio of 0.2:0.4:2 (yield 80 %). This complex is also sparingly soluble in aromatic hydrocarbons. Both compounds are extremely sensitive to air. They can be interconverted in accordance with the equation:

$$\underset{(1)}{Ti[COT]_2} \underset{\text{COT; 80 °C; 40 hr, 94 \%}}{\overset{(C_2H_5)_2AlH;\ 60\ °C;\ 40\ hr;\ 95\ \%}{\rightleftharpoons}} \underset{(2)}{Ti_2[COT]_3}$$

Ethanol reacts spontaneously with a suspension of *(2)* in $C_6H_{12}$ giving 1,3,5- and 1,3,6-cyclooctatrienes (88:12), in 90 % yield, together with titanium ethoxide. Under the same conditions, *(1)* gives 1,3,5- and 1,3,6-cyclooctatrienes and cyclooctatetraene (51:37:12) in a total yield of 70 %.

The complexes *(1)* and *(2)* react with formaldehyde or $CO_2$ under pressure (*ca.* 50 atm) to form unsaturated hydroxymethyl or carboxyl derivatives of unsaturated eight-membered rings, which were converted in several steps into methylcyclooctanes. Mono-, di-, and trimethylcyclooctanes were obtained in every case; we also obtained these products analogously from methyl iodide and cyclooctatetraenedisodium. It must be concluded from the formation of mono-, di-, and trisubstituted derivatives of cyclooctane that transmetalation takes place during the reactions of both the titanium complexes and the cyclooctatetraenedisodium, and that the reaction does not occur exclusively in the 1,4-position, as described by *Reppe et al.*[2] for $Na_2[COT]$.

The chemical behavior of the cyclooctatetraene-titanium complexes indicated that the cyclooctatetraene molecules are bonded to the titanium atom at least partly as quasiaromatic, planar 10 π-electron systems, *i.e.* as dianions[3].

The "club sandwich" structure proposed for *(2)* has been confirmed in principle by X-ray analysis[4]. The structure of *(1)* is not yet known.

The presence of dianions is also indicated by the following synthesis:

$$TiCl_4 + 2\ Na_2[COT] \xrightarrow{C_6H_6,\ 70\ °C,\ 72hr,\ 53\ \%} Ti[COT]_2 + 4\ NaCl$$

With this method we prepared the complexes $V[COT]_2$, $Cr_2[COT]_3$, $Mo_2[COT]_3$, $W_2[COT]_3$, Co[COT], and Ni[COT].

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German version: Angew. Chem. 78, 942 (1966)

[1] Ger. Pat. 1191375 (April 28th, 1960/Dec. 19th, 1965), Studiengesellschaft Kohle, Mülheim/Ruhr.

[2] *W. Reppe et al.*, Liebigs Ann. Chem. *560*, 1 (1948).

[3] *Th. Katz*, J. Amer. chem. Soc. *82*, 3784 (1960).

[4] *H. Dietrich* and *H. Dierks*, Angew. Chem. *78*, 943 (1966); Angew. Chem. internat. Edit. *5*, 899 (1966).

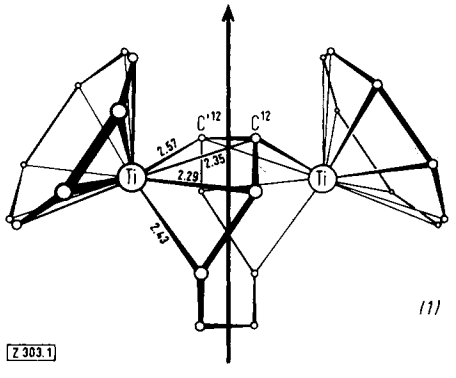
## Crystal Structure of Tri(cyclooctatetraene)dititanium

By Dr. H. Dietrich and Dr. H. Dierks

Fritz-Haber-Institut der Max-Planck-Gesellschaft, Berlin-Dahlem (Germany)

The π-complex tri(cyclooctatetraene)dititanium *(1)* prepared by *Wilke et al.*[1] crystallizes in thin, yellow leaflets, space group Fdd 2 ($C_{2v}^{19}$), $a = 14.41$, $b = 35.99$, $c = 7.25$ Å; $V = 3760$ Å$^3$, X-ray density 1.448 g/cm$^3$, $n = 8$.

The crystals were studied by three-dimensional X-ray diffraction (filtered copper $K_\alpha$ radiation, multifilm technique). The reflection intensities were estimated visually by means of a reference scale and were corrected for absorption.




*(1)*

Z 303.1

The molecules of *(1)* contain two titanium atoms and three cyclooctatetraene rings and have a two-fold axis that passes through the middle ring. The two outer rings are planar (C–C distance 1.39 Å) and are attached symmetrically each to one titanium atom (all Ti–C distances 2.35 Å). The adjacent atoms C-12 and C'-12 of the middle ring are apparently bonded to both titatium atoms although the Ti–1/C-12 and Ti–2/C'-12 distances are very long (2.57 Å).

The anomalous dispersion effect due to the two titanium atoms plays a significant role in the structure refinement presently being carried out, because the two-fold axis of the molecule is also a polar axis of the crystal[2]. The present value $R = 11$ % thus rises to 20 % if the structure factors for inverted structures are used in the calculations.

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[1] *H. Breil* and *G. Wilke*, Angew. Chem. *78*, 942 (1966); Angew. Chem. internat. Edit. *5*, 898 (1966). We thank Prof. *Wilke* for the tri(cyclooctatetraene)dititanium crystals.

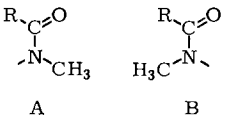
[2] *D. H. Templeton, A. Zalkin*, and *T. Ueki*, Amer. Crystallogr. Ass. Meeting 1966, Abstr. p. 40.

## Magnetic Anisotropy of the Amide Group

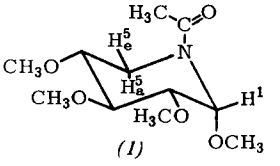
By Dr. H. Paulsen and K. Todt

Chemisches Staatsinstitut, Institut für Organische Chemie, Universität Hamburg (Germany)

Studies of the long-range coupling[1], the intramolecular nuclear Overhauser effect[2], the paramagnetic contact shift[3], as well as by the benzene dilution method[4] showed that in amides in which rotation about the N–CO bond is restricted, protons in the arrangement A (*cis* to the carbonyl group) are shielded more strongly than in arrangement B. The corresponding $CH_3$ NMR signal therefore occurs at higher fields for form A than for form B. We have found that this assignment is valid for freely rotating methyl groups, but has to be differentiated for sterically fixed protons.



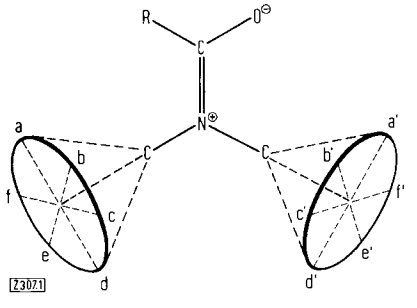
A B



*(1)*

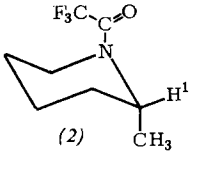
Integration of signal intensities as well as double resonance experiments show that in *(1)*[5] the assignment of the double resonance signals from both $H_a^5$ and $H_e^5$ is reversed. Equatorial protons ($H_e^5$ and $H^1$), which are in the plane of the amide group, give a signal at lower field for form A than for form B. On the other hand, the axial protons (such as $H_a^5$ and the protons of the glycosidic $OCH_3$ group), which are outside the plane of the amide group, give a signal for form B at lower field than that for form A, which corresponds to the assignment for freely rotating methyl groups.

The figure gives a generalized representation of the anisotropic effect of the amide group. The possible proton positions are indicated by letters on the circles. Two regions can be distinguished: the "plane region" in the plane of the amide group with the positions *aa'* (equatorial protons), in which *a* is shielded more strongly than *a'*, and the "out-of-plane region", in which *cc'* (axial protons) are opposed, and position *c'* is shielded more strongly than *c*. The positions *ee'* are equivalent to *cc'*.

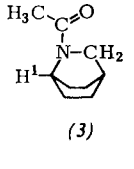



Z 307.1

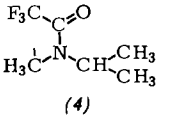
For compound *(2)* we assume a conformation in which the methyl group is axial[5]. $H^1$ lies in the plane region and its assignment is typical of *aa'*. The methyl group, since it lies in the out-of-plane region, shows a typical *cc'* assignment. In the fixed structure *(3)*, $H^1$ lies in the plane region and



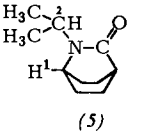
*(2)*



*(3)*



*(4)*



*(5)*

gives two signals with the *aa'* assignment. The protons of the $CH_2$ group in *(3)* have orientations between axial and equatorial, namely the positions *bb'* and *ff'*, respectively. We found only a small degree of splitting for this group. The protons are on the border of the plane and the out-of-plane regions, *i.e.* the shielding between *b* and *b'* is about the same, as is that between *f* and *f'*. Since the influence of *dd'* presumably is small, owing to the larger distance from the carbonyl bond, averaging of the effects of all positions *a–f* and *a'–f'* on the anisotropy shows that freely rotating methyl groups give signals corresponding to the out-of-plane region.

In *(4)* the freely rotating $CH_3^1$ group shows two signals corresponding to the ou-tof-plane region, the CH group signal pair corresponding to the plane region. This shows that in *(4)* a conformation in which the CH proton lies in the plane of the amide group is slightly preferred. Our assignment for the plane region agrees with theoretical calculations[6], which are in contradiction to the assignment for freely rotating methyl groups. Our assignments were made by the benzene dilution method, double resonance, and for *(4)* by F–C–C=N–C–H long-range coupling, to which *cis* > *trans* applies. An independent assignment follows from compound *(5)* with a fixed amide group, for which we found $\tau = 6.4$ for $H^1$ and $\tau = 5.4$ for $H^2$. The isopropyl group in *(5)* has the same orientation as in *(4)*.

Comparison of amides with thioamides in the spectra of *N,N*-dimethylacetamide and *N,N*-dimethylthioacetamide by long-range coupling and the benzene dilution method shows their magnetic anisotropies to be opposite. In thioamides the plane region evidently has a larger cone of influence, so that the assignment of the freely rotating methyl group coincides with that of the plane region.

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# CONFERENCE REPORTS

## Surface-active Compounds

The *Deutsche Akademie der Wissenschaften zu Berlin* and the *Chemische Gesellschaft in der DDR* were hosts to the IIIrd International Symposium on Surface-active Compounds in Berlin from the 29th to the 31st March 1966. The following are abstracts of the some of the lectures of particular interest to chemists.

### Reactions Occurring on Hydrogenation of Unsaturated Fatty Acids to Unsaturated Fatty Alcohols

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Berlin-Adlershof and Rodleben (Germany)

Mono- and poly-unsaturated carboxylic acids may be converted into unsaturated alcohols by selective, high-pressure hydrogenation. None of the known catalysts acts so selectively as to avoid completely reduction of the C=C double bonds, the amount of such "side reaction" depending on the nature of the acid.

Pure oleic, elaidic, erucic, brassidic, 10-undecenoic, 2-octadecenoic, ricinoleic, linoleic, ricinenic, linolenic, and α- and β-eleostearic acids were hydrogenated under identical conditions (300 °C at 300 atm) in a 250-ml shaking autoclave with a catalyst of copper-cadmium (Cu:Cd = 3:1 to 4:1) that had been precipitated by sodium carbonate solution.

The alcohols were isolated after hydrolysis of the hydrogenation product and were identified by IR-spectroscopy and determination of their iodine and saponification values.

Oleic, elaidic, erucic, and brassidic acids were reduced almost quantitatively to oleyl, elaidyl, erucyl, and brassidyl alcohols, respectively. The selectivity of reduction of the COOH group decreases with increasing number of C=C double bonds. Linoleic acid is thus reduced to a mixture of unsaturated alcohols, with about 20% of the C=C bonds being saturated; little conjugation (*ca.* 4%) occurs in this reaction. The IR spectra indicate that 30% of the alcohols have *trans*-double bonds if only one *trans*-double bond is assumed per molecule.

Linolenic acid gives only 50% of alcohols, 70% of the double bonds being retained. If the reaction time is prolonged, the proportion of *trans*-double bonds increases with saturation. α- and β-Eleostearic acids give a 58% yield of a fatty alcohol mixture in which less than half the original double bonds remain. Under the conditions given above, ricinenic acid cannot be hydrogenated at all.

Migration of C=C double bonds was established by ozonization of the hydrogenation product and gas-chromatographic investigation of the oxidative ozonide fission products. With 9-octadecenoic acids there is migration to the 10,11-, 11,12-, and 8,9-positions; with 13-docosenoic acids there are similar amounts (*ca.* 5:1:2%) of migration to the 14,15-, 15,16-, and 12,13-positions. Analysis is harder for polyenoic acids because the same fragments are formed as a result of structural isomerism as of partial hydrogenation.

### New Synthesis of Surface-active Urethanes of Sucrose

*W. Gerhardt*, Berlin-Adlershof (Germany)

Surface-active derivatives of sucrose have been obtained by a new method. Carbamic esters are prepared by treating reactive alkyl halides with alkali cyanate and a carbohydrate R'OH in an aprotic solvent, particularly dimethylformamide:

$$RX + KNCO \rightarrow R{-}NCO + KX$$
$$RNCO + R'OH \rightarrow R{-}NH{-}COOR'$$

The alkyl isocyanates formed as intermediates can be isolated.

If a long-chain n-alkyl halide is used with sucrose as the alcoholic component, the *N*-n-dodecylurethane of sucrose is obtained; it can also be prepared by reaction of n-dodecyl isocyanate with sucrose in dimethylformamide. The new process does not directly require the alkyl isocyanate, which is often not readily accessible.

The halogen compound used may be an alkyl bromide at *ca.* 95 °C or the chloride at *ca.* 145 °C. If alkali bromide is added to the reaction mixture, alkyl chlorides are transhalogenated to yield alkyl bromides, which then react at *ca.* 95 °C.

Halogenated fatty acids also react with sucrose and potassium cyanate in dimethylformamide, yielding *N*-substituted urethanes of sucrose. Hydrolysis leads to salts of *N*-(carboxyalkyl)urethanes of sucrose, which are characterized by greater solubility in water.

Water-solubility can also be enhanced by oxyethylation of the OH group [conversion of R—OH into R-$(OC_2H_4)_n$—OH]. For this purpose, either oxyethylated sucrose is treated with an alkyl isocyanate, or ethylene oxide is added to an *N*-alkylurethane of sucrose.

A further variation is the use of alkanesulfonyl chlorides as halogen compound; *N*-(alkylsulfonyl)urethanes of sucrose are obtained.

## Formation of Epoxides on Liquid-phase Oxidation of Olefins

*Anneliese Greiner*, Berlin-Adlershof (Germany)

Reactive epoxides are of great interest in the preparation of surface-active compounds. There has hitherto been no simple process for direct oxidation of long-chain olefins to epoxides.

1-Dodecene was therefore investigated with a view to controlled oxidation. Use of pure oxygen leads to formation of considerable amounts of carbonyl compounds and carboxylic acids. An oxygen-nitrogen mixture at 130 °C containing 12 vol-% of oxygen was found to be the most favorable for epoxide formation. Earlier work had shown the striking efficiency of ozone for initiation of oxidation reactions[1]. Addition of ozone influences the primary step in the oxidation, namely, formation of hydroperoxide, which occurs at the carbon atom next to the double bond. Therefore, ozone at a concentration of *ca.* 1 to 3 vol.-% was added to the gas mixture used for our oxidations. In all these experiments there was an increased rate of oxidation and increased formation of epoxides.

A further increase in the yields of epoxide was achieved by addition of 5 % of 1-dodecene ozonide. On the assumption that the increased yield was due not merely to the peroxidic decomposition products from the ozonide, but that the carbonyl compounds formed in this decomposition were also involved, oxidations were carried out with addition of carbonyl compounds (50 % of 1-dodecene, 45 % of liquid paraffin, and 5 % of dodecanal; 130 °C; $N_2$:$O_2$ = 7:1 v/v); these conditions led to yields of 1,2-epoxydodecane amounting to 50 % of the 1-dodecene used.

It was shown by gas chromatography that 1,2-epoxydodecane was formed, but that the epoxide fraction contained also 1-dodecen-3-ol and -3-one. The position of the double bond was unchanged in the unused 1-dodecene.

## Alkylarenesulfonates Derived from Petroleum Hydrocarbons

*P. Hahn*, Rodleben (Germany)

Because "tetrapropylenebenzenesulfonate" ($C_{12}$-substituted benzenesulfonate with mixed alkyl radicals derived by tetramerization of propene) prepared from petrochemicals is not readily biodegradable, alternative starting materials to tetrapropylene have been sought.

As alternatives to 1-alkenes, normal alkanes obtained by the molecular-sieve process are being increasingly used for production of alkylbenzenes. In Table 1 the distribution of chain lengths, content of n- and iso-compounds, and mean chain length $\bar{n}$ of a Fischer-Tropsch paraffin mixture (A, Mepasin I) are compared with those of the paraffins obtained by the Parex[*] process (B, C) from petroleum fractions.

Table 1. Components of paraffin mixtures of various origins.

| Hydrocarbon | Weight-% | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $C_8$ | $C_9$ | $C_{10}$ | $C_{11}$ | $C_{12}$ | $C_{13}$ | $C_{14}$ | $C_{15}$ | Total | $\bar{n}$ |
| A Mepasin I | | | | | | | | | | |
| normal | 0.6 | 3.0 | 13.6 | 31.1 | 21.3 | 7.2 | 1.4 | 0.9 | 79.1 | 11.4 |
| iso | | 0.4 | 1.4 | 6.2 | 7.8 | 4.5 | 0.6 | | 20.9 | |
| B n-Paraffin $C_{10}$—$C_{14}$ | | | | | | | | | | |
| normal | | | 3.1 | 44.3 | 43.4 | 5.1 | | | 95.9 | 11.7 |
| iso | | | | 0.1 | 0.7 | 2.3 | 1.0 | | 4.1 | |
| C n-Paraffin $C_{10}$—$C_{13}$ | | | | | | | | | | |
| normal | | 0.4 | 3.2 | 45.5 | 39.5 | 8.7 | 0.2 | | 97.5 | 11.6 |
| iso | | | 0.1 | 0.2 | 1.2 | 1.0 | | | 2.5 | |

The mixture thus contains 96—98 % of normal alkanes of such chain lengths and in such proportions as to make it a suitable starting material for preparation of alkylbenzenes.

The monochloroalkanes required for synthesis of alkylbenzenes were obtained by thermal chlorination of the paraffins. To obtain optimal yields of monochlorides with minimal formation of by-products, the paraffin mixture is chlorinated to 6—8 wt.-% chlorine content (cf. Table 2). The chloroalkanes were then converted with benzene and $AlCl_3$ into n-alkylbenzenes which were fractionated, sulfonated with oleum, and neutralized. Table 3 gives the composition of

Table 2. Products of chlorination of a Mepasin-I fraction of $n$ = 11 to 6 wt.-% chlorine content with $Cl_2$ at 85 °C.

| $C_nH_{2n+2-x}Cl_x$ | Weight-% Cl | | | | |
|---|---|---|---|---|---|
| | Continuous, No. of reactors | | | | Discontinuous |
| $x$ | 1 | 2 | 3 | 4 | |
| 0 | 73.22 | 71.96 | 71.59 | 71.30 | 70.64 |
| 1 | 19.89 | 22.04 | 22.84 | 23.29 | 24.65 |
| 2 | 5.18 | 4.91 | 4.65 | 4.65 | 4.25 |
| 3 | 1.37 | 0.91 | 0.76 | 0.76 | 0.45 |
| 4 | 0.34 | 0.17 | 0.17 | 0.00 | 0.00 |

Table 3. Composition (wt.-%) of sodium alkylbenzenesulfonates (yellowish) derived from various hydrocarbon mixtures.

| Paraffin mixture | Neutral oil | $Na_2SO_4$ | NaCl | $Na_2CO_3$ | ABSNa | I value |
|---|---|---|---|---|---|---|
| Mepasin I | 0.9 | 10.8 | 1.78 | 0.19 | 86.3 | 8 |
| n-Paraffin $C_{10}$—$C_{14}$ | 1.0 | 10.8 | — | 0.28 | 87.9 | 5—10 |
| n-Paraffin $C_{10}$—$C_{13}$ | 0.9 | 9.2 | — | 0.34 | 89.6 | 5 |

the resulting sodium alkylarenesulfonates, as well as the iodine number of the unbleached end product which is a further control of quality.

No difference from the behavior of Mepasin I could be found in relation to the total synthesis of alkylbenzensulfonates. Alkylbenzenesulfonates prepared from normal paraffins are more susceptible to biological oxidation because of their predominantly straight-chain structure.

## Electrochemical Investigation of the Adsorption of Surface-active Materials at the Phase Boundary Mercury/Electrolyte

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We have studied the adsorption of triethyl phosphate and polyethylene oxide ($\bar{M}$ = 1000), separately and in admixture, at the phase boundary mercury/electrolyte by Breyer alter-

[1] *G. Wagner*, J. prakt. Chem. *15*, 327 (1962); *27*, 297 (1965).
[*] VEB Leuna-Werke.

nating-current polarography and tensammetry. The lowering of capacity $\Delta C$ and the height of the tensammetric waves were used as measures of the degree of surface coverage, $\Theta$. The influence of electrode potential $E$, concentration of sorbate, and drop interval $t_m$ were measured. Triethyl phosphate has moderate surface activity. Equilibrium values are obtained that are independent of $t_m$ (rapid diffusion to the surface at the relatively high concentrations, $c_{\Theta=0.5} = 7 \times 10^{-4}$ mole/l). The adsorption isotherm determined from the lowering of capacity is S-shaped. *Frumkin*'s interaction constant $a = 1.57$.

Polyethylene oxide is strongly adsorbed at the interface ($c_{\Theta=0.5} = 1.7 \times 10^{-5}$ mole/l), and the desorption potential is relatively high ($E_- = -1.76$ V). Lower oxide concentrations lead to measurable restriction of diffusion towards the surface. The lowering of capacity is thus proportional to $c$ and $t_m^{1/2}$.

When an electrode surface is completely covered with triethyl phosphate, this can be displaced gradually and finally completely replaced in the boundary layer by polyethylene oxide. The same replacement effect is observed when the drop interval $t_m$ is increased, this leading to increased diffusion of the polyethylene oxide which, although present in lower concentration, is more strongly adsorbed. With the less surface-active triethyl phosphate, which is present in higher concentration in the solution, an equilibrium is almost always set up (rapid diffusion), so that the process is independent of time. If, however, the surface is half-covered with polyethylene oxide, the free part of the surface can become occupied by triethyl phosphate, and at very high concentrations of the phosphate it may displace the oxide from the surface. The alternating-current polarogram shows three characteristic potential regions: in the central area surrounding the origin of the electrocapillary curve there is mixed adsorption of triethyl phosphate and polyethylene oxide; outside this, in both the positive and the negative direction, there are areas of adsorption of polyethylene oxide; and finally two areas with no adsorption.

## The Effect of Chain Length on the Ability of Aliphatic Amines to Render Quartz Hydrophobic

*J. Kloubek*, Prague (Czechoslovakia)

The dependence of their ability to render minerals hydrophobic on the hydrocarbon chain length of aliphatic amines has been studied by many authors in flotation experiments. Their results indicate that the logarithm of the concentration ($c_F$) of amine in solution for a specific flotability is linearly dependent on the number ($n$) of carbon atoms in the chain:

$$n = a_1 \log c_F + b_1 \quad (1)$$

where $a_1$ and $b_1$ are constants of various values according to the results from the literature.

The surface charge on floating quartz depends on the pH of the solution. This charge has an effect on the adsorption of amines similar to that of electrolytes on micelle formation in solution, *i.e.* it increases the formation of hemi-micelles. This follows from the pH-dependence of the slope of the curve of $\log c_F$ *vs.* $n$. Further, this dependence shows that adsorption on the quartz surface at high pH probably occurs by the same mechanism as does separation of amine molecules from solution when the solubility limit is exceeded.

Within certain limits, moreover, the basicity ($pK_a$) and the logarithm of the solubility ($S$) depend linearly on the chain length. Combination of these relations with eq. (1) leads to an expression relating the flotation activity to basicity and solubility of the molecule, namely:

$$\log c_F = a_3(-b_3 pK_a + \log S + c_3) \quad (2)$$

where $a_3$ and $c_3$ depend on the experimental conditions and $b_3$ is the constant determined by the slope d log $S$/ d $pK_a$.

A similar relation between flotation activity, basicity, and solubility was previously found for 5,6,7,8-tetrahydro-1- and -2-naphthylamine and their $N$-methyl derivatives[1].

The ability to effect flotation depends on the formation of hemi-micelles on the surface of the mineral. *Fuerstenau*[2] expressed the concentration ($c_{HM}$) of hemi-micelle formation by:

$$c_{HM} = A' \exp[(W_e' - n\varphi')/kT] \quad (3)$$

where $A'$ is a proportionality constant, $W_e'$ is proportional to the electrostatic adsorption energy, and $\varphi'$ is the free energy of cohesion of a $CH_2$ group.

Eq. (3) permits closer specification of the relation (1). Eq. (3) can be extended if we assume that $W_e'$ is proportional to $pK_a$ and the surface charge ($M$) on the quartz also in the case of $c_F$, and that adsorption is influenced by hydrophobic forces related to the chain length of the adsorbed amine and to the pH of the solution. These assumptions seem to be experimentally substantiated; they are partly confirmed by eq. (2). Relation (4) follows as a measure of floatability:

$$c_F = A' \exp[(-a_5 pK_a M - n\varphi' - nb_5 pH)/kT] \quad (4)$$

where $A'$ is proportionality constant, $Wc'$ is proportional reproduces the experimental results up to pH 10. The sudden drop in floatability at higher pH values is probably caused by a change in the quartz surface and its increased solubility.

## Preparation of Hydrogen Sulfate Esters by Reaction of Higher Aliphatic Alcohols with Sulfamic Acid

*S. M. Loktew* and *E. L. Wulach*, Moscow (USSR)

We have used cetyl alcohol and the $C_{12}$–$C_{18}$ alcohol fraction to study the common features of their esterification including the influence of reaction conditions (temperature, duration of reaction, relative quantities, *etc.*) and the nature and amount of the catalyst.

Esterification in the presence of urea leads to 96–98% conversion of cetyl alcohol and 87% conversion of the $C_{12}$–$C_{18}$ fraction. For cetyl alcohol and the $C_{12}$–$C_{18}$ fraction the relative molar quantities acid:alcohol:urea were 115–120:100:10–20 or 110–130:100:10–20, respectively, the temperature 105 and 110 °C, respectively, and the reaction time 6–8 and 2 hr, respectively. Optimization by a statistical method of the esterification of the $C_{12}$–$C_{18}$ alcohol fraction in the presence of urea and poly(ethoxyalkyl)phenol as catalysts led to elucidation of conditions that gave 89% (*p*-toluidine method) and 96% (hydrolysis method) of esterification. These conditions were a molar ratio acid:alcohol:urea:poly(ethoxyalkyl)phenol = 115:100:12:5.5. The surface properties of ammonium salts of the hydrogen sulfates of the $C_{12}$–$C_{18}$ alcohols are comparable with those of sodium lauryl sulfate. The results indicate the following reaction mechanism:

$$H_3\overset{\oplus}{N}\text{–}S\overset{\ominus}{O}_3 + :B \rightleftarrows H_3N + B:SO_3 \text{ (slow)}$$

$$ROH + B:SO_3 \rightarrow ROSO_3H + :B \text{ (fast)}$$

The catalytic activities of more than 50 Lewis bases (:B) (amides, amines, ethers, *etc.*) have been studied. Decrease in activity parallels decrease in electron-donor properties. The catalysts studied can be divided into two types: *1.* substances whose nucleophilic center arises by mesomeric $\pi$-electron shift (dimethyl sulfoxide, pyridine *N*-oxide, *N,N*-dimethylacetamide, dimethylformamide, tetrahydrothiophene dioxide, thiourea, urea, butyl butyrate, acetonitrile, nitrobenzene). *2.* Substances whose nucleophilic center is a localized lone electron pair (pyridine, quinoline, 2-pyridinecarboxylic acid,

[1] *J. Kloubek*, Collect. czechoslov. chem. Commun. *31*, 3526 (1966).

[2] *D. W. Fuerstenau, T. W. Healy*, and *P. Somasundaran*, Trans. Soc. Mining Engr. *229*, 321 (1964).

2-bromopyridine, 2-fluoropyridine, dioxane, hexyl methyl ether). The intermediate reaction of catalysts of the first group with sulfamic acid occurs through π-bonds. These catalysts have high polarity and low basicity; there is a correlation between catalytic activity and basicity. The intermediate reaction of catalysts of the second group with sulfamic acid occurs through σ-bonds. Catalysts of this group have lower polarity than those of the first group; catalytic activity is observed at sufficiently high basicity. Within this group also there is correlation between catalytic activity and basicity.

## Reaction of Sulfonyl Chlorides with Alkylaluminum Compounds

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Triethylaluminum and ethylaluminum sesquichloride react with aliphatic and aromatic sulfonyl chlorides in the molar ratio 1:1 in non-aromatic solvents such as methylene chloride, giving better than 95% yields of the corresponding aliphatic and aromatic sulfinic acids and ethyl chloride. It is assumed that electrophilic attack of the aluminum compound on the sulfonyl chloride is followed by a synchronous process in which the chlorine is removed cationically from the sulfur and combines with the ethyl group (which has become negative) of the organoaluminum compound, yielding ethyl chloride. Hydrolysis of the aluminum sulfinate formed at the same time gives the corresponding sulfinic acid.

When twice the molar amount of organoaluminum compound is used, there is a characteristic difference between the modes of reaction of aliphatic and aromatic sulfonyl chlorides. Either of the ethylaluminum compounds with aromatic sulfonyl chlorides in the molar ratio 2:1 gives, besides ethyl chloride, more than 75% of the corresponding ethyl sulfoxide and small amounts of ethyl sulfide. A second mole of organoaluminum compound has no influence on the reaction of aliphatic sulfonyl chlorides; the corresponding alkanesulfinic acid is always formed.

The electron density at the sulfur atom is considered responsible for these differring modes of reaction. The aluminum sulfinate resulting from the first reaction step permits alkylation of the sulfur if the electron density on the latter is sufficiently reduced by an electron-attracting substituent for attack by the negative ethyl group to be succesful. The same results attend the use of alkylaluminum compounds containing longer alkyl chains. Thus reaction of tri-n-hexylaluminum with benzenesulfonyl chloride (2:1) gives 70% of n-hexyl phenyl sulfoxide.

The economy of this one-stage process can be considerably improved by carrying out the reaction in two independent steps. In the first step a cheap alkylaluminum compound is used for preparation of the aluminum sulfinate, *e.g.* ethylaluminum dichloride or ethylaluminum sesquichloride; then in the second step the desired sulfoxide is prepared by using an alkylaluminum with a longer alkyl radical. Thus dichloroaluminum benzenesulfinate, obtained from ethylaluminum dichloride and benzenesulfonyl chloride (1:1) in a first step, reacts with di-n-hexylaluminum chloride to give n-hexyl phenyl sulfoxide in 61% yield. Tri-, di-, and mono-alkylaluminum compounds can all be used for these reactions; monoalkylaluminum compounds are preferred because of the greater utilization of the alkyl groups.

## Concentration of Hemoglobin Solutions by Flotation

*J. Spurný* and *B. Jakoubek*, Prague (Czechoslovakia)

Dilute solutions of hemoglobin can be concentrated by foaming. We have studied pure hemoglobin solutions as well as solutions to which a quaternary ammonium base has been added (*e.g.* ethoxycarbonylpentadecyltrimethylammonium chloride). The flotation time was not limited, so that the simple relations

$$M_P = M_R + M_K$$

and $$c_P V_P = c_R V_R + c_K V_K$$

hold, where $M_P$, $M_R$, and $M_K$ are the total amounts of protein dissolved in the original solution, in the residual solution, and in the concentrate, respectively, $c_P$, $c_R$, and $c_K$ are the corresponding concentrations, and $V_P$, $V_R$, and $V_K$ are the corresponding volumes.

We were interested particularly in the dilution of the initial solution and in the concentration range the method can be used, to what extent the protein content of the concentrate can be raised above that of the original solution, and what yields can be obtained. We consider that the quaternary ammonium bases form complexes with proteins.

| | Concn. range (g/ml) | Degree of concn. $Q = (c_K - c_P)/c_P$ | Yield [%] | pH |
|---|---|---|---|---|
| Without quat. base | $0.06 \times 10^{-3}$—$0.3 \times 10^{-3}$ | 0.10— 4.86 | 39—97 | 8.4 |
| With quat. base ($c = 10^{-4}$ g/ml) | $5 \times 10^{-7}$—$1.0 \times 10^{-4}$ | 0.96—10.3 | 79—98 | 8.6 |

For the concentration of pure hemoglobin solutions (without addition of quaternary salt) the following relations between volume of concentrate and concentration of the original solution hold:

$$V_K = k'(c_K - k)$$

and $$V_K = V_P(c_P - c_K)/(c_K - c_R)$$

where $k'$ and $k$ are constants with the values $15.67 \times 10^4$ ml²/g and $3.3 \times 10^{-5}$ g/ml, respectively.

[VB 3 IE]

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## Kinetics of Non-Isothermal Decompositions

By H. Jüntgen[*], Essen (Germany)

Non-isothermal reactions in nature and in industry are influenced by the variation of temperature with time. For simplicity, investigations are confined to reactions at constant rates of heating. Some general equations have been derived for this case. In particular, for the rate of gas evolution per unit temperature change, $dV/dT$ ($V$ = volume of gas formed up to temperature $T$) in thermal decompositions as a function of the temperature $T$, we find, for a reaction order $n = 1$:

$$\frac{dV}{dT} = \frac{k_0 V_0}{m} \exp\left(-\frac{E}{RT} - \frac{k_0 RT^2}{mE} e^{-E/RT}\right)$$

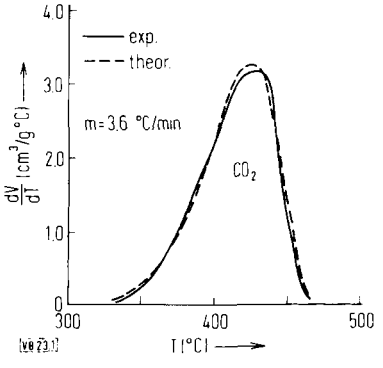
and for $n \neq 1$:

$$\frac{dV}{dT} = \frac{k_0}{m} e^{-E/RT}\left[V_0^{-(n-1)} + (n-1)\frac{k_0 RT^2}{Em} e^{-E/RT}\right]^{-n/(n-1)}$$

The shapes and positions of the maxima of these functions depend on the rate of heating $m = dT/dt$, the order $n$ of the reaction, the activation energy $E$, and the frequency factor $k_0$; the quantity $V_0$ (volume of gas evolved at $t = \infty$), being a proportionality factor, simply produces a parallel displacement of the curves. If $n$ is known, the quantities $E$ and $k_0$ can be determined from the observed gas formation at a given rate of heating $m$ by regression analysis with the aid of an electronic computer. Whether or not $n$ has been chosen correctly can be judged from the correlation coefficient and residual scatter.

The method was illustrated with the aid of three experimental examples, in which finely divided samples with helium passing through them were decomposed in an accurately adjustable oven at a constant rate of heating. The rate of gas formation was determined from the measured constant flow rate of the flushing gas and by continuous mass-spectrometric concentration measurements.

The reproducibility of the method was checked in the decomposition of basic magnesium carbonate. The figure shows that the calculated rate of decomposition agrees closely with that observed. The activation energy is 42.6 ± 1.4 kcal/mole, and the frequency factor is $(3.7 \pm 0.5) \times 10^{12}$ min$^{-1}$, assuming $n = 1$. The technically significant influence of the rate of heating can be shown very clearly in the case of 4 $MgCO_3 \cdot Mg(OH)_2 \cdot 5H_2O$: at low rates of heating ($m < 10$ °C/min), the basic carbonate liberates $CO_2$ directly between 400 and 450 °C, whereas at high rates of heating ($m < 100$ °C/min), it is first converted into magnesite, and decomposes only above 600 °C to give MgO.




The pseudo-unimolecular reduction of sulfuric acid to $SO_2$ on activated coke, which is important in new flue-gas desulfurization processes, can also be represented as a first-order reaction. An activation energy of 17 kcal/mole and a frequency factor of $5 \times 10^5$ min$^{-1}$ are obtained. For the first-order decarboxylation of ferulic acid, which was studied at a heating rate of 5.6 °C/min, an activation energy of 27.7 kcal/mole and a frequency factor of $3.6 \times 10^{-11}$ min$^{-1}$ are found.

[Lecture at Heidelberg (Germany), June 20th, 1966] [VB 23 IE]

German version: Angew. Chem. *78*, 948 (1966)

[*] *K. H. van Heek, H. Jüntgen,* and *W. Peters,* Ber. Bunsenges. physik. Chem., in press; *K. H. van Heek,* Dissertation, Technische Hochschule Aachen, 1965.

## Reactions of Strongly Electropositive Metals with Graphite and with Metal Dichalcogenides

*W. Rüdorff,* Tübingen (Germany)

Graphite reacts with solutions of alkali and alkaline-earth metals in liquid ammonia, forming metal ammine-graphite compounds. According to the concentration of the metal, europium or ytterbium gives compounds $([C_{16-18}]M(NH_3)_3)_n$ (2nd stage) and $([C_8]M(NH_3)_2)_n$ (1st stage) [1]. With graphite the blue ammoniacal solutions of Be, Mg, Al, Ba, Ce, and Sm prepared electrolytically with an anode of the appropriate metal give metal - graphite compounds such as $([C_{30}]Mg(NH_3)_{2-3})_n$ (4th stage) and $([C_{18}]Sm(NH_3)_3)_n$ (2nd stage). Further, compounds can be prepared having two metals in an ordered layer structure, *e.g.* a 1st stage $([C_{30}]MgK_2(NH_3))_n$ from a 4th stage magnesium-graphite and potassium, or a 1st stage $([C_{10}]BeK_{0.62}(NH_3))_n$ with $I_c = 31$ Å [2] from a 5th stage beryllium-graphite. Electrolysis with a uranium anode in the presence of KI leads to a graphite containing uranium and potassium $([C_{18}]UK_{0.18}(NH_3)_3)_n$.

Magnetic measurements show that $M^{2+}$ and $M^{3+}$ ions are present in ytterbium- and samarium-graphite, the proportion of $M^{3+}$ ions increasing with rising temperature, whereas europium-graphite contains only $Eu^{2+}$ ions. Europium-graphite (1st stage), like the metal, shows strong dependence of susceptibility on the field strength at low temperatures.

Sulfides such as $MoS_2$, $WS_2$, $ReS_2$, and $TiS_2$ that crystallize with layer lattices, as well as the corresponding selenides, react with metals dissolved in liquid ammonia. Compounds such as $K_{0.5}WS_2$, $K_{0.8}TiS_2$, and $NaTiSe_2$ are formed, in which metal layers are intercalated between the $MX_2$ layers. The properties of these compounds (pyrophoric nature, reaction with water with evolution of $H_2$, magnetic behavior) indicate that they are essentially intermetallic compounds. The transition to ionic thiometalates can be followed in the isostructural series $Na_{0.8}TiS_2$–$NaVS_2$–$NaCrS_2$. ($NaVS_2$, prepared from $Na_2S$ and $V_2S_3$, has the following properties: black; slowly decomposed by water without evolution of $H_2$; $I_a = 3.57$ Å, $I_c = 19.68$ Å; $\mu_{eff} = 2.1$ BM at 293 °C; $\varkappa = 5.9$ ohm$^{-1}$ cm$^{-1}$.

[Lecture at Hannover (Germany), June 23rd, 1966] [VB 15 IE]

German version: Angew. Chem. *78*, 948 (1966)

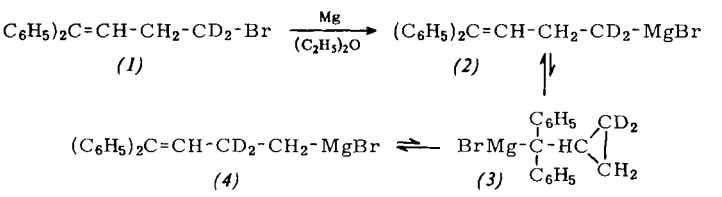
[1] In the first stage the metallic reactant forms a layer between *each* pair of graphite layers parallel to the basal plane of the lattice, in the second stage between each second pair of such layers, and so on.

[2] $I_c$ denotes the lattice parameter in the c-direction.

# SELECTED ABSTRACTS

**Photochemical formation of bicyclo[3.1.0]hex-2-ene and 3-vinylcyclobutene** was observed by *J. Meinwald* and *P. H. Mazzocchi* on irradiation of ether solutions of 1,3-cyclohexadiene. The products were identified by mass, NMR, and IR spectroscopy. It had previously been assumed that 1,3-cyclohexadiene gives only polymers and 1,3,5-hexatriene. / J. Amer. chem. Soc. *88*, 2850 (1966) / –Kr. [Rd 540 IE]

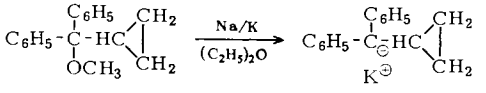
**The allylmethyl-cyclopropylmethyl rearrangement** of the Grignard reagent from [1,1-$D_2$]-1-bromo-4,4-diphenyl-3-butene *(1)* has been studied by *M.E.H.Howden, A. Maercker, J. Burdon,* and *J. D. Roberts.* The solution of this organometallic compound (ether, 20 °C) shows a $^1$H–NMR spectrum corresponding to an equilibrium mixture of equal parts of compounds *(2)* and *(4)*; the assumed intermediate *(3)* cannot be present in the equilibrium mixture to an extent greater than 0.3 %. With $CO_2$ or $HgBr_2$ the non-deuterated system *(2)* ⇄ *(3)* ⇄ *(4)* gives only open-chain products; use of $D_2O$ affords [4-D]-1,1-diphenyl-1-butene as sole deuterated hydrocarbon (97 % yield). Equilibration is much




faster ($\tau^1/_2 = 30$ hr at 27 °C) than when the phenyl substituents are not present ($\tau^1/_2 = 30$ hr at 27 °C). / J. Amer. chem. Soc. *88*, 1732 (1966) / –Eb. [Rd 532 IE]

**Reactive copolymers of styrene as carriers for proteins and enzymes** have been prepared by *G. Manecke* and *H.-J. Förster*. Copolymerization of 4- or 3-fluorostyrene with methacrylic acid and divinylbenzene, followed by nitration, led to hydrophilic, insoluble copolymers which contained dinitrofluorophenol groups and swelled readily in methanol. At room temperature the copolymers absorb up to 54% of the available 4-aminobenzoic acid from a 0.4% solution of 4-aminobenzoic acid in 0.1 N $NaHCO_3$; high molecular weight proteins, on the other hand, are absorbed only to a small extent or not at all. The copolymers react with a 2% diastase solution in 0.1 N $NaHCO_3$. The enzyme activities obtained were determined by iodometric study of the degradation of starch. The enzyme-charged resins retain their activity for long periods on storage under phosphate buffer at 4 °C. Makromolekulare Chem. *91*, 136 (1966) / –Hl. [Rd 554 IE]

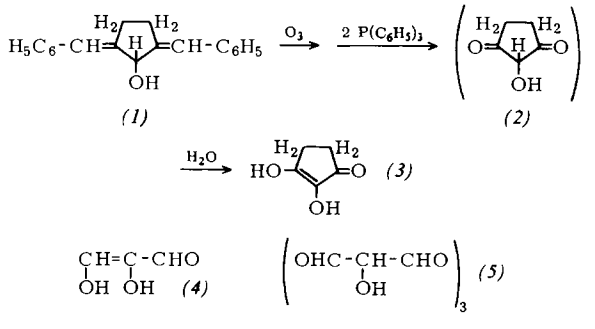
**Cyclopropyldiphenylmethylpotassium (α-cyclopropylbenzhydrylpotassium)** *(1)* was obtained by *A. Maercker* and *J. D. Roberts* from the ether *(2)* by use of sodium/potassium alloy. The NMR spectrum of its THF solution in the region for aromatic protons agrees substantially with that of triphenylmethyl-lithium. The salt *(1)* affords cyclopropyldiphenylmethane almost quantitatively on hydrolysis. Although, when M = MgBr, > 99.7% of the form $(C_6H_5)_2C{=}CH{-}CH_2{-}CH_2{}^{\ominus}M^{\oplus}$ is present in the equilibrium mixture, no indication of this form could be found when M = K.



*(2)* *(1)*

The deep-red color of the potassium compound indicates delocalization of the negative charge into the phenyl rings. With the less electropositive magnesium the effect of the phenyl groups does not suffice to overcome the strain in the three-membered ring. Li is intermediate between K and Mg in this respect. If the red ethereal suspension of salt *(1)* is treated with LiBr, decolorization occurs and carboxylation then leads to a carboxylic acid (72% yield) which gives no $^1$H–NMR signal in the cyclopropane region. Addition of THF to the ethereal solution of *(1)* and LiBr regenerates the color of the cyclopropyldiphenylmethyl anion and carboxylation then gives a mixture of carboxylic acids in which the cyclopropane derivative preponderates. This is the first case of allylmethyl-cyclopropylmethyl rearrangement produced by change of the solvent. / J. Amer. chem. Soc. *88*, 1742 (1966) / –Eb. [Rd 531 IE]

**A new route to reductones** consists, according to *G. Hesse*, *E. Bayer*, and *P. Thieme*, in fission of doubly α,β-unsaturated alcohols such as *(1)* by ozone in $CH_2Cl_2$ or $CH_2Cl_2$/ether at –78 °C. Alcohols of type *(1)* are readily accessible by reduction of α,α′-dibenzylidene ketones with tetrahydroborates. Triphenylphosphine at low temperature is a good reagent for reduction of the ozonide, proceeding by way of

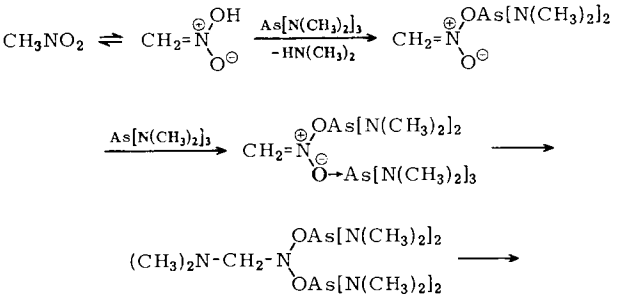


*(1)* *(2)* *(3)*

*(4)* *(5)*

2-hydroxy-1,3-cyclopentanedione *(2)*, which rearranges to the reductone *(3)*. Triose reductone *(4)*, reductic acid *(3)*, and 4,5-dihydropyrogallol are prepared in 41%, 36%, and 29% yield, respectively. In the synthesis of compound *(3)* by ozonization in methanol and subsequent catalytic hydrogenation the hemiacetal of tartronaldehyde is formed and trimeric tartronaldehyde *(5)* can be isolated on cautions concentration of the solution. / Chem. Ber. *99*, 1810 (1966) / –Ma. [Rd 524 IE]

**Amination-dehydration of nitromethane by tris(dimethylamino)arsine** has been observed by *H. Weingarten*. This arsine reacts with nitromethane exothermally, developing large amounts of dimethylamine and dimethylcyanamide *(1)* (80% yield). A possible reaction mechanism is:

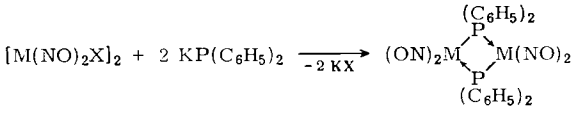


$$(CH_3)_2N{-}C{\equiv}N + 2\ OAs[N(CH_3)_2] + 2\ HN(CH_3)_2$$

*(1)*

/ Chem. Commun. *1966*, 293 / –Ma. [Rd 523 IE]

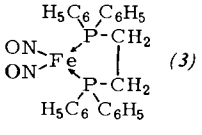
**Nitrosyl compounds of metals of the iron group with bivalent phosphino groups as bridging ligands** have been described by *W. Hieber* and *G. Neumair*. For example, dinitrosyliron bromide and dinitrosylcobalt chloride with $(C_6H_5)_2PK$ in



M : Fe, Co — *(1)*, M : Fe

X : Cl, Br — *(2)*, M : Co

tetrahydrofuran afford the tetranitrosyldi-μ-phosphinodimetal complexes *(1)* and *(2)*, respectively. These products are very stable thermally and chemically; the cobalt compound *(2)* melts at 180 °C (decomp.), the iron compound *(1)* at 310 °C. Reduction of dinitrosyliron iodide with sodium amalgam in THF in presence of an excess of ethylenebis(diphenylphosphine) gives the pale yellow, crystalline ethylenebis(diphenylphosphino)dinitrosyliron, for which structure *(3)* is proposed; the monomeric structure



*(3)*

was supported by osmometric determinations of molecular weight in benzene. Reaction of dinitrosylcobalt chloride with an equimolar amount of ethylenebis(diphenylphosphine) leads to a binuclear complex *(4)* containing phosphino bridges:

$$[Co(NO)_2Cl]_2 + C_2H_4[P(C_6H_5)_2]_2 \rightarrow [Cl(ON)_2Co{\leftarrow}P(C_6H_5)_2{-}CH_2]_2$$

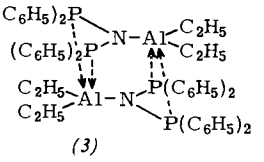
*(4)*

Use of an excess of the phosphine and simultaneous reduction with sodium amalgan gives the reddish-brown, halogen-free, binuclear compound $Co_2(NO)_2[C_2H_4(P(C_6H_5)_2)_2]_3$. The IR spectra of all the compounds are discussed. / Z. anorg. allg. Chem. *342*, 93 (1966) / –Sch. [Rd 533 IE]

**Phosphorus-aluminum compounds with pentacoordinated aluminum** have been described by *D. F. Clemens, H. H. Sisler,* and *W. S. Brey jr.* Triethylaluminum with, for instance, tetraphenyldiphosphine or bis(diphenylphosphino)methylamine gives the complexes *(1)* (m.p. 99–101 °C, yield 60 %) and *(2)* (m.p. 130–132 °C, yield 80 %), respectively. The authors conclude from IR and NMR measurements that the products contain pentacoordinated aluminum.

$(C_6H_5)_2P\text{-}P(C_6H_5)_2 \cdot Al(C_2H_5)_3$ *(1)*

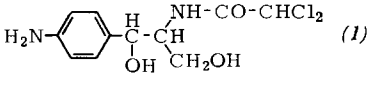
$H_3C\text{-}N[P(C_6H_5)_2]_2 \cdot Al(C_2H_5)_3$ *(2)*



*(3)*

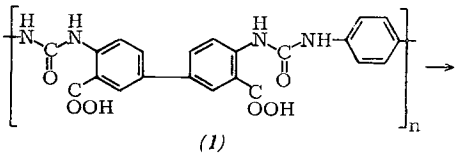
On interaction of bis(diphenylphosphino)amine and triethylaluminum, ethane is evolved and a dimeric compound is formed for which structure *(3)* with pentacoordinated aluminum is proposed. Reaction of tetramethyldiphosphine with triethylaluminum, however, affords a 1:2 adduct $(CH_3)_2P-P(CH_3)_2 \cdot 2Al(C_2H_5)_3$ (b. p. 102 °C / 0.1 mm) containing the usual tetracoordinated aluminum. This difference is ascribed to the higher basicity of tetramethyldiphosphine than of tetraphenyldiphosphine. / Inorg. Chem. *5*, 527 (1966) / –Sch. [Rd 537 IE]

**Chloramphenicol-specific antibodies** have been observed by *R. N. Hamburger* in immunized rabbits. The formation of the antibody was demonstrated by precipitin- and complement-fixation reactions with "reduced chloramphenicol", namely, D-*threo*-1-*p*-aminophenyl-2-dichloroacetamido-1,3-propanediol *(1)* that has been coupled to rabbit-serum albumin. Immunization of the rabbits was effected with *(1)* that had been coupled by diazotization to ox γ-globulin. Reduced chloramphenicol couples also with human serum albumin and affords an antigen for determination of chloramphenicol antibodies. $10^{-5}$ g (= $4\times10^{-4}$ mole) of chloramphenicol suffices for detection by quantitative complement fixation. / Science (Washington) *152*, 203 (1966) / –De. [Rd 538 IE]

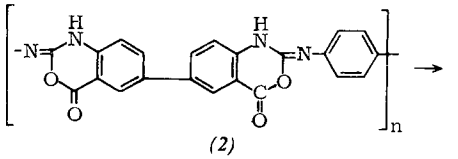


*(1)*

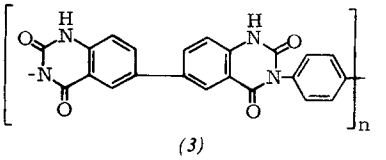
**New thermostable aromatic polyquinazolinediones** have been synthesized by *N. Yoda, R. Nakanishi,* and *M. Kurihara.* Condensation of aromatic diisocyanates (*e.g. p*-phenylene diisocyanate) with 4,4′-diamino-3,3′-biphenyldicarboxylic acid in the melt or in solution at temperatures of up to 180 °C yields a polyurea *(1)*, which, when heated in vacuum at 230 to 320 °C, undergoes cyclodehydration to a polymer *(2)* containing 2-imino-6*H*-2,3-dihydro[1,3]benzoxazine-6-one groups. Further heating leads to intramolecular rearrangement to the thermodynamically more stable polyquinazolinedione *(3)*. When heated in air up to 650 °C at 6 °C/min the polymer *(3)*, the structure of which has been confirmed by IR



*(1)*



*(2)*



*(3)*

analysis, exhibits a weight loss of only 20 %. Under nitrogen this weight loss occurs only at 860 °C. These polymers are also highly resistant to heat. The polyquinazolinediones are stable to strong acids and alkalis, and insoluble in most organic solvents, but soluble in fuming nitric acid and cold concentrated sulfuric acid. / J. Polymer Sci. B, Polymer Letters *4*, 11 (1966) / –Hl. [Rd 555 IE]

# BOOK REVIEWS

**Die Antibiotica** (The antibiotics). Edited by *R. Brunner* and *G. Machek*. Vol. II. Die Mittleren Antibiotica (The medial antibiotics). Verlag Hans Carl, Nuremberg 1965. 1st ed., xvi, 992 pp., bound DM 145.– (*ca.* $36).

This ambitious book on antibiotics, which was written by a group of Austrian scientists, deals with the chemistry, biochemistry, and clinical use of these compounds, and is the first comprehensive German-language work on this important class of substances. The present second volume of the three-volume handbook contains detailed chapters on macrolides, amino acids and oligopeptides, polypeptides, peptolids, antibiotics containing sugars, and polyenes. Special antibiotics containing nitrogen heterocycles and antibiotics with special structures are also discussed. Other chapters deal with the use of antibiotics in animal nutrition, in the conservation of foods, and in the protection of plants. Recent studies on resistance and on semi-synthetic penicillins are discussed in an appendix.

In the individual chapters, experts describe the chemistry, fermentation and biosynthesis, methods of determination, resorption, distribution and elimination, action spectra, action mechanisms, and toxicities of the compounds; their use in human and veterinary medicine is described in particular detail.

More emphasis on stereochemistry would have been desirable in many places, *e.g.* in the discussion of the macrolides. A hydroxyl group has been omitted from the open-chain formula of oleandrose on page 56. While the text is otherwise very lucid, the description of attempts to elucidate the configuration of cycloheximide (p. 630) is rather confusing. The formula given on this page is that of *cis*-(–)-2,4-dimethylcyclohexanone. Contrary to the statement on page 891, the repressor is nowadays regarded as an allosteric protein or as a compound of such a protein with RNA.

The book is outstanding in its layout and contents, and should prove a mine of information for anyone concerned

with any problem in the antibiotics field, particularly since publications that are difficult to obtain are also considered. The literature is covered in part up to 1964, including many patent references. The printing and presentation of the book are very good. However, it would have been better to reproduce the formulae from drawings rather than by typesetting. The volume contains a detailed author and subject index.

*H. Grisebach* [NB 520 IE]

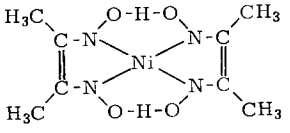
**Advances in Inorganic Chemistry and Radiochemistry.** Vol. 7. Edited by *H. Emeléus* and *A. Sharpe*. Academic Press, New York-London 1965. 1st ed., 449 pp., several illustrations, $15.50.

The present volume[*] reflects a general unrest in current inorganic chemical research, which is overlapping to an increasing extent with the marginal fields of organic chemistry. Thus only two of the six contributions are devoted to pure inorganic chemistry, the "Halides of Phosphorus, Arsenic, Antimony, and Bismuth" by *L. Kolditz*, and the "Hydride Complexes of the Transition Metals" by *M. L. H. Green* and *D. J. Jones*. The organic component makes an appearance in "Phthalocyanines" by *A. B. P. Lever* (despite the fact that this contribution deals with metal-nitrogen bonds), becomes more prominent in "Organoaluminum Compounds" by *R. Köster* and *P. Binger* and in "Carbosilanes" by *G. Fritz*, *J. Grobe*, and *D. Kummer*, and finally becomes dominant in the "Reactions of Chelated Organic Ligands" by *Qu. Fernando*.

The presentation and layout of this volume, as of the earlier ones, is impeccable. Special mention should be made of the editors' constant efforts to include contributions by specialists from all over the world.

The first five contributions named above are consistent with the high regard in which the "Advances" are held. However, the article on "Reactions of Chelated Organic Ligands" leaves one with the impression of having been carried back a century. The ignorance and indifference shown in this article regarding the complicated and versatile bonding, valence, and nomenclature rules for the 10 "inorganic" elements could scarcely be surpassed.

Thus *every* bond, whether ionic or covalent, coordinate, dative back-donation, or hydrogen bond, is indicated by a valence line. Lone electron pairs are not shown, so that the reader is left to deduce the origin of the bonding electrons for himself. This is possible with some loss of time except where the author, from a desire to surround each carbon atom with four valence lines and each nitrogen atom with three, presents completely new structural formulae, as on p. 206 for bis(diacetyldioximato)nickel(II) ("Ni dimethylglyoxime"). Here the diacetyldioxime has become an ethylene derivative, and if one lone electron pair is assigned to each N atom to avoid an electron sextet, the Ni atom must supply at least four electrons for the bonds to the N atoms. According to the author, this complex forms a chlorine adduct with hydrogen chloride:

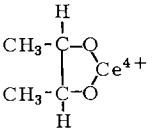


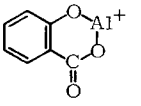
$$(C_4H_7O_2N_2)_2Ni + 2\ HCl \rightarrow (C_4H_8O_2N_2)_2Ni{\cdot}Cl_2$$

Similarly, the reaction of manganese(III) ion with oxalate ion is reported (p. 240) to proceed, *via* a chelate, by regrouping of bonds, and *via* free-radical states, according to the overall equation:

$$C_2O_4^{2-} + Mn^{3+} \rightarrow 2\ CO_2 + Mn^{2+}$$

whereas even first-year chemistry students are taught that electrons cannot disappear in redox reactions. Oxidation numbers and (formal) ionic charges also are mixed up indiscriminately, as in the examples:





Of the five equations in the scheme (LXXXIII) on p. 243, four do not balance; careful perusal of the article reveals an abundance of other errors and absurdities.

To protect the reputation of the "Advances", the editors should in future have the courage to reject such contributions, or at least take the patience to edit them carefully.

*U. Wannagat* [NB 504 IE]

**The Ring Index – A List of Ring Systems Used in Organic Chemistry.** Supplement III (1962–1963) to the 2nd edition. Rings 11525–14265. American Chemical Society, Washington 1965. 1st ed., vi, 546 pp., numerous illustrations, $10.00.

The third supplement to the second edition of the Ring Index has now been published[*]. It contains all the new ring systems described in the literature and referred to in Chemical Abstracts between January 1, 1962 and December 31, 1963. This amounts to a total of 2741 compounds, whereas the corresponding figures for 1960/1961 and 1957–1959 were about 1800 and 2000, respectively. This again reflects the accelerated growth of knowledge in the natural sciences. The ring index now includes 14 265 cyclic systems.

An appendix to the third supplement contains addenda and corrections to the earlier volumes. The addenda consist mainly of names and references for new hydro or dehydro derivatives or for ring systems formerly known only as components of compounds. The corrections also include references to better numbering and alternative nomenclature.

The Ring Index needs no special recommendation. It is so useful that any volume that carries on the good work must be regarded as welcome.

*H. Grünewald* [NB 511 IE]

**CRC Handbook of Chemistry and Physics.** Edited by *R. C. Weast*, *S. M. Selby*, and *C. D. Hodgman*. The Chemical Rubber Co., Cleveland, Ohio 1965. 46th ed., about 1700 pp., numerous illustrations, $16.00.

The 46th edition of the "Handbook of Chemistry and Physics" contains 200 more pages of tables and other information than the 45th edition, so that the book now contains more than 1700 pages and almost 450 tables.

New features include tables on superconductivity, physical constants of organometallic compounds, the thermal conductivity of gases, the surface tension of liquid elements, and trade names of dyestuff intermediates. Other tables have been revised, *e.g.* the table on buffer solution, but in the reviewer's opinion this section is still too brief. For example, a survey of the buffer solutions commonly used in biochemistry is missing.

Several mathematical tables have been rearranged, so that they are now vertical instead of horizontal, and there is no doubt that a new table (23 pages containing every imaginable conversion factor will be particularly welcome.

Special care should be given in future editions to the clear definition of the data listed in the tables. For example, it is not very significant to give values for the toxicity of gases and vapors (in ppm or mg/l) without explaining what has been taken as the measure of toxicity. It is also unfortunate that

[*] Vol. 5 is reviewed in Angew. Chem. *77*, 63 (1965); Angew. Chem. internat. Edit. *4*, 102 (1965), Vol. 6 in Angew. Chem. *78*, 500 (1966); Angew. Chem. internat. Edit. *5*, 530 (1966).

[*] Cf. Angew. Chem. *77*, 688 (1965); Angew. Chem. internat. Edit. *4*, 725 (1965).

the only information offered regarding a table containing values of heats of formation, free energies of formation, the logarithms of the equilibrium constants of the formation reactions, and the entropies of compounds is that "all values are expressed as kilo-cals". The Handbook contains such a wealth of information that it would be regrettable if its value were to be diminished by inaccuracies of this nature.

*H. Grünewald* [NB 512 IE]

**The Organic Chemistry of Titanium.** By *R. Feld* and *P. L. Cowe*. Butterworths, London 1965. 1st ed., viii, 213 pp., 6 illustrations, several tables, bound £2/12/6.

The chemistry of organic titanium compounds has been developing rapidly for more than ten years. Research in this field has received impetus from the discovery of Ziegler catalysts. The scientific and patent literature has become so extensive that a survey of the entire field in the form of this monograph is very welcome. The material has been concisely and lucidly arranged in 12 chapters, and the numerous compounds discussed are summarized in tables together with their properties. Extensive lists of references, also covering the patent literature, are given at the end of each chapter. The following classes of compounds are discussed: organometallic compounds of titanium, titanate esters and ester chlorides, chelates, products of the reaction of titanium compounds with polyalcohols, carboxylic acid derivatives (titanium acylates), compounds of titanium with organic derivatives of other metals, compounds containing the group Ti–O–Si, addition compounds of titanium halides, and derivatives of bi- and trivalent titanium.

The chapters on the organometallic compounds of titanium and their use as polymerization catalysts will find particular interest among specialists, but the selection of the references leaves something to be desired. A welcome feature of this book is the fact that the many applications are illustrated on the basis of an extensive patent literature.

On the whole, this handy book provides an excellent survey of the organic compounds of titanium.

*H. Bestian* [NB 522 IE]

**Valence Theory.** By *J. N. Murrell, S. F. A. Kettle*, and *J. M. Tedder*. John Wiley & Sons Ltd., London 1965. 1st edit., xiii + 401 pp., numerous figs., bound £2.10.– (about $7.–).

In recent years theoretical chemistry has become of ever increasing importance in the training of chemists. So it is understandable why the number of new books, and in particular of introductory textbooks, in this field is very great. According to the preface, *Murrell, Kettle* and *Tedder*'s "Valence Theory" is intended for first year chemistry students and for graduates who have not specialized in theoretical chemistry. It is divided into two parts: The first five chapters give a descriptive account of the atomic theory and the foundations of the theory of chemical bonding; it is intended for the beginner. The second and by much the larger part of the book demands a knowledge of the fundamentals of differential, integral, and vector calculus; it offers a more mathematical description of the quantum-mechanical methods of theoretical chemistry. In 13 chapters it treats atomic theory, MO and VB theory, ligand-field theory, π-electron systems, and chemical reactivity. Individual sections are concerned also with electron-deficient compounds, the inductive and the resonance effect, donor-acceptor complexes, and the hydrogen bond. In this way the theoretical methods of organic and inorganic chemistry are clearly presented and explained with examples. Particular mention should be made of the chapter on symmetry and ligand-field theory, which introduces the concepts of group theory extremely briefly but in easily intelligible form and includes detailed examples of its use.

The authors state their aim as closing the gap between the more qualitative description in *Coulson*'s "Valence" and the formal-mathematical treatment in *Eyring, Walter*, and *Kimball*'s "Quantum Chemistry". In this they have been completely successful, not least by means of the numerous problems at the end of each chapter; indeed the mathematically less advanced chemist obtains a complete understanding of the methods of quantum chemistry only by personal intensive participation. There is, therefore, value in the idea of giving indications for solution of the problems in a first appendix and complete solutions in a second.

*Murrell, Kettle*, and *Tedder*'s "Valence Theory" is a book which, it is to be hoped, as many chemists as possible will work through. It is very warmly recommended to all.

*M. Klessinger* [NB 490 IE]

**pH and potentiometrische Titrierungen** (pH and Potentiometric Titrations). By *F. L. Hahn* and *R. E. Fresenius*. Methoden der Analyse in der Chemie (Methods of Chemical Analysis), Vol. 3, Akademische Verlagsgesellschaft, Frankfurt a.M. 1964, 1st ed., x, 110 pp., DM 18.– (*ca.* $4.50).

The first part of this book deals with the calculation of the pH value of aqueous solutions of acids and bases. In keeping with the limited size of this section (12 pages), which is evidently intended as a sort of introduction, the discussion of pH and the calculation or estimation of pH values stops at a rather elementary stage. At the same time a new terminology for acid-base systems ("basacid systems") is suggested, which at first seems rather unfamiliar and unconventional, but which on closer examination convinces by its consistence. The remainder of the book is mainly devoted to the determination of the end-point in potentiometric titrations, and it is repeatedly emphasized that the end-point of a potentiometric titration does not always coincide with the maximum of the recorded curve. Around this central theme are grouped a number of further discussions on various sources of error and on the determination of end-points by interpolation and extrapolation. Unfortunately, the advances in equipment in the last 25 years are completely ignored, apart from a passing reference to the glass electrode and automatic recording titration instruments; moreover, no mention is made of titrations in non-aqueous systems. This is undoubtedly a good book, but it has unfortunately been published 25 years too late. However, the theoretical discussions in the book are still valid; they are consistently thought out and clearly formulated. However, in present-day determinations requiring extreme accuracy, dropwise titrations with a tap buret are no longer used, but are replaced by instrumental methods.

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# Relation of Microbes to Blood-Group Active Substances [*]

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*Substances with blood-group ABH(0) specificity are not confined to human red blood cells. Rather, such substances are ubiquitous antigenic surface structures which Nature has preserved throughout the phylogenetic development from microbes to man. – It could be shown experimentally that so-called "pre-existing natural" antibodies can result from inapparent immunization by these widely distributed antigens. – The blood-group specific structures of bacteria are chemically closely related to the determinant structures of the human blood-group ABH(0) glycoproteins. The situation is more complicated for the blood-group active substances from higher plants; these give extraordinary immunochemical reactions and two of their blood-group specific monosaccharides precipitate antibodies. – Recently the nature of the M and N blood-group antigens of erythrocyte surfaces has been elucidated. They are the main antigens of the second of at least 14 human blood-group systems. These substances, which are glycoproteins, are also excellent myxovirus receptors and inhibitors. The NN antigen is the first reported physically homogeneous, chemically defined and highly blood-group active cell surface structure of human origin. As surface structures, blood-group active substances appear to be frequently endowed with receptor properties in addition to those for blood-group antibodies.*

## 1. Introduction

The title of this article speaks deliberately of blood-group active substances rather than of blood-group substances, since the latter term nowadays generally denotes blood-group ABH(0) and $Le^a$ specific glycoproteins occuring in the epithelial secretions of man and higher animals [1–5]. The term "blood-group substances" is justifiable only on the basis of historical development, *i.e.* the discovery of these substances on the surface of human erythrocytes [1]; their isolation from epithelial fluids shows the dubious nature of this term.

Blood-group active substances, on the other hand, are ubiquitous surface structures possessing receptor properties, which in addition to their function as receptors of antibodies may have other physiologically more important tasks [6]. These surface structures appear to represent the realization of a structural principle which has been retained from the lowest to the highest forms of life through all stages of phylogenetic development [7, 8]. The blood-group active substances, which are by no means confined either to the blood or to man, are receptors in the sense defined by *Paul Ehrlich* [9, 10].

The function of the blood-group substances (at present 14 blood-group systems are known in man, including more than 60 factors) is only partially understood. We shall not discuss

[*] Own investigations reported here were supported by the National Science Foundation, the National Institutes of Health, the American and Chicago Heart Associations, the John A. Hartford Foundation, and the Atomic Energy Commission.

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their role in blood transfusion [11,12], in mother-fetus incompatibility [13–15], as bifidus factor [16,17], or their relation to the intrinsic factor [18].

## 2. The Origin of "Pre-existent Natural" Blood-Group Antibodies

Antigens are discovered, determined, and characterized by their ability to react with antibodies, and the discovery of the first blood-group system, ABH(0) [1], was based on the surprising pre-existence of the blood group anti-A and anti-B antibodies. Every individual over 6 months old possesses those blood-group antibodies of the ABH(0) system that are not directed against its own blood-group antigens. Their origin is a long-standing mystery of immunobiology, since it is not necessary that the individual in question should ever have been in contact with erythrocytes containing the corresponding antigens. The prevalent theory of the last 40 years was that these antibodies were hereditary [5,19,20]. It was assumed therefore that the gene controlling the formation of blood group A was linked with a gene controlling the formation of anti-B antibodies. The same was postulated for antigen B and anti-A antibodies. However, antibodies are, by definition, serum globulins formed or modified in response to an antigenic stimulus.

*Madeleine Dupont* [21] proposed that the human anti-blood group A and B isoagglutinins result from exogenous stimuli and represent cross-reacting antibodies. Although this view was discarded even by *Landsteiner* [21a], it was supported by others [5,19–24].

This argument appeared to be amenable to experimentation in at least two ways, particularly after it had become known that blood-group A, B, and H(0) activities are widespread in Nature [24–25a]. First, one could raise animals capable of forming such antibodies under germfree conditions. If the antibodies in question are gene products, they ought to be present to the same degree both in the germfree and in the normal animal; if, on the other hand, they are caused by environmental factors they could be absent from germfree animals. Secondly, it should be possible to increase isoagglutinins of normally low titer by immunization in the "normal" way, *i.e.* by inhalation or swallowing of widespread antigens.

It has been known for a long time that chickens of many races regularly form human anti-B blood-group antibodies when they reach the age of about 20 days [26,27]; these antibodies, too, have been regarded as gene products. We therefore tested the correctness of this assumption in germfree chickens as well as chickens reared under ordinary conditions from the same hatch. It was found [28] (Figure 1) that germfree White Leghorn chickens possessed no anti blood-group B specific antibodies 45 days after hatching, whereas chickens raised under ordinary conditions showed about the same titer as normal humans. Feeding of blood-group B active

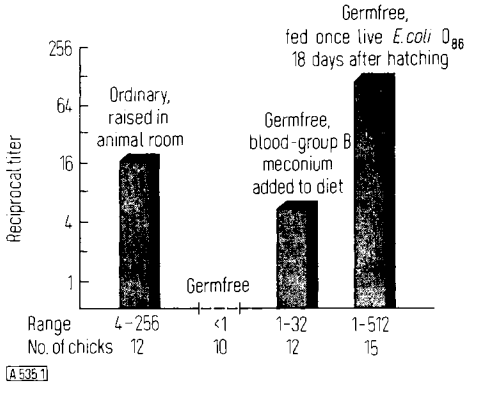


Fig. 1. Anti-human blood-group B isoagglutinins in 45-day-old White Leghorn chicks (average weight of normal chicks 489 g, of germfree chicks 545 g) [28].

meconium extracts or spraying them into the germfree tanks led to a moderate anti-B titer. A single feeding of live blood-group B active *Escherichia coli* $0_{86}$ produced an extremely high anti-B titer in germfree chickens. Feeding of bacteria having no blood-group activity did not lead to the formation of blood-group antibodies.

We also carried out feeding experiments in man [29], although the conditions were not as "ideal" as those described above. The results (Table 1) show that isoagglutinins can result from immunogenic stimuli both in children and in adults. Feeding of *Escherichia coli* $0_{86}$ killed by desiccation to infants suffering from severe diarrhea at an age when they begin to form isoagglutinins led, within one week, to a highly significant 32-fold increase in the titer of anti-B antibodies. The titer began to decrease slightly only after several months. This shows that the ingestion of even dead *E. coli* stimulates *de novo* isoagglutinin formation in infants or increases pre-existing levels in adults suffering from severe intestinal disorders. Such diseased individuals

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Table 1. Stimulation of blood-group isoagglutinins by feeding killed blood-group active *E. coli* $O_{86}$ [29].

| Individual | Age at beginning of experiment | *E. coli* feeding schedule | Reciprocal agglutinin titer | | |
|---|---|---|---|---|---|
| | | | preingestion | after ingestion | |
| | | | | 7–28 days | 5–8 months |
| 6 infants, diarrhea | 7–15 weeks | 1 g/day, 3–7 days | < 1–4 | 32–128 | 16–64 |
| 5 infants, healthy | 7–15 weeks | nothing | < 1–4 | < 1–4 | 2–8 |
| M.L. ulcerative colitis | adult | 2 g/day, 1 day | 16 | 256 | 32 |
| G.A. cancer of colon | adult | 2 g/day, 1 day | 32 | 128–256 | |

were chosen since their intestines have an increased permeability towards macromolecules. In order not to upset the intestinal flora, we did not feed living bacteria in large quantities.

These investigations show that "normal" hemagglutinins can develop due to immunogenic stimuli. The findings are important for aspects of blood transfusion and can probably be generalized. Only the antibody-producing apparatus is inherited, but not the specific antibodies themselves [29–31].

## 3. Blood-Group Specific Substances in Bacteria

*E. coli* $O_{86}$ with which the experiments mentioned in Section 2 were carried out has an unusually high blood-group activity, but blood-group specificity is not rare among gram-negative bacteria, which constitute the bulk of the human intestinal flora (Table 2). Of 282 bacterial strains, 137 showed A, B, or 0 specificity or a combination thereof [32]. Only a random selection of these bacteria is shown in the table; also the activities were frequently low.

Table 2. Distribution of blood-group activity among gram-negative bacteria [32].

| Genus | Strains tested | $A_1$ | B | H(0) | $A_1BH(0)$ | $A_1B$ | $A_1H(0)$ | BH(0) | Inactive |
|---|---|---|---|---|---|---|---|---|---|
| *Escherichia* | 135 | 8 | 18 | 22 | 6 | 3 | 3 | 4 | 71 |
| *Salmonella* | 19 | 1 | 2 | 9 | 0 | 0 | 1 | 0 | 6 |
| *Arizona* | 3 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 |
| *Klebsiella* | 42 | 2 | 6 | 4 | 3 | 1 | 1 | 5 | 20 |
| *Citrobacter* | 24 | 2 | 2 | 2 | 0 | 2 | 2 | 3 | 11 |
| *Pasteurella* | 8 | 0 | 1 | 0 | 0 | 0 | 0 | 2 | 5 |
| *Proteus* | 20 | 0 | 6 | 2 | 0 | 0 | 0 | 1 | 11 |
| *Pseudomonas* | 15 | 1 | 1 | 2 | 0 | 0 | 1 | 0 | 10 |
| *Serratia* | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| *Alcaligenes* | 8 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 6 |
| *Shigella* | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| *Herrellea* | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 282 | 14 | 38 | 44 | 9 | 6 | 9 | 17 | 145 |

The immunological simulation of human blood-group ABH(0) substances by toxic bacterial lipopolysaccharides can go so far that they become adsorbed onto human erythrocytes and thus change the genetically determined blood-group specificity of the red cells [33, 34]. This has to be taken into account in blood transfusions. Further, the ability of the erythrocytes with their enormous surface area to bind toxic substances of this type suggests a transport and detoxifying function of red blood cells that has so far been largely neglected [33–35]. These functions and the possibility of therapeutic application of soluble erythrocyte membrane components to block toxins are being investigated in our laboratory [34].

We shall now discuss the chemical and immunological relations between bacterial B specific substances isolated from *E. coli* $O_{86}$ and the glycoprotein from human ovarian cysts. Table 3 shows that the isolated lipopolysaccharide is at least as active as highly purified human glycoprotein from ovarian cysts. We have further shown that *E. coli* $O_{86}$ not only specifically inhibits hemagglutination and stimulates the formation of anti-B antibodies, but also absorbs anti-blood-group B antibodies [24, 32, 33]. Hyperimmune anti-B sera retard the growth of *E. coli* $O_{86}$ in the absence of complement [24], and kill this bacterium if complement is present [36]. This is the first demonstration of a pathophysiological role of blood-group antibodies outside the field of the blood groups proper.

The blood-group active complex was extracted from *E. coli* $O_{86}$ B:7 with pyridine/water [37] or phenol/water [38], fractionally precipitated with ethanol [33], and ultracentrifuged until two-dimensional agar-gel diffusion showed only one line with human anti-blood-group B serum. The sugar components of this lipopolysaccharide and of the human glycoprotein obtained from ovarian cysts are shown in Table 4. All blood-group active bacteria studied contained at least three of the

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Table 3. Blood-group B active polysaccharides.

| Active substance | Minimum amount (μg/ml) completely inhibiting 4 hemagglutinating doses of human anti-B [a] |
|---|---|
| *E. coli* $O_{86}$ lipolysaccharide | 1 |
| *E. coli* $O_{86}$ whole bacteria | 10—20 |
| Human ovarian cyst glycoprotein | 1—2 |
| Human meconium glycoprotein | 2 |
| Horse stomach glycoprotein | 10 |

[a] For explanation of terminology see, *e.g.*, [6].

Table 4. Carbohydrate components of blood-group B specific antigens, characteristic values (%). The underlined sugars are components of the human blood-group ABH(0) substances [4, 5, 34].

| Sugar | *E. coli* $O_{86}$ lipopolysaccharide | Human ovarian cyst glycoprotein |
|---|---|---|
| D-Galactose | + | + |
| Glucose | + | 0 |
| Galactosamine | + } 17.5 | 5 } 19 |
| Glucosamine | + } | 14 } |
| Fucose | 7 | 15 |
| Neuraminic acid | < 1 | + |
| Heptose | + | 0 |
| K.D.O. [a] | 4.5 | 0 |

[a] Only positive Warren reaction used for demonstration.

four sugars which are characteristic of the human blood-group ABH(0) specific glycoprotein. In each case the sugar mainly responsible for the specificity of a human blood-group substance was also present in the corresponding bacterial substance [32].

The blood-group specificity of human glycoproteins is based on recurring oligosaccharide chains spread over the surface of the macromolecule [39,40]. We therefore investigated whether similar structures are responsible for the B specificity of bacterial antigens [41, 34]. Mild acid hydrolysis of the purified lipopolysaccharide with a water-soluble ion-exchange resin [41] produced dialysable blood-group B specific oligosaccharide fractions, which could be obtained by preparative paper chromatography in a yield of about 5% by weight [34, 8, 41]. The most active of these preparations is about 10 times as active as α-D-galactopyranosyl-(1→3)-D-galactose, the active disaccharide of the human B blood-group substance [42, 40, 39]. Quantitative analysis of the products of total hydrolysis of the bacterial oligosaccharides (12 hours, 2 N HCl, 100 °C) indicated them to be penta- to octasaccharides [34,41].

Although the composition of these oligosaccharides is similar to that of the human blood-group B specific structures obtained by mild acid hydrolysis, they differ in important aspects. The oligosaccharides isolated from bacteria are more active; this may be explained by the fucose present in each case (1 molecule per oligosaccharide) [34,41], which is absent from the blood-group B specific oligosaccharides of human origin obtained by acid hydrolysis [39,40,42]. A further difference is the presence of galactosamine in the bacterial oligosaccharides [34,41], as opposed to the presence of glucosamine in the human oligosaccharides [39,42,40]. All B active *E. coli* $O_{86}$ oligosaccharides contained glucose, which is absent from human B glycoprotein [4,5], and which is not involved in B specificity [6].

D-Galactose must be linked to *E. coli* $O_{86}$ terminally by an α-glycopyranosidic linkage, since coffee-bean α-galactosidase destroys the blood-group B activity of the macromolecule as well as of the oligosaccharides isolated from it with liberation of galactose; concomitantly, blood-group H(0) activity occurs *de novo* [43]. These findings correspond to those obtained with oligosaccharides from ovarian cyst glycoproteins [44,45]. The coffee-bean α-galactosidase uncovers non-reducing fucose structures which become accessible to eel anti-H(0) antibodies.

After exposure to α-galactosidase, an increase in the cross-reactivity of the macromolecule with antipneumococcus type XIV horse serum could be observed [34], suggesting that non-reducing β-galactosyl units (probably linked to *N*-acetylhexosamine) are present on the surface of the molecule [45a]. This is consistent with our observation that *E. coli* β-galactosidase [46] liberates galactose [34] after the α-glycosidically linked galactose has been split off. β-*N*-Acetylhexosaminidase [47] liberates 1 mole of *N*-acetylgalactosamine from oligosaccharides pretreated with both galactosidases.

On the basis of the chemical, serological and enzymatic investigations described above and in analogy to the findings of other authors on blood-group B specific structures in man [39,40], it seems possible that the oligosaccharide structure shown in Fig. 2 occurs in *E. coli* $O_{86}$ and is responsible for its blood-group B specificity.

*O*-α-D-Gal-(1→3)-*O*-β-D-Gal-(1→3 or 1→4)-GalNAc-R
|
α-L-Fuc

Fig. 2. Tentative formula of the blood-group B active structure occurring in *E. coli* $O_{86}$. R contains glucose and may also contain galactose and galactosamine [34,43].

Rigorous chemical proof of this structure, however, is still lacking. Serological results support the view that the fucopyranosyl residue is linked to the subterminal β-galactosyl by an α-glycosidic linkage, since H(0) specificity developed *de novo* as a result of treatment with α-galactosidase of the lipopolysaccharide (after dialysis) and of B active oligosaccharides obtained from it [43, 34]. The linkage of a fucosyl residue to a β-galactosyl structure does not prevent the hydrolytic removal of the β-galactosyl group (5 days' incubation, enzyme:substrate, 1:3 by weight) [47a]. A related structure differing in that it contained *N*-acetylglucosamine instead of *N*-acetylgalactosamine and fucose linked to


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it has recently been observed in *Salmonella* group U [48]; this salmonella group carries the 0 antigen 43, the blood-group B specificity of which has been described earlier [32].

It is apparent that the chemical findings on the blood-group active oligosaccharides of gram-negative bacteria are consistent with the earlier, purely immunological observations [24, 25, 25a, 28, 32, 33, 49] of the close relation of structures of *E. coli* $0_{86}$ and of other bacteria to the human blood groups ABH(0).

## 4. Blood-Group Specific Substances in Higher Plants

We found blood-group specific substances not only in bacteria, but also in higher plants and viruses. These blood-group active antigens are not to be confused with plant agglutinins [50]. For the active substances isolated from the yew tree *(Taxus cuspidata* and *baccata)* as well as from the sassafras tree *(Sassafras albidum)*, the chemical situation differs from that observed for blood-group active substances in bacteria [51–54]. We were able to isolate physico-chemically homogeneous polysaccharides from the twigs of these plants by extraction with water and fractionation with organic and inorganic solvents. As an example, Table 5 shows data for the sassafras polysaccharide.

Table 5. Physical data for the highly purified blood-group H(0) active sassafras polysaccharide [54].

| | |
|---|---|
| $[\alpha]_D^{23}$ ($H_2O$, 1 dm) | +63.2° (c = 0.25) |
| $S_{20}$, w (S) | 8.5 (c = 0) |
| $10^7 D_{20}$, w ($cm^2\ sec^{-1}$) | 2.0 (c = 0.5) |
| $M_w$ | $2.5 \times 10^5$ (from $S$ and $D$) |
| $\eta_{sp}/c$ (dl/g) | 2.5 ($c = 0.018$; $G = 0$) |
| $M_w$ | $4.6 \times 10^5$ (by light scattering) |
| $f/f_o$ | 2.6 |

The blood-group H(0) activity of these preparations, measured with eel antiserum, is as high as that of the most active preparations of human origin (Table 6). In contrast to the human blood-group glycoproteins, these plant polysaccharides inhibit human, rabbit, or plant anti-H(0) agglutinins only weakly or not at all, but they are antigenic, though only in a minority of the immunized chickens and rabbits [24, 54].

Table 6. Carbohydrate components of blood-group H(0) active macromolecules [32, 51, 52, 54].

| | Human glycoprotein | *Sassafras albidum* polysaccharide | *Taxus cuspidata* polysaccharide | *E. coli* $O_{128}$ lipo-polysaccharide |
|---|---|---|---|---|
| Blood-group activity (μg/ml) determined with eel serum and human erythrocytes | 3 | 3 | 3 | 6 |
| Monosaccharides after hydrolysis | L-Fucose | 3-*O*-Methyl-D-galactose | 2-*O*-Methyl-L-fucose | Fucose |
| | *N*-Acetyl-D-glucosamine | Galactose | Galactose | *N*-Acetylglusosamine |
| | | Glucose | Arabinose | *N*-Acetylgalactosamine |
| | *N*-Acetyl-D-galactosamine | L-Arabinose | Xylose | Galactose |
| | | Xylose | Rhamnose | Glucose |
| | | Rhamnose | Glucose | Heptose(s) |
| | D-Galactose | Galacturonic acid | | |

Not only hemagglutination inhibition, but also agar-gel diffusion and strictly quantitative precipitin tests (Fig. 3) have shown that blood-group H(0) substances of man and from yew (not shown in Fig. 3) and sassafras are immunologically equivalent when measured with eel serum, although the three substances differ considerably

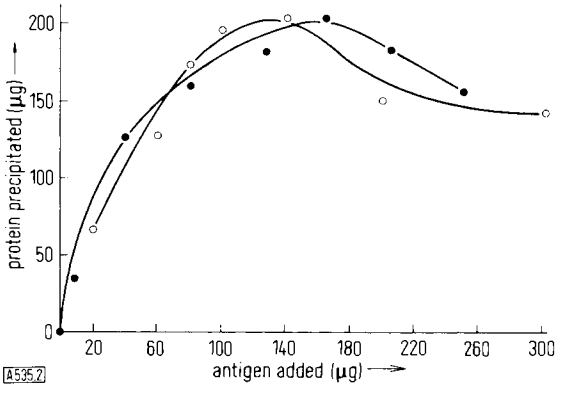


Fig. 3. Precipitation of human H(0) active glycoprotein (○) (Morgan human ovarian cysts 277/PI/WS PR XXXIII) and H(0) active polysaccharide from Sassafras (●) (Sassafras C-70 PR XXIV) with eel anti-H(0) serum [54].

in their chemical properties. Although the molecules are of approximately the same size [4, 52, 54], the blood-group H(0) active substances from plants, unlike those of human origin, contain neither nitrogen nor fucose, although the L-form of this sugar in α-glycopyranosidic linkage has been considered to be predominantly responsible for the blood-group H(0) specificity of human H(0) substances [55, 56]. Rather, 2-*O*-methyl-L-fucose


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was found to be the blood-group active sugar in the yew [51,52], a sugar up to that time not known to occur in Nature. The blood-group specificity in the sassafras polysaccharide is based on the very rare 3-*O*-methyl-D-galactose [54]. Table 6 shows the composition of some blood-group H(0) active antigens. Galactose is the only sugar that sassafras polysaccharide and human ovarian cyst glycoprotein have in common. This sugar, however, does not play a primary role in the blood-group H(0) activity, and is H(0) inactive [55–58]. Among the other monosaccharides of the sassafras polysaccharide, only arabinose could be expected to be blood-group H(0) active [55,57]; however, it proved to be the D-enantiomer [54], whereas only the L-form is active. Remarkably, the sassafras polysaccharide molecule contains 355 3-*O*-methyl-D-galactose residues (based on a molecular weight of $2.5 \times 10^5$) [54]; one molecule of H(0) cyst substance contains about the same number of blood-group active sugar residues in the form of L-fucose [59]. The composition of the sassafras polysaccharide is shown in Table 7.

Table 7. Components of the blood-group active sassafras polysaccharide [54].

| Structural units | % | Moles per mole sassafras polysaccharide |
|---|---|---|
| 3-*O*-Methyl-D-galactose | 25.0 | 355 |
| Rhamnose | 26.0 | 445 |
| Xylose | 9 | 171 |
| Galactose | 8 | 124 |
| Galacturonic acid | 5.6 | 78 |
| L-Arabinose | 5 | 95 |
| Glucose | 2 | 31 |
| Acetyl | 11.33 | 660 |

The close immunological relation between the blood-group H(0) specific macromolecules of man and of higher plants as shown by four different methods, *i.e.* hemagglutination inhibition, quantitative immunoprecipitation, two-dimensional agar-gel diffusion, and immunization is surprising, as the blood-group substances in man, in *Taxus*, and in *Sassafras* are chemically completely different. These findings point to the limitations of immunological methods, particularly when heterologous reagents such as most blood-group antibodies are used (see [54]). However, the unreliability of immunochemical reactions may be apparent rather than real as will now be shown [54,60,68].

## 5. On the Specificity of Heterologous Immunochemical Reactions

We studied the problem of the identical blood-group specificities of different sugars by means of synthetic model substances [57,53], and by investigating natural products containing methyl sugars [58]. Some cardiac glycosides and antibiotics have the same serological specificity when measured with certain reagents as the human blood-group substance H(0), although they are quite different chemically [58]. This is illustrated by the structure of the active odoroside H which arises from inactive odorotrioside G monoacetate by removal of two molecules of glucose or one of gentiobiose (as well as one acetyl group) [61] (Fig. 4). A similar situation

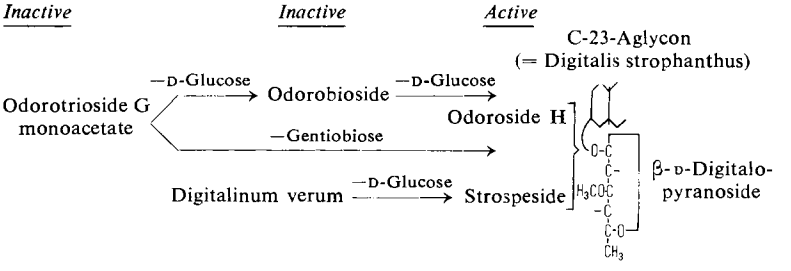


Fig. 4. Transformation of blood-group H(0) inactive into H(0) active cardiac glycosides

pertains to the transformation of inactive Digitalinum verum to active strospeside (Fig. 4). If an unusual sugar such as digitalose (3-*O*-methyl-D-fucose) is a constituent of a cardiac glycoside, it is always directly linked to the aglycon [62]. Only digitalose-containing substances having this sugar in terminal position are active [58].

It will be seen from the immunochemical reactions described so far that antibodies,if their specificity is known, may serve as reagents in the elucidation of chemical structures provided interpretations are advanced with caution. Thus, linkage and nature of uronic acid were correctly predicted in a polysaccharide where it occurred only once per approximately 40 sugar units [63]. We successfully used eel serum and the related *Lotus tetragonolobus* reagent [58] to predict the position of the second *O*-methyl group in the D-fucose of the cardiac glycoside strebloside [64], as well as the position and ring form of the blood-group active sugar 3-*O*-methyl-D-fucose in the disaccharide part of the antibiotic chartreusin [65,66].

All substances found to be blood-group H(0) active by means of eel serum or lotus reagent had a hapten with at least one methyl group. We therefore investigated systematically the methyl ethers of L- and D-fucose and of D-galactose and their methyl glycosides. A number of these compounds were synthesized and crystallized for the first time [57,53]. Table 8 shows some striking

[57] *G. F. Springer* and *P. Williamson*, Biochem. J. *85*, 282 (1962).

[58] *G. F. Springer* and *P. Williamson*, Vox Sanguinis *8*, 177 (1963).

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[66] *H. Schmid*, *W. v. Philipsborn*, *W. Eisenhuth*, and *O. A. Stamm*, Helv. chim. Acta *47*, 1475 (1964).

examples of the activities of fucose and galactose derivatives, which show that some enantiomorphs are of identical blood-group activity and at least as active as

Table 8. Blood-group H(0) active sugars [57, 53, 54].

| Test substance | Minimum amount (mg/ml) completely inhibiting 4 hemagglutinating doses [a] |
|---|---|
| | Eel serum agglutinin |
| L-Fucose series [b]: | |
| L-Fucose | 0.1 |
| 2-*O*-Methyl-L-fucose | 0.05 |
| 3-*O*-Methyl-L-fucose | 0.05—0.1 |
| 2,3-Di-*O*-methyl-L-fucose | 0.05 |
| D-Fucose series [c]: | |
| 3-*O*-Methyl-D-fucose | 0.05 |
| 2,3-Di-*O*-methyl-D-fucose | 0.05 |
| D-Galactose series [d]: | |
| 3-*O*-Methyl-D-galactose | 0.1 |
| 2,3-Di-*O*-methyl-D-galactose | 0.1 |

[a] Inhibitor concentration before dilution with agglutinin solution and erythrocyte suspension.

[b] Methyl substituents at C-4 and/or C-5 inactivate.

[c] Methyl substituent at C-5 inactivates active methyl ethers.

[d] Methyl substituents at C-4; at C-6; at C-2, C-4, and C-6 do not activate the inactive mother substance D-galactose.

L-fucose (for a complete list of active as well as inactive fucose and galactose methyl ethers and their methyl glycosides see [53,54,57]. These observations did not at first seem to fit in with the classical view of the specificity and especially stereospecificity of serological and biological reactions in general; a plausible explanation was advanced by *Kabat*, however [67].

Not only enantiomorphs, but also quite different sugars such as L-fucose and 3-*O*-methyl-D-galactose can possess equal activities. These results were first obtained with semiquantitative hemagglutination inhibition assays. Strictly quantitative precipitin inhibition tests led to the same result [57,53]. Our experiments and conformation studies on models have shown [53,54,60] that the minimal complementary structure for the eel antibody is smaller than a single sugar and hence can be present in several otherwise unrelated monosaccharides [53,54,57,60]. Such a small complementary structure has so far never been considered for either anti-carbohydrate or anti-protein antibodies. This minimum complementary structure appears to consist of a methyl substituent attached equatorially to a pyranose ring; adjoining is an ether oxygen. On a contiguous C atom is an axial oxygen-carrying substituent in *cis* position to the methyl group. The situation is similar for the anti-H(0) reagent of *Lotus tetragonolobus*.

Another phenomenon difficult to reconcile with the concepts of classical immunochemistry was observed in our studies on fucose and galactose methyl ethers: the anti-H(0) antibodies of most, but not all, eel anti-H(0) sera could be precipitated with 3-*O*-methyl-D-fucose and 3-*O*-methyl-D-galactose [54,60] (Fig. 5). The precipitate consists of the anti-H(0) specific protein of the eel serum, which in the ultracentrifuge behaves as a single component with the properties of a 7 S γ-globulin [68,54,60]. The antibody can be recovered quantitatively from the precipitate, and shows unchanged activity in the hemagglutination and precipitin tests [60,68]. The two precipitating sugars probably are the smallest uncharged haptens yet described that are capable of precipitating antibodies [54]. The precipitation can be specifically inhibited with haptens such as α-methyl-L-fucopyranoside and 2-*O*-methyl-L-fucose.

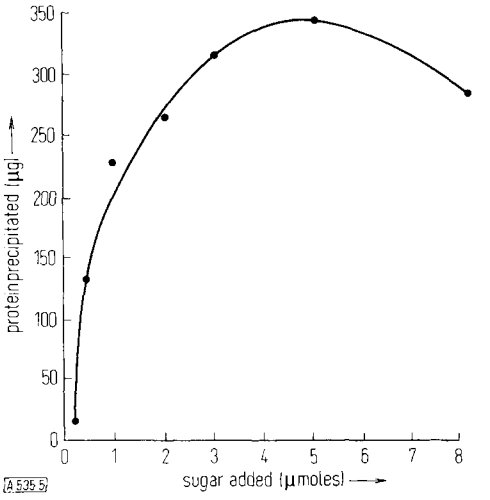


Fig. 5. Precipitin curve obtained with eel anti-H(0) serum and 3-*O*-methyl-D-fucose [60,68]. (Antiserum, 0.5 ml eel M', total test vol. 1.5 ml.)

The mechanism of this precipitation is difficult to explain on the basis of the lattice theory, since these low molecular weight haptens have no characteristic recurrent groups, such as would be required to create a three-dimensional network between hapten and eel antibody units. Vapor-pressure osmometry and cryoscopy gave no indication of aggregation of the sugar molecules in solution [68]. However, both haptens carry at least one lipophilic group, which can enter into "hydrophobic bonding". *Karush* [69] assumes that each non-polar group in an antigenic determinant [*] has a decisive influence on the stability of an antigen-antibody complex. The situation in our case, however, is complex since certain modifications such as reduction on C-2 or 2-*O*-methylation and/or methylglycosidation of the two 3-*O*-methyl sugars abolish their precipitating ability and convert them into potent neutralizing haptens (Table 9) [60,68].

We also found substances in higher plants which neutralize specifically and in low concentration the

Table 9. Transformation of antibody-precipitating monosaccharides into inhibitors by changes on a single C atom [60].

| Precipitant | Inhibitor | % inhibition [a] rel. to L-fucose (100 %) |
|---|---|---|
| 3-*O*-Methyl-D-galactose | 2,3-Di-*O*-methyl-D-galactose | 100—200 |
| 3-*O*-Methyl-D-fucose | 2,3-Di-*O*-methyl-D-fucose | 100—200 |
| | 2-Deoxy-3-*O*-methyl-D-fucose | 100 |
| | Methyl-α-3-*O*-methyl-D-fucopyranoside | 200—500 |
| | Methyl-β-3-*O*-methyl-D-fucopyranoside | 500 |

[a] Inhibition of hemagglutination *and* of precipitation.

[67] *E. A. Kabat*, Biochem. J. *85*, 291 (1962).

[68] *G. F. Springer, K. A. Roberson, B. Kolecki*, and *A. Bezkorovainy*, unpublished.

[*] For definitions see [6].

[69] *F. Karush*, Advances Immunology *2*, 10 (1962).

Table 10. Inhibition of anti-Rh agglutinins by substances obtained from higher plants [70]. Anti-M, N, A, and B sera were not inhibited.

| Non-dialysable extracts from twigs of | Smallest amount (mg/ml) which completely inhibits 4 agglutinating doses of the following antisera: | | | | | | |
|---|---|---|---|---|---|---|---|
| | $Rh_o$ [a] | rh′ | rh″ | hr′ | hr″ | P | 0 [b] |
| *Syringa sp.* | 0.2–0.6 | 5 | 2.5 | 2.5 | ±5 | NA [c] | NA |
| *Forsythia giraldiana* (purified) | 0.1 | | | | | NA | NA |
| *Taxus cuspidata* | NA | NA | NA | NA | NA | NA | 0.002 |
| Human erythrocytes, A.F., stroma [71] | 0.3–0.6 | 5 | NA | 0.6 | 5 | 2.5 | 2.5 |

[a] Arithmetic average obtained with 5 different sera. [b] Eel serum. [c] N.A. = inactive.

effect of antibodies of the rhesus system (Rh) [70]. Table 10 shows the results obtained with extracts of lilac and forsythia branches. As can be seen, lilac extracts inhibited all antibodies of the Rh system. The extracts were even more active than rhesus-active preparations from human erythrocytes [71]. The plant material, however, had physical and chemical features quite different from those of the human material. Lignin components kindly given us by Prof. *K. Freudenberg* [72] were also found to be active. Dr. *Ph. Levine* informed us that lilac extracts precipitate in agar with anti-Rh sera. Caution must be exercised in interpretation of these surprising observations in spite of their specificity. It remains to be shown that the inhibitors react with the combining site of the antibody directly and not in a way akin to an allosteric effect.

## 6. Blood-Group Specific Substances in Viruses

Myxoviruses were studied as representatives of the viruses. The last two aspects of this review will be discussed using them as an example. One is a problem of their surface structure and the other one of the substrate of their action. Influenza viruses type A and B as well as fowl-pest virus were investigated with regard to their blood-group activity [73–75].

All viruses were cultivated in chicken eggs. All virus preparations and vaccines, including chromatographically purified preparations, showed significant A blood-group and Forssman antigen specificity in their non-dialysable residue, which retained its antigenicity. This activity could not be separated from the intact virus and increased with increasing purification (see Table 11). The A-like substances of the influenza and fowl-pest virus probably are components from the cytoplasm of the host [76–80]. Chicken embryos are known to contain A blood-group antigen and Forssman antigen [81–83]. Treatment of myxoviruses with ether led to the enrichment of the A activity mainly in the ether phase; some also seemed to be associated with the hemagglutinins [75]. Subcutaneous injection of the macromolecular part of commercial influenza virus vaccine and of highly purified influenza viruses into human volunteers led to the formation of considerable quantities of anti-A isoagglutinin and isohemolysin [74, 75, 84] (Table 12).

Table 11. Blood-group activity of influenza virus preparations (macromolecular part after heating at 95 °C) [74].

| Preparation | C.C.A. [a] | Smallest amount (mg/ml) [b] which completely inhibits 4 agglutinating doses of the following antisera: | |
|---|---|---|---|
| | | $A_1$ | $A_2$ |
| Commercial vaccine (non-dialysable, 0.40–1.13 mg/ml) | 800 | 1.2 | 0.3–0.6 |
| Asian Jap. 305 $A_2$-influenza virus, chromatographed | 2000 | 0.3 | 0.05–0.1 |
| 1. non-dialysable | | | |
| 2. Supernate (11.5%) of centrifugate of 1. at 1600 g | | 0.05 | 0.01 |
| 3. Sediment (88.5%) | | 0.6 | 0.1 |

[a] C.C.A. = chicken cell agglutinating units per mg, calculated from determinations before heating and dialysis.

[b] Inhibitor concentration before dilution with selected hyperimmune sera and erythrocyte suspension. Final concentration: 1/3 of the values given. No inhibition in the B–anti-B and 0–anti-H(0) systems (inhibitor concentration up to 10 mg/ml).

Table 12. Increase in isohemolysin titer of 10 volunteers (blood group 0) after subcutaneous injection (2–5 mg within 24 hours) of the non-dialysable part of chromatographically purified influenza virus preparation (Asian Jap. 305 $A_2$ virus) [75].

| Max. increase in hemolysin titer [a] (two-fold geometrical dilution) | Number of cases | | |
|---|---|---|---|
| | Sera tested against erythrocytes | | |
| | $A_1$ | B | Sheep |
| 64-fold | | | 1 |
| 16- to 32-fold | 3 | 2 | 1 |
| 4- to 8-fold | 4 | 6 | 4 |
| < 4-fold | 3 | 2 | 4 |

[a] End point: last tube with at least 25% hemolysis.


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[71] *I. Wolff* and *G. F. Springer*, Proc. 10th internat. Congress Soc. Blood Transfusion, Stockholm 1964. Karger, Basel 1965, p. 511.

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[73] *G. F. Springer* and *H. Tritel*, Science (Washington) *138*, 687 (1962).

[74] *G. F. Springer* and *R. Schuster*, Klin. Wschr. *42*, 821 (1964).

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[82] *E. Witebsky* and *J. Szepsenwol*, C. R. Séances Soc. Biol. Filiales *115*, 221 (1934).

[83] *R. Harris*, *G. S. Harrison*, and *C. J. M. Rondle*, Acta genet. statist. Med. *13*, 44 (1963).

[84] Communicable Disease Center, Influenza Surveillance Report No. 73: Influenza vaccine and ABO incompatibility. U.S. Dept. of Health, Education and Welfare, Public Health Service IV: 12–14, 1962.

The extremely close relationship between the A blood-group and the Forssman antigens has also been proved chemically[85]. Our experiments were carried out with relatively large amounts (3-5 protective doses of influenza virus vaccine) of chicken-egg grown influenza virus preparations. The possible deleterious effects of vaccination with such substances for mother-fetus relationships (*e.g.* mother blood group 0, fetus blood group A) especially for abortions and the high degree of cytotoxicity of the Forssman antibody have been discussed elsewhere[74,85,85a]. The problem of immunizing the mother with substances which share antigenic components with the embryo but not with the mother is of general importance because of the possible ensuing damage to the fetus. According to our investigations, the A-like antigen seems to be a component of the host cytoplasm, which is incorporated almost unchanged and may be enriched by the myxoviruses. It therefore seems probable that influenza viruses in persons infected with it incorporate the host's own blood-group active substances which are not normally antigenic for the host. Thus an increase in isoagglutinin titer as a result of ordinary influenza virus infection seems unlikely[74] and has not been observed in more recent epidemological studies[86].

## 7. The Blood-Group Substances of the MN System

This report began with human blood-group substances and at its conclusion we return to them. We and somewhat later a group of Finnish workers have discovered a second relation between influenza viruses and blood-group substances[87,88]: Influenza viruses specifically destroy the main antigens of the second human blood-group system[89,90], the MN system (Table 13). After publication of these results, other workers contributed to the elucidation of the chemical nature of the MN

Table 13. Action of influenza viruses and "Receptor Destroying Enzyme" on human red-cell antigens [87]. The blood-group antigens $A_1$, B, H(0), Le$^a$, Le$^b$, S, s, P, Jk$^a$, K, k, Fy$^a$, Rh$_o$, rh', rh'', hr', and hr'' are not inactivated.

| | Human blood-group agglutinogen | | | |
|---|---|---|---|---|
| | M | N | Lu$^a$ | Lu$^b$ |
| *Influenza virus* | | | | |
| Type A | | | | |
| Melbourne | + | + | + | + |
| Swine $S_{15}$ | + | + | + | + |
| Type B | | | | |
| Lee | + | + | + | + |
| *Vibrio cholerae* | | | | |
| Receptor Destroying Enzyme | + | + | — | 0 |

+ = inactivated; — = not inactivated; 0 = not tested.

blood groups[91–93]. We succeeded in isolating highly active, immunogenic MM, MN, and NN substances from erythrocytes. These are glycoproteins[6,8,94–96]. More recently, we obtained an N-like glycoprotein in satisfactory yield from human meconium[6,8,95,96].

The method of isolation of these antigens consisted in gentle extraction of either erythrocyte stroma or crude meconium in the presence of electrolytes, differential centrifugation and fractionation on agar gel as well as Sephadex columns with preceding and subsequent precipitation by organic and inorganic solvents followed by renewed differential centrifugation and final electrodialysis[96]. Heating damaged the erythrocyte substances biologically and chemically. We obtained the N and N-like antigens in physico-chemically homogenous form[95] and characterized them biologically and chemically[6,8,94–96].

Table 14 contains physical data for the NN antigen and the antigen isolated from meconium (Me–Vg). The NN antigen has a somewhat higher molecular weight and a somewhat higher diffusion coefficient, but a lower viscosity than the meconium substance[95]. The high $f/f_0$ values point to a marked asymmetry of the two preparations. Both antigens are levorotatory, and absorb between 255 and 282 mμ. The strongly negative charge of the glycoproteins was shown by their migration, as a single band, to the anode between pH 4.5 and 9.2. The NN antigen behaved on Whatman No. 1 paper like human serum albumin, and the Me–Vg antigen like α-globulin. The mobility of both antigens was somewhat lower on cellulose acetate.

Table 14. Physical data on highly purified blood-group N active human antigens [95].

| | Erythrocyte Antigen (NN) Ca 825 | Meconium Antigen (Me–Vg) Ca 851 |
|---|---|---|
| $S_{20,w}$ (S) | 12.8 ($c$ = 0) | 10.8 ($c$ = 0) |
| $10^7$ $D_{20,w}$ (cm$^2$ sec$^{-1}$) | 1.67 [a] | 1.41 ($c$ = 0) |
| $\bar{V}$ (ml/g) | 0.68 | 0.63 |
| $M_w$ | 595000 | 520000 |
| $f/f_0$ | 2.34 | 2.96 |
| $[\alpha]_D^{29}$ ($H_2O$, 1 dm) | −27.0° ($c$ = 0.1) | −32.4° ($c$ = 0.5) |
| $\eta_{rel}$ (0.85% NaCl, 37.5 °C) | 1.052 [b]; 1.099 [c] | 1.707 [b]; 2.408 [c] |
| $A$ 1%/274 mμ | 10.90 | 4.49 |

[a] Average of values at 8.9 and 4.4 mg/ml; not concentration dependent.
[b] $c$ = 0.5%. [c] $c$ = 1.0%.

A striking feature is the apparent ability of the NN antigen to dissociate into subunits. Thus one preparation obtained by us earlier by only slightly harsher means had a molecular weight of 150000, *i.e.* a quarter of


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that given in Table 14. The existence of aggregation-disaggregation phenomena in the red-cell antigens is further supported by the following observations: the asymmetry of the boundaries of our preparation in the ultracentrifuge [95], as well as the extraction from erythrocytes with hot alkaline phenol solution [97], of a glycoprotein having similar chemical and biological properties to those of the substance described here [6,8,96] but with a molecular weight of only about 30000. Moreover, an inhomogeneous NN antigen preparation dissociated into subunits of molecular weight of 30000 after addition of alkyl sulfate detergents [98]. It must be emphasized that the NN antigen with the highest molecular weight also showed by far the highest activities (based on equal weights). The isolated antigens are nearly lipid-free [96].

macromolecule. Table 15 (columns 3 and 4) clearly shows that different human anti-N sera possess different specificity. But all human sera differ in their affinity from those produced in rabbits. Yet human *and* rabbit antisera react with parts of the same receptor surface, those of rabbits apparently with a larger area [96]. The agglutinin from *Vicia graminea*, on the other hand, reacts with a surface structure of the NN macromolecule different from that responsible for N specificity. Our results [100a,96] indicate that the *Vicia* reagent, contrary to widely held belief, does not react with part of the NN specific receptor but either with a genetic precursor of both, the NN and MM antigens, or that the *Vicia* specificity is heterophile and accompanies these antigens only accidentally.

Table 15. NN and Me–Vg antigens: activity *in vitro* and enzymatic inactivation [96].

| Antigen | Treatment | Smallest amount (mg/ml) inhibiting agglutination of human erythrocytes by 4 agglutinating doses | | | | |
|---|---|---|---|---|---|---|
| | | Anti-N | | | | |
| | | Man (Armst.) | Man (Kon. SN-6, Stur 25543) | Rabbit [55–57] | *Vicia graminea* | Influenza virus PR 8 |
| NN [a] | None | 0.01–0.02 | 0.6–2.0 | 0.1 | 0.003–0.005 | 0.003 |
| Ca 825 | R.D.E. [b] | N.A. [c] | N.A. | N.A. | 0.003 | 0.425 |
| | Trypsin | N.A. | N.A. | 2.5 | N.A. | 0.135 |
| Me–Vg [a] | None | N.A. | N.A. | N.A. | 0.1 | 0.03 |
| Ca 851 | R.D.E. | N.A. | N.A. | N.A. | 0.1 | > 1 |
| | Trypsin | N.A. | N.A. | N.A. | 0.1 | 0.03 |

[a] Inactive with 3 human and 4 rabbit anti-M sera.
[b] Receptor Destroying Enzyme.
[c] N.A. = no inhibition of agglutination with 10 mg/ml or less.

Biological data for the two antigens are given in Table 15. The antigens are not only blood-group substances of high activity, but also, as can be seen from the last column, extremely potent myxovirus inhibitors. The meconium antigen was less active when tested with influenza virus of type A (PR 8 and Melbourne) but it was 4 times as active as the NN antigen against the B strain of type Maryland 1/59 [96].

NN and MM substances are good antigens; they are useful for production of blood-group specific antisera [6, 8,96]. The meconium (Me–Vg) antigen possesses the serological specificity measured with the *Vicia* reagent. N specificity is not demonstrable either with human or animal antisera. Its immunogenicity in the production of anti-N sera is poor. Only 1 of 17 rabbits formed anti-N specific antibodies after immunization with Me–Vg antigen [96].

The NN antigen is an excellent example of the mosaic structure of blood-group antigens in general [100,96]. Investigations of its serological properties showed that antibodies of different origin with the same overall specificity are nevertheless adapted to react preferentially with not absolutely identical structures on the same

The isolated NN antigen showed signs of damage to its biological activity towards some human anti-N antibodies in spite of the relatively mild extraction and purification procedures (Table 15, column 4) [96].

Influenza viruses and "receptor destroying enzyme" (R.D.E.) of *Vibrio cholerae* and *Clostridium perfringens* as well as proteolytic enzymes destroy blood group N activity and also the antiviral properties of the NN antigen. Treatment of the NN antigen and the desialized NN antigen with galactose oxidase or *D.pneumoniae* β-galactosidase destroyed *Vicia* specificity. It is remarkable that galactose oxidase destroyed in addition N specificity measured with human anti-N serum (Armstrong) and, to a lesser extent, that measured with rabbit serum [96]. Neither of the two latter enzymes affected the antiviral activity. The receptor properties of the NN antigen determined with the plant extract from *Vicia graminea* were also inactivated by proteases but not by sialidases. Analogous results were obtained with all these enzymes on the MM antigen [6,8,96]. α-Galactosidase, *E. coli* β-galactosidase, β-hexosaminidase, and lysozyme had no influence on the blood-group and virus receptors of the NN and MM antigens. None of these enzymes inactivated the *Vicia* receptor of the Me–Vg antigen [96].

Enzymatic hydrolyses first showed the importance of sialic acid for blood-group N and M specificity [87,88,91, 93,96] as did mild acid hydrolysis [100a,96]. Our most recent findings with galactose oxidase and the analysis of

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dialysable degradation products of the NN antigen indicate that galactose probably is necessary for full N activity of the macromolecule or haptens isolated from it. This galactose is present either in subterminal position or less likely as a branch adjoining sialic acid. This interpretation is based not only on the effect of galactose oxidase on the N activity but also on the composition of the blood-group N specific haptens obtained by mild acid and pronase hydrolysis. These haptens possessed as carbohydrate components 1–2 *N*-acetylneuraminic acid residues per 1–2 galactose residues. The presence of hexosamine may not be essential for activity [96, 101]. Dialysable hexosamine- and sialic acid-containing structures have also been isolated which either have no activity [96] or which were not examined for activity [102]. *Vicia*-receptor specificity of the NN and MM antigens appears to depend on galactose [99, 96] in β-glycosidic linkage [96]. Therefore sialyl, sialyl-galactopyranosyl and β-galactopyranosyl groups appear to determine virus and blood-group specificity.

NN and Me–Vg antigens are glycoproteins. Galactose is the predominating carbohydrate (molar basis) in both antigen preparations discussed here. However, in some earlier NN preparations sialic acid was the most abundant carbohydrate by a small margin [8]. Both antigens contain large amounts of *N*-acetylneuraminic acid, galactosamine, glucosamine, and mannose and the Me–Vg antigen also a large quantity of fucose. The ratio glucosamine:galactosamine is *ca.* 0.75, an extraordinarily low figure for a glycoprotein. Both antigens, but especially the Me–Vg substance, possess components with chromatographic properties of *N,O*-diacetylneuraminic acid; these substances have hitherto not been found in man [8, 96].

Table 16. Carbohydrate components of highly purified NN and Me–Vg antigens [96].

| Structural units | NN-antigen Ca 825 | | Me–Vg-antigen Ca 851 | |
|---|---|---|---|---|
| | (wt-%) | Moles per mole antigen | (wt-%) | Moles per mole antigen |
| Acetylneuraminic acid | 16.2 | 312 | 10.4 | 175 |
| Galactosamine | 4.32 | 144 | 7.50 | 217 |
| Glucosamine | 3.1 | 103 | 15.03 | 436 |
| Galactose | 11.1 | 367 | 20.3 | 586 |
| Mannose | 5.4 | 179 | 7.5 | 216 |
| Glucose | 0.3 | 10 | 1.7 | 49 |
| Methylpentose | 0.7 | 25 | 8.4 | 266 |

Tables 16 and 17 show the composition of both antigens. The values add up to approximately 100% since the NN antigen contains approximately 10% of water and 2.5% of ash; these figures are 14 and 0.7% for the Me–Vg antigen. The molar ratio sialic acid:total hexosamine:galactose is close to 1:1:1 in the NN antigen and almost 1:4:5 in the Me–Vg antigen.

Table 17. Amino acid analysis of the NN and Me–Vg antigens [96].

| Amino acid | NN-antigen (wt-%) | [a] | [b] | Me–Vg-antigen (wt-%) | [a] | [b] |
|---|---|---|---|---|---|---|
| Aspartic acid | 2.93 | 131 | 6.3 | 0.92 | 36 | 6.3 |
| Threonine | 4.26 | 213 | 10.3 | 2.99 | 131 | 22.8 |
| Serine | 3.58 | 203 | 9.8 | 1.34 | 66 | 11.5 |
| Glutamic acid | 4.21 | 170 | 8.2 | 1.04 | 37 | 6.4 |
| Proline | 2.93 | 151 | 7.3 | 1.85 | 83 | 14.4 |
| Glycine | 1.46 | 116 | 5.6 | 0.55 | 38 | 6.6 |
| Alanine | 2.21 | 148 | 7.2 | 0.72 | 42 | 7.3 |
| Valine | 3.07 | 156 | 7.5 | 0.57 | 25 | 4.3 |
| Isoleucine | 2.52 | 114 | 5.5 | 0.37 | 15 | 2.6 |
| Leucine | 4.07 | 185 | 8.9 | 0.72 | 29 | 5.0 |
| Tyrosine | 1.78 | 58 | 2.8 | 0.15 | 4 | 0.7 |
| Phenylalanine | 1.85 | 67 | 3.3 | 0.33 | 10 | 1.7 |
| Lysine | 2.31 | 94 | 4.5 | 0.35 | 13 | 2.3 |
| Histidine | 2.08 | 80 | 3.9 | 0.25 | 8 | 1.4 |
| Arginine | 2.54 | 87 | 4.2 | 0.35 | 10 | 1.7 |
| Methionine | 2.46 | 98 | 4.7 | 0.92 [c] | 28 [c] | 4.9 [c] |
| Sum | 44.26 | 2071 | | 13.42 | 575 | |
| Tryptophan | 0.00 | | | 0.01 | | |
| $NH_4^+$ | 0.77 | 255 | | 0.77 | 222 | |
| Methionine sulfoxide | | | | 0.06 | | |

[a] Moles of amino acid/mole of antigen (nearest whole number).
[b] Moles amino acid/moles total amino acid.
[c] Including methionine sulfoxide.

Threonine, serine, leucine, and glutamic acid are the predominant amino acids in the NN substance, whereas proline ranges before serine, and alanine is fourth in the meconium antigen. The sum of acidic amino acids amounts to approximately three quarters and that of the basic ones to two thirds of the hydroxyamino acids in the NN antigen; the corresponding figures for the Me–Vg antigen are one third and one sixth. Both antigens are characterized by their low content of aromatic amino acids (except proline); tryptophan and cystine are absent. The amino acid composition of both antigens resembles that of the ABH(0) blood-group substances from ovarian cysts [103, 104].

It was attempted to elucidate the nature of the carbohydrate-peptide linkage in both antigens by alkali degradation following the procedures of *Anderson, Hoffman,* and *Meyer* [105] and *Kabat* and associates [106]. The results are given in Table 18. Galactosamine and galactose as carbohydrates, and threonine and serine as amino acids are the constituents involved in this linkage in both antigens since they are destroyed by β-elimination [96]. In addition, 30% glucosamine is destroyed in

Table 18. Components of NN and Me–Vg antigens, destroyed by 0.5 N NaOH at 23 °C (63 hours) [96]. (Other structural units were not destroyed).

| Component | % Destruction NN Antigen Ca 825 | Me–Vg Antigen Ca 851 |
|---|---|---|
| Hexosamine, total | 48 | 43 |
| Galactosamine | 80–90 | 61 |
| Glucosamine | 0 | 30 |
| Galactose | 66 | *ca.* 30 |
| Threonine | 48 | 46 |
| Serine | 39 | 34 |
| Tyrosine | 56 | 0 |


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the Me–Vg antigen. The results further indicate for both antigens destruction of part of the carbohydrates by an additional "peeling reaction" since approximately twice as many sugar residues as amino acid residues are destroyed in the NN antigen; the proportion is even 5:1 for the Me–Vg antigen [96].

It can be concluded from the sum of the chemical and biological results that the sugar chains have a length of only 4–6 monosaccharides in the NN antigen but that they must be considerably larger in the meconium antigen. The immunological specificity is probably determined by small oligosaccharide groupings on these chains: multiple units of not more than 2 sugars for *Vicia* specificity and not more than 4 for human N specificity (measured with the Armstrong anti-N serum). The total number of chains with N specificity as determined with human anti-N serum is at most approximately 300 per molecule of antigen Ca 825 [96].

The MM and NN antigens possess more than one biological function. Therefore they can serve as models not only in blood-group serology, biochemical genetics of man and in virology but in a number of other fields. The NN antigen is the first physically homogeneous, chemically defined cell membrane component of a mammal which possesses blood-group activity of the same order as that of the best ABH(0) glycoproteins, determined with their corresponding antibodies, but isolated from body secretions.

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# Isotope Effects in Organic Chemistry and Biochemistry

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*The present article shows the extent to which isotope effects are likely to be encountered in the use of isotope techniques and what problems are studied with primary and secondary isotope effects. By way of example, the results of studies on E2 reactions, particularly in the Hofmann degradation, are discussed, followed by a discussion of some "analytical isotope effects". Finally, the problems encountered and the information that can be obtained from isotope effect studies on enzyme reactions, and the advantages and disadvantages of competitive and non-competitive techniques are described. In addition to a survey of isotope effects in dehydrogenase reactions, new isotope effects encountered in the dehydrogenation of T-labeled alcohols are reported.*

## I. Introduction

When stable or radioactive isotopes are used as tracers in organic chemistry and biochemistry, it is usually assumed that the various nuclides of an element behave in the same way, *i.e.*, that there is no discrimination between labeled and unlabeled molecules in chemical or physical operations. However, quantitative investigation shows that some such discrimination does exist. These isotope effects [1–9a] are due mainly to differences in the masses of the nuclides and the resulting differences in the zero-point energies of the bonds (cf. Fig. 1). Some (very small) isotope effects are due to other properties of the nuclei, such as the quadrupole moment and the magnetic moment.

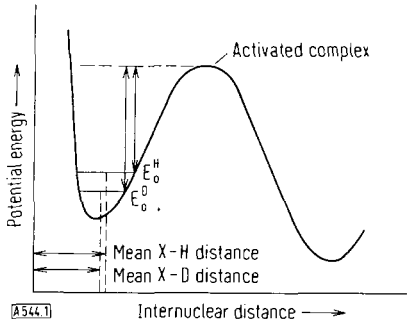


Fig. 1 Potential energy of a molecule HX and of the transition state. The asymmetry of the potential energy curve (exaggerated for clarity) results in a slightly shorter equilibrium internuclear distance in DX than in HX. The different zero-point energies $E_0^H$ and $E_0^D$ lead to different activation energies for reactions of HX and DX (arrows) and are the principal cause of the kinetic isotope effect.

The smaller the relative difference between the masses of two nuclides, the less pronounced are the isotope effects. Thus already in the carbon isotopes the isotope

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effects generally are not very important. On the other hand, isotope effects must always be taken into account in the use of the hydrogen isotopes, since often experimental results can be interpreted only in this way, particularly in a reaction in which bonds formed by the hydrogen isotope itself or adjacent bonds are broken.

The main reasons for the publication of more than 100 original papers and several reviews[5–8] on isotope effects alone in 1964 are:

1. The so-called *kinetic isotope effect* can be used in the study of reaction mechanisms.

According to the theory of absolute reaction rates[9a,b], the kinetic isotope effect is equal to the quotient of the equilibrium constants for the formation of the transition states in the unlabeled and labeled compounds, respectively (cf. the discussion of equilibrium isotope effects under 2 below). The calculation is therefore possible when the vibrational frequencies of the ground state and of the transition state of the reactants are known[3,4,9,9a,10]. The frequencies in the transition state are unknown; the frequencies in the ground state and the isotope effect, however, can be measured. One can therefore obtain information about the transition state in this way. *Wolfsberg* and *Stern*[10] and *Willi*[11–13] calculated theoretical isotope effects for concrete transition states on the basis of the ideas developed by *Bigeleisen* and others [1–4]. Computer programs have been developed for the calculation of the influence of various parameters on the isotope effects[10,10a].

The problems most frequently studied in current experimental work are that of the rate-determining step of a sequence of reactions and that of the extent to which a bond has already been broken or formed in the transition state.

2. The *equilibrium isotope effects* observed in exchange equilibria are of industrial importance in isotope separation. For example for the exchange reaction used for the production of heavy water[14],

$$H_2O + HDS \underset{k_2}{\overset{k_1}{\rightleftharpoons}} HDO + H_2S$$

the equilibrium constant at 25 °C is $k_1/k_2 = K = 2.2$ (this is an extreme value, most values being nearer to 1).

The knowledge or estimation of equilibrium isotope effects also is of interest in the preparation of compounds labeled with hydrogen isotopes and in biochemical studies. In biochemical reaction sequences, *e.g.* glycolysis, proceeding in tritiated water it is found that for reversible reaction steps resulting in equilibration, the hydrogen isotope content of a given position in the intermediates differs from the isotope content of the water only because of an equilibrium isotope effect. However, if reversibility is incomplete, the isotope contents are smaller, since the splitting of a water molecule always involves an intramolecular isotope effect, which frequently amounts to about 3.5–4 in the case of HOD and about 7 in the case of HOT (cf. Section V.4).

The equilibrium constant for the distribution of an isotope between two molecules A and B in the reaction A + B′ ⇌ A′ + B is given by

$$K = \frac{Q_{A'}\,Q_B}{Q_A\,Q_{B'}} \prod^{3n-6} \frac{e^{-1/2u_{A'}}}{e^{-1/2u_A}} \prod^{3n-6} \frac{e^{-1/2u_B}}{e^{-1/2u_{B'}}}$$

where

$n$ = number of degrees of freedom
$Q_i$ = partition function of $i$-th molecule in the ground state
$u = h\nu/kT$
$h$ = Planck's constant
$\nu$ = frequencies of the normal modes
$k$ = Boltzmann's constant
$T$ = absolute temperature.

At the temperatures normally encountered in organic chemistry and biochemistry, the equation

$$K = \frac{e^{-\Sigma h\nu/2kT_{(A')}}\;\; e^{-\Sigma h\nu/2kT_{(B)}}}{e^{-\Sigma h\nu/2kT_{(A)}}\;\; e^{-\Sigma h\nu/2kT_{(B')}}}$$

holds approximately. For the complete calculation of examples see[9a,14a].

There is a close relation between equilibrium isotope effects and reaction mechanisms. Thus the change in rate constants when $D_2O$ is used instead of $H_2O$ as solvent for acid- or base-catalysed reactions is often used to distinguish between different mechanisms[15–20a]. However, definite conclusions can be drawn only if the order of magnitude of the isotope effect for a certain mechanism can be calculated theoretically. Equilibrium isotope effects are important in geology also[21,22].

3. As will be shown in Section V, isotope effects are very important in biochemistry, and will contribute further to a deeper insight into biochemical mechanisms.

4. So-called "analytical isotope effects" are observed in analytical tracer studies. Labeled compounds generally can be used only if they can be purified to constant specific radioactivity by recrystallization, distillation, or a continuous distribution method. Owing to isotope effects, this is sometimes impossible because of incomplete establishment of exchange equilibria and kinetic effects.


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## II. Primary and Secondary Kinetic Isotope Effects

### 1. Primary Isotope Effects

According to the theory of absolute reaction rates [9a,9b], the maximum kinetic isotope effect at a given temperature is obtained when the bond is completely broken in the transition state. However, in the removal of a proton from a carbon atom by a base, for example, the proton becomes bonded to the base B as it is removed from the carbon. The maximum isotope effect therefore occurs at the point of "half-separation" C···H···B. If, on the other hand, the proton in the transition state is more strongly bonded to the C atom (C··H····B), or to the base (C····H··B), the isotope effects are smaller.

The mathematical treatment of this effect is given by *Westheimer* [23] and by *Bigeleisen* [9]. On the basis of theoretical considerations and calculations, however, *Willi* and *Wolfsberg* [23a] concluded that a pronounced maximum of the isotope effect as a function of the breaking and formation of bonds in the transition state depends on the form of the potential barrier separating the reactants from the products. No experiments confirming this view appear to have been published.

In reactions involving several stages, isotope effects can naturally be observed only if the bond to the isotope is broken in the rate-determining step (primary isotope effect). The maximum isotope effect in the rupture of carbon-hydrogen bonds is generally $k_H/k_D$ [*] = 8.3 at 0 °C, $k_H/k_D$ = 6.9 at 25 °C, *etc.* [4]. However, this is true only if the proton transfer takes place without tunnelling [24a].

In the 2,6-lutidine-catalysed iodination of [2-D]-2-nitropropane for example, it was found that $k_H/k_D$ = 24 at 25 °C, whereas in the same reaction with pyridine as catalyst $k_H/k_D$ = 9.8 [24]. It was concluded that sterically hindered slow proton transfers can in general exhibit extremely large isotope effects. The electrophilic aromatic substitution of D or T generally exhibits only slight kinetic isotope effects or none at all [6]. However, larger values can occur under certain steric conditions. In the bromination of 1,3,5-tri-t-butyl[2-D]benzene in the presence of silver ions it was found that $k_H/k_D \geqslant 3.6$ [26d], and a value of 4.75 was obtained in the bromination of deuterated 2,4-dibromo-1,3,5-trimethoxybenzene [26e]. In oxidations [27–32], on the other hand, the hydrogen isotope effects are usually close to the maximum value.

Isotope effects for tritium are often calculated from those for deuterium with the aid of the equation [25]

$$(k_H/k_D)^{1.44} = k_H/k_T$$

(but cf. also [26]).

In addition to the relatively large isotope effects of the hydrogen isotopes, many effects with the nuclides $^{13}C$, $^{14}C$, $^{15}N$ $^{18}O$, and $^{34}S$ or $^{35}S$ have been measured [4].

Values of up to 1.086 at 11 °C [26a] have been reported for $k_{12C}/k_{13C}$ in $S_N2$ reactions; in $S_N1$ reactions, on the other hand, the isotope effects are much smaller, and sometimes even inverted [26b]. The effects for $^{12}C/^{14}C$ may be assumed to be twice as large. In the decarboxylation of [*carboxy*-$^{14}$C]benzoic acid and its derivatives, isotope effects of 1.068 to 1.18 have been observed at 210 and 238 °C [26c], whereas the maximum value expected was 1.057 [3]. Most of the values found for $k_{14N}/k_{15N}$ are less than 1.03.

Other types of reactions in which primary isotope effects have been measured for the nuclides D,T, $^{13}C$, $^{14}C$, $^{15}N$, and $^{34}S$ are solvolysis, decarboxylation, elimination, fragmentation, and isomerization [4]. A review has also been published [32a] on isotope effects in the unimolecular decomposition of simple alkanes and alkyl radicals. An example of isotope effects in metal-catalysed reactions is the decomposition of deuterated formic acids [32b].

### 2. Secondary Isotope Effects

Detailed and critical treatments and reviews of the secondary isotope effect have been published by *Halevi* [8] and others [33]. In the secondary isotope effect, no bond to the nuclide in question is broken in the rate-determining step. Here also equilibrium and kinetic isotope effects can be distinguished.

The difference in the dissociation constants of $C_6H_5-CH_2-COOH$ and $C_6H_5-CD_2-COOH$ ($K_H/K_D$ = 1.12) is a secondary equilibrium isotope effect. Similarly, $C_6H_5-CD_2-NH_2$ is a stronger base than

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[32b] *G. M. Schwab* and *A. M. Watson*, Trans. Faraday Soc. *60*, 1833 (1964).

[33] *R. E. Weston jr.* in: Annual Reviews of Nuclear Science. Annual Reviews, Inc., Palo Alto 1961, p. 439.

$C_6H_5-CH_2-NH_2$ ($K_a^H/K_a^D = 1.13$)[34]. These values appear to be uncertain, and isotope effects of 1.06[34] to 1.03[34a] have been reported for $CH_3COOH$ and $CD_3COOH$. On the other hand, the differences in the rates of the Hofmann degradation of

$$(CH_3)_3N^{\oplus}C^{\alpha}HT-C^{\beta}H_2-C^{\gamma}H_3\ OH^{\ominus} \qquad (1)$$

$$(CH_3)_3N^{\oplus}-C^{\alpha}H_2-C^{\beta}HT-C^{\gamma}H_3\ OH^{\ominus} \qquad (2)$$

(if HOH, and not HOT, is eliminated), and

$$(CH_3)_3N^{\oplus}-C^{\alpha}H_2-C^{\beta}H_2-C^{\gamma}H_2T\ OH^{\ominus} \qquad (3)$$

in relation to the unlabeled compound are secondary isotope effects. In the case of *(1)*, a so-called α-isotope effect occurs in the breaking of the C–N bond, and a β-isotope effect in the breaking of the $C^{\beta}$–H bond; *etc.*

Following *Streitwieser*[34b], *Halevi*[8] distinguishes between secondary isotope effects of the first and second kind. The criterion for this distinction is whether or not the bond to the isotope changes its steric orientation as a result of the reaction. For example, the transition of a deuterated C atom from $sp^3$ to $sp^2$ hybridization is an effect of the first kind, as is the Hofmann degradation of *(1)* and *(2)*; the degradation of *(3)*, on the other hand, is an effect of the second kind.

Since a methyl group, for example, often is completely deuterated, the isotope effects are generally referred to 1 D (*e.g.*, $\Delta\Delta F = (RT/n)\ln(k_H/k_D)$, where $n$ is the number of D atoms per molecule).

*Collins*[35] also found an example of a secondary $^{14}C$ isotope effect in the reaction of $C_6H_5-{}^{14}CO-CH_3$ with 2,4-dinitrophenylhydrazine ($k_{12C}/k_{14C} = 1.0085 \pm 0.0004$). However, it is doubtful whether any conclusions can be drawn on the basis of such small effects.

The theories on the secondary isotope effect are involved and in part contradictory[8, 33]. Therefore we shall give only a few physical facts that are closely related to the chemical reactivity, and frequently confirmed rules on the direction and magnitude of the effects in various types of reactions.

There are fundamentally two views:

1. Secondary isotope effects may be regarded as substituent effects, a C–D bond having a stronger +I effect than a C–H bond[8, 10, 13, 33, 34, 36, 37] and a $CD_3$ group exhibiting weaker hyperconjugation than a $CH_3$ group[53].

2. Secondary hydrogen isotope effects can be explained by the smaller bulk of deuterium[33a], *i.e.* by the smaller amplitude of vibration of D as compared with H[41].

Hydrogen isotope substitution affects dipole moments, nuclear quadrupole coupling constants, and optical activity. From the slight anharmonicity of the molecular energy function (Morse function)[9b], it is possible (cf. Fig. 1) to derive a small difference in electron distribution between C–H and C–D bonds, resulting in slight bond shortening and slightly stronger electron donation by a C–D bond than by a C–H bond[8].

The dipole moments of $ND_3$, $CD_3ND_2$, DCNO, and $(CH_3)_3CD$ are 0.01 to 0.04 Debye larger than those of the corresponding hydrogen compounds[38–38b]. It can therefore be stated that a C–D bond exerts a stronger inductive effect than a C–H bond. Thus $C_6H_5-CD_2-COOH$ and $C_6H_5-CD_2-\overset{\oplus}{N}H_3$ are less dissociated than the undeuterated compounds. The influence of deuterium becomes particularly clear in a comparison of the nuclear quadrupole coupling constants of $CH_3X$ and $CD_3X$ (X = halogen). The C–X bonds are more strongly ionic in the deuterated compounds.

The same conclusion is reached by a study of the effect of deuteration on the chemical shifts of nuclear magnetic resonance signals. The $^1H$ signals of $-CH_2D$ are displaced by 0.015 ppm relative to those of $-CH_3$[39], and the $^{19}F$ signals of $-CF_2D$ by 0.60 ± 0.05 ppm relative to those of $-CF_2H$[40]. However, in a recent comparison of *m*-fluorotoluene and [*methyl*-$D_3$]-*m*-fluorotoluene, the expected shift of the $^{19}F$ signal was not observed[40a]. Electron spin resonance measurements on deuterated benzene, naphthalene, and cyclooctatetraene also failed to show any stronger electron-donating action of deuterium[40d].

The C–D bond is less polarizable than the C–H bond; this property results in optical asymmetry in compounds of the type $R^1R^2CHD$. A theory developed to explain the optical activity due to isotope effects is based on the interaction of light with the various atoms and isotopes[40c]. *Streitwieser*[36] refers to the similarity of the optical rotatory dispersion curves of $CH_3-CH_2-CH_2-CHD(OH)$, $CH_3-CHD(OH)$, and $CH_3(CH_2)_5CH(OH)-CH_3$[40b].

It is concluded from these facts that this "electronic isotope effect"[8] may be treated as a true substituent effect. The effect of replacement of a hydrogen atom in a C–H bond by D is qualitatively similar to that of replacement by a $CH_3$ group. The replacement of a $CH_3$ by a $CD_3$ group has a similar effect to that of replacement by $C_2H_5$ or even by $(CH_3)_3C$.


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The "transmission" of isotope effects *via* multiple bonds and benzene nuclei has been discussed by *Shiner* and *Kriz* [53].

The effects observed on replacement of H by D or T can be explained in another way: *Bartell* [41] believes that both the α- and the β-deuterium isotope effects are due to the greater amplitude of vibration of C–H bonds as compared with C–D or C–T bonds. The repulsive forces between H atoms are consequently greater than those between H atoms and deuterium or tritium, or between deuterium atoms or tritium atoms. Moreover, the repulsion between non-bonded atoms fixed to an $sp^3$ carbon atom is greater than that between atoms attached to C atoms in the $sp^2$ state. Consequently, the energy gain resulting from the decrease in repulsive forces in going from $sp^3$ to $sp^2$ hybridization is greater in protium compounds than in deuterium or tritium compounds. It may be deduced from this that in a transition from the $sp^3$ to the $sp^2$ state, H compounds will react faster than D or T compounds; this is a well established rule [36,42–46]. The reverse is true in transitions from the $sp^2$ to the $sp^3$ state [8,46,47].

This has also been confirmed for a free-radical reaction. In the polymerization of styrene, [α-D]-, [β,β-$D_2$]-, [α-T]-, and α,β-*trans*-$T_2$-styrene react faster than unlabeled styrene [47a].

The smaller bulk of $CD_3$ groups as compared with $CH_3$ groups has been clearly shown by *H. C. Brown* [33a]. The quaternization of 2-trideuteriomethylpyridine exhibits an inverse secondary isotope effect of 0.97 with methyl iodide, 0.96 with ethyl iodide, and 0.935 with isopropyl iodide. The value found for 2,6-bis(trideuteriomethyl)pyridine was 0.92. Since 3-trideuteriomethylpyridine and 4-trideuteriomethylpyridine exhibit only insignificant isotope effects, *Brown* considers any explanation of secondary isotope effects other than by steric effects as unacceptable.

The same conclusion is suggested by the fact that only 2,6-bis(trideuteriomethyl)pyridine has a greater heat of reaction (by 0.23 kcal/mole) with $BF_3$, than the undeuterated compound, and not the 3- and 4-methyl compounds.

*Streitwieser et al.* [48] first demonstrated the influence of D in the α-position in $S_N1$ solvolyses (transition state with $sp^2$ character), and interpreted it as being due to the higher energy gain of the H compound on transition from the $sp^3$ to the $sp^2$ state in the activated complex. They described an approximation with which $k_H/k_D$ can be determined from the (generally known) vibration frequencies of the unlabeled starting material and of the product. Values of 1.12 to 1.15 are found for $k_H/k_D$ of many acyclic compounds, and somewhat higher values for cyclic compounds [8,33].

Very small or even inverse isotope effects are observed in $S_N2$ reactions. Thus we found [49] $k_H/k_T = 0.96$ for the quaternization of pyridine with [T]methyl iodide (see also [8]). The solvolysis of halides and tosylates has been intensively studied [50,51]; inverse isotope effects were observed throughout this work. (Cf. also calculations by *Willi* [13]).

The possibility of using secondary isotope effects to obtain a better insight into the course of solvolysis reactions has been discussed by *Lee* and *Wong* [52]. In the solvolysis of [1,1-$D_2$]-2-cyclopentylethyl, [1,1-$D_2$]-2-(2-cyclopentenyl)ethyl, and [1,1-$D_2$]-2-(3-cyclopentenyl)-ethyl *p*-nitrobenzenesulfonates, an appreciable isotope effect is observed only for the third compound, for which $k_H/k_D = 1.07$ per D. It was concluded from this result that the transition state has partial $S_N2$ character, and in agreement with *Streitwieser* [34], that neighboring group effects are involved.

In the formation of methyl radicals from 1-trideuteriomethyl-2-phenylethyl hypochlorite an α-deuterium isotope effect of 1.15 per D was observed, in good agreement with the results obtained in $S_N1$ reactions and unimolecular thermal cleavages [46].

That the secondary isotope effect of $k_H/k_D = 1.09$ in the hydrolysis of [1,1,1-$D_3$]-4-chloro-4-methyl-2-pentyne [53] depends very little on the solvent is strong evidence that the hyperconjugation of a $CD_3$ group is weaker than that of a $CH_3$ group, since steric effects cannot be involved in this case [53].

In addition to the much-studied $S_N1$ and $S_N2$ reactions [54], secondary isotope effects have been used to investigate Diels-Alder reactions [55]. The results suggest a four-center reaction with a transition state situated largely on the reactant side.

Other steric isotope effects due to deuteration have been observed in the racemization of 9,10-dihydro-4,5-dimethylphenanthrene [56]. Samples deuterated in the methyl or methylene groups racemize more rapidly. A distinct isotope effect was also observed in the racemization of 2,2′-dibromobiphenyl-4,4′-dicarboxylic acid [57].

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## III. Isotope Effects in E2 Reactions such as the Hofmann Degradation

The study of isotope effects in E2 reactions is interesting in that *two* bonds in the transition state are broken "simultaneously". One may therefore ask, *e.g.* in the Hofmann degradation of quaternary cations of the type $(CH_3)_3N^{\oplus}-C^{\alpha}H_2-C^{\beta}H_2-R'$, how this "simultaneous" rupture depends on R, *i.e.* isotope effects can be used in an attempt to establish whether the rupture of the C–N bond or that of the $C^{\beta}$–H bond is faster. We therefore determined the $^{14}C$ and T isotope effects in the Hofmann degradation of the quaternary ammonium cations listed in Table 1 [42–44].

Table 1. Summary of the primary $^{14}C$ and T isotope effects ($IE_{exp}$) found by us [43–45], and comparison with some D isotope effects found by various authors (recalculated for T) in the Hofmann degradation of quaternary ammonium cations $(CH_3)_3N^{\oplus}R$.

| R | $IE_{exp.}$ converted to 40 °C [a] | R | $IE_{exp.}$ converted to 60 °C [a] | Ref. |
|---|---|---|---|---|
| $^{14}CH_2-CH_3$ | 1.05 [b] | $CH_2-CH_2T$ | 3.0 [a, b] | [43–45] |
| $^{14}CH_2-CH_3$ | 1.06 [b] | $CH_2-CH_2T$ | 2.8 [a, b] | [43–45] |
| $^{14}CH_2-C_2H_5$ | $1.07_3$ | $CH_2-CHT-CH_3$ | $2.8_6$ [a] | [43–45] |
| $^{14}CH_2-CH_2-C_6H_4-NO_2$-*p* | $1.03_4$ | $CH_2-CHT-C_6H_5$ | 4.2 [a] | [45] |
| $^{14}C(CH_3)_3$ | $1.06_4$ | $CH_2-CHT-C_6H_4-NO_2$-*p* | 8 ± 1.6 [a] | [45] |
| $CH_2-^{14}CH_2-CH_3$ | $1.03_8$ | | 12 ± 4 | [66] |
| | | $CH_2-CD_3$ | 14 | [60] |
| | | $CH_2-CD_2-C_6H_5$ | 3.9 | [59] |

[a] For experimental details, conversion of the values found at various temperatures to 40 or 60 °C, discussion of error, *etc.*, see [43–45].

[b] Various conditions.

Though isotope effects were already known for the breaking of $C^{\beta}$–H bonds [58–60], the only value known for the rupture of the C–Y bond (Y = N,S) was $k_{32S}/k_{34S} = 1.0015$ for the elimination of dimethyl sulfide from β-phenethyldimethylsulfonium bromide [61]. Later this value was revised to 1.0065 [61a].

*Arey et al.* found [62] a $^{15}N$ isotope effect of 1.017 for $(CH_3)_3N^{\oplus}-CH_2-CH_3$ at 60 °C and 1.009 for $(CH_3)_3N^{\oplus}-CH_2-CH_2-C_6H_5$. The electron-attracting phenyl group therefore decreases the isotope effect in the rupture of the C–N bond. Our $^{14}C$ isotope effects (Table 1) are in good agreement with this conclusion and showed even more clearly that the isotope effect is increased by electron donors such as methyl groups (cf. R = $C_3H_7$ with R = $C_2H_5$), and greatly decreased by electron-attracting groups such as *p*-$NO_2-C_6H_4$.

The determination of the isotope effect of $(CH_3)_3N^{\oplus}C(CH_3)_3$ was of interest, since the t-butyl group exhibits particularly small isotope effects in $S_N1$ reactions, presumably because of the strengthening of the bonds between the tertiary carbon and the methyl groups in the carbonium ion [63]. As can be seen, the tertiary butyl group exhibits no peculiarities in the Hofmann degradation.

$k_{32S}/k_{34S}$ for $(CH_3)_2S^{\oplus}-C(CH_3)_3$ is 1.007 [64]. The $^{15}N$ isotope effect in the degradation of $(CH_3)_3N^{\oplus}-CH_2-CH_2-C_6H_4-X$-*p*, where X = H, $CH_3O$, and Cl, does not vary with X [65].

Whereas the isotope effects found for the rupture of the C–N bond were mutually compatible and reasonable, this was not so for the cleavage of the $C^{\beta}$–H bond when all known values were taken into account. The tritium isotope effects found by us and the isotope effects from the literature are listed in Table 1. For ease of comparison, all values are converted to 60 °C and the deuterium values were converted to tritium values [45].

It can be seen that the tritium isotope effect with substituents in the β-position increases in the order $CH_3 \leqslant H < C_6H_5 < C_6H_4-NO_2-p$ [*].

As can be seen, a large hydrogen isotope effect in the Hofmann degradation is accompanied by a small carbon isotope effect, and *vice versa*. What does this tell us about the transition state? For electron-attracting groups, such as phenyl and *p*-nitrophenyl, the hydrogen isotope effects are large, showing that the release of the proton must have reached approximately the half-way stage in the transition state ("half-release", cf. Section II.1). The question then arises of whether the release of the proton in the presence of alkyl groups has progressed beyond or has not yet reached the "half-released" state, since smaller isotope effects are observed in this case.

[58] For elimination reactions see *D. V. Banthorpe* in *E. D. Hughes*: Reaction Mechanisms in Organic Chemistry, Vol. 2. Elimination Reactions. Elsevier, Amsterdam-New York 1963.

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[*] *E. M. Hodnett* and *J. J. Sparapany*, Pure appl. Chem. *8*, 385 (1964), reported a much smaller value; however, this was not determined directly as in the earlier measurements by *Hodnett* [66] and by us [45], but was found indirectly from the kinetic and secondary isotope effects. This procedure seems unsuitable in view of the polymerization of *p*-nitrostyrene.

The value for $(CH_3)_3N^{\oplus}-CH_2-CD_3$ [60] deviates strongly from this sequence. Since the primary object of these studies [60] was not the determination of the isotope effects, a relatively large error is possible: *V. J. Shiner* and *M. L. Smith*, personal communication.

A group R that facilitates the removal of a proton (relative shift of the E2 elimination to a transition state with carbanion character) may be assumed to hinder the release of a leaving group that takes the electron pair with it, and *vice versa*. It may also be assumed that a negative charge on $C^{\beta}$ cannot be stabilized by an alkyl group, and that under the influence of the positive charge on the nitrogen, the irreversible displacement of electrons to form the products consequently occurs already on slight loosening of the $C^{\beta}$–H bond in the transition state. In the case of aryl groups, the negative charge formed can be better stabilized, so that the proton can move farther away before the irreversible electron transfer takes place.

These assumptions are supported by the secondary isotope effects. If the transition state in the Hofmann degradation were similar in structure to the final products, relatively large secondary isotope effects should occur. However, as we have found for the quaternary ammonium cations with R = $CH_2$–CHT–$CH_3$, $CH_2$–$CH_2$–$CH_2T$, and CHT–$C_2H_5$, this is not so; we obtained values of 1.33, 1.10, and 1.10 respectively [43].

These conclusions are in disagreement with the assumption [67,68] that in the Hofmann degradation of quaternary ammonium cations the rupture of the $C^{\beta}$–H bond is already relatively far advanced in the transition state. Since the isotope effect of the ethyl compound [60] (R = $CH_2$–$CD_3$) is much greater than that of the phenethyl compound (R = $CH_2$–$CH_2$–$C_6H_5$), *Ayrey et al.* [62] also assumed that the $C^{\beta}$–H bond has reached the "half-release" stage in the ethyl compound, and has progressed beyond this stage in the phenethyl compound. However, since our extensive measurements showed that the ethyl and propyl compounds (R = $CH_2$–$CH_2T$, $CH_2$–CHT–$CH_3$) have a much smaller isotope effect than the phenethyl and nitrophenyl compounds(R = $CH_2$–$CH_2$–$C_6H_5$, $CH_2$–CHT–$C_6H_4$–$NO_2$-*p*), the conclusions of *Ayrey et al.* [62] agree with ours only in that the rupture of the $C^{\beta}$–H bond is further advanced for compounds with electron-attracting groups than for compounds with alkyl groups.

In our opinion, the Hofmann degradation shows clearly what is involved in the determination of isotope effects and what conclusions can be drawn. Particularly for hydrogen isotope effects, a definite conclusion can be drawn only from a large value (cf. however [23a]). It is advantageous to label all points of a molecule at which bonds are broken of formed, and to determine whether or not isotope effects occur. Generally it is also useful to study a reaction as a function of the substituents at the reacting centers.

Systematic studies of this type were carried out [69] for the Dieckmann condensation, the Wolff rearrangement, the hydrolysis of benzyl chloride and *para*-substituted benzyl chlorides, and the substitution of 3-chloro-1-butene by diethylamine. In this last case the $^{14}C$ isotope effects for [1-$^{14}C$]-, [2-$^{14}C$]-, and [3-$^{14}C$]-3-chloro-1-butene were found to be 1.057 ± 0.007, 1.074 ± 0.003, and 1.079 ± 0.003. The chlorine isotope effect $k_{35Cl}/k_{37Cl}$ was found to be 1.0112 ± 0.0006. This is a particularly good example, since it shows that in the reaction

$$(C_2H_5)_2NH + CH_2{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}H{-}Cl \rightarrow (C_2H_5)_2N^{\oplus}CH_2{-}CH{=}CH{-}CH_3 + Cl^{\ominus}$$

all the bonds of 3-chlorobutene-1 are influenced in the transition state.

## IV. "Analytical" Isotope Effects

If hydrogen-labeled compounds are subjected to simple separations, *e.g.* recrystallization or distillation, which are less efficient methods than multi-stage distribution, surprisingly large isotope effects can nevertheless occur when such a separation is associated with a chemical reaction.

In the recrystallization of [1-T]mannose phenylhydrazone from 60% aqueous methanol, for example, we found that the labeled molecules crystallize more slowly [70,71]; $k_H/k_T = 1.12$. Owing to the importance of recrystallization in the purification of labeled compounds, this observation was checked by the National Bureau of Standards, Washington, who confirmed our results [71]. This large isotope effect probably is due to the fact that the mutarotation of one or more forms of mannose phenylhydrazone is rate-determining for the crystallization.

A second example is the distillation of aqueous solutions of [T]formaldehyde [42]. The reaction involved probably is the hydration and dehydration of the formaldehyde. As mentioned in the discussion of secondary isotope effects, D- and T-labeled molecules react more slowly than unlabeled molecules in $sp^3 \rightarrow sp^2$ transitions, and correspondingly faster in $sp^2 \rightarrow sp^3$ transitions. In T-labeled formaldehyde, therefore, for the equilibria

$$CH_2O + H_2O \underset{k_{H(-H_2O)}}{\overset{k_{H(+H_2O)}}{\rightleftharpoons}} CH_2(OH)_2 \quad \text{and}$$

$$CHTO + H_2O \underset{k_{T(-H_2O)}}{\overset{k_{T(+H_2O)}}{\rightleftharpoons}} CHT(OH)_2$$

$$k_{H(+H_2O)} < k_{T(+H_2O)} \text{ and } k_{H(-H_2O)} > k_{T(-H_2O)}.$$

Thus in T-labeled formaldehyde the equilibrium is displaced further towards the hydrated form than in the unlabeled compound, so that [T]formaldehyde is less volatile. Equilibria with the dimer, methylene glycol, or with oligomeric oxymethylene hydrates may also play some part.

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Remarkable isotope effects occur in the paper and column chromatography of T-labeled aldosterones [72]. The change in the ratio T/$^{14}$C in intermolecularly doubly labeled samples was followed. In the paper chromatography of aldosterone diacetate, for example, the ratio T/$^{14}$C for 4 segments of the spot, which were cut out across the flow direction, were 11.2, 8.5, 6.3, and 5.6. Similar fractionations were observed in chromatographic cloumns. It was shown that the fractionation takes place, not on the basis of the $^{14}$C labeling, but only on the basis of the tritium labeling [*].

It is not surprising, therefore, that small molecules with different hydrogen isotope contents, *e.g.* methanes [74], and ethanes [75], can be completely or largely separated by normal chromatographic methods. The effects depend not only on the number of hydrogen isotopes, but also on their position. Thus *Lee* and *Rowland* [76] separated position-isomeric T-labeled olefins such as propylene ($CH_2T-CH=CH_2$ from $CH_3-CT=CH_2$ and $CH_3-CH=CHT$), *cis*-butene ($CH_2T-CH=CH-CH_3$ from $CH_3-CT=CH-CH_3$), as well as 1-butene ($CH_3-CHT-CH=CH_2$ from $CH_3-CH_2-CH=CHT$ and/or $CH_3-CH_2-CT=CH_2$). Traces of tritium in hydrogen gas can be accumulated on an alumina-iron oxide column at −183 °C [77]. Examples of isotope effects occurring in column- or gas-chromatographic separations are listed in Table 2.

Table 2. Isotope effects in chromatographic separations [a].

| Chromatography method | Compound | Isotope effect (in retention vol-% [b]) | Ref. |
|---|---|---|---|
| Ion exchange | [$^{14}$C] Amino acids | −0.123 to 0.338 | [77a] [77b] |
| | [T]-2-Aminopurine | −2.4 | [77c] |
| | [$^{14}$C]Formic acid | 0.62 at 6 °C<br>0.32 at 35.4 °C | [77d] |
| Paper | [6,7-$T_2$]Estradiol | 0.75 | [77e] |
| | [1, 2-T]-Aldosterone diacetate | 0.2 | [77f] |
| Column | [T]Formic acid | 2.4 | [77g] |
| | [*methyl*-T]Methoxy-acetic acid | 1.01 | [77g] |
| | [T]Linoleic acid | 0.41 | [73] |
| | [T]Cholesterol acetate | up to 0.49 | [72] |
| | [1, 2-T]Aldo-sterone diacetate | up to 0.73 | [77f] |
| | [1, 2-T] Aldosterone | up to 1.63 | [77h] |
| Gas | [T]Steroids | up to −1.15 | [77i] |
| | [D]Trimethylsilylated carbohydrates | up to 2.62 | [77j] |

[a] We are grateful to Dr. *P. D. Klein* for making a manuscript available to us before publication.

[b] Retention volume per cent is the percentage difference between the retention volume at which 50% of the unlabeled and 50% of the labeled compound are eluted. Negative values indicate that the labeled compound flows more rapidly.

## V. Isotope Effects in Biochemistry

In addition to the equilibrium, kinetic, and solvent isotope effects defined above other isotope effects can be observed in biological systems, *e.g.* changes in permeability, morphologic and genetic changes, changes in growth rates, and even inability of the cells to survive [78]. The strongest effects are again produced by hydrogen isotopes. However, if the steps involved in the process are known, the overall effects can be traced to primary and secondary isotope effects of labeled substrates in enzyme reactions and the influence of $D_2O$ on substrates and enzymes [79–82].

Generally the labeled and the unlabeled compounds are present together and the enzyme-kinetic measurements are competitive. The proportion of the labeled compound is characterized by atom weight percentage or by the specific radioactivity. With deuterium, 100% isotopic substitution can be obtained; in such instances kinetic measurements can be carried out on each substrate individually. This case, which is designated as *non-competitive* or *independent* [4], will be discussed first.

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## 1. Isotope Effect and Enzyme Mechanism

### a) Non-competitive Measurements

Isotope effects of enzymatic reactions with a single substrate can be expressed by the isotope effects of the maximum rate $V$ and of the Michaelis constant $K_m$. For the reaction of an enzyme E with a substrate S or a labeled substrate S', we have, in the simplest case[83]:

$$\begin{aligned} &E + S \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} ES \xrightarrow{k_{+2}} E + P \\ &E + S' \underset{k'_{-1}}{\overset{k'_{+1}}{\rightleftharpoons}} ES' \xrightarrow{k'_{+2}} E + P' \end{aligned} \quad (1)$$

From equation (1) we obtain the equations for the initial rate, $v_i$:

$$v_i = \frac{V}{1 + K_m/[S]}; \quad v'_i = \frac{V'}{1 + K'_m/[S']} \quad (2)$$

For substrate saturation, we have:

$$V = k_{+2}\,[E_0] \quad (3)$$

where $[E_0] = [E] + [ES]$.

By definition, $K_m$ is equal to the substrate concentration at which $v_i = V/2$. Moreover, it follows from equation (1) that:

$$K_m = \frac{k_{+2} + k_{-1}}{k_{+1}} \quad (4)$$

If equilibrium between the enzyme, the substrate, and the complex ES has been established ($k_{+2} \ll k_{-1}$), $K_m$ is practically equal to the dissociation constant $K_s$ of the complex ES:

$$K_m \approx \frac{k_{-1}}{k_{+1}} = K_s \quad (5)$$

Equation (2) is used to find the constants $V$, $V'$, $K_m$, and $K'_m$, and from these the isotope effects $V/V'$ and $K_m/K'_m$ are calculated.

In a single-substrate reaction, an isotope effect of $V$ indicates that an isotope-substituted bond is broken or formed in the rate-determining step. An isotope effect of $K_m$ can, if condition (5) is satisfied, serve as a measure of the relative affinity of the substrates being compared. For $K_m/K'_m > 1$, the isotope-substituted substrate is more firmly bound than the unlabeled substrate.

From equation (2), the isotope effect of the initial rate $v_i$, which is the quantity that can be measured directly, is:

$$\frac{v_i}{v'_i} = \frac{V[S]\,(K'_m + [S'])}{V'[S']\,(K_m + [S])} \quad (6)$$

For equal substrate concentrations ($[S] = [S']$), there follow equation (7) at substrate saturation and equation (8) at low substrate concentrations.

$$\frac{v_i}{v'_i} = \frac{V}{V'} = \frac{k_{+2}}{k'_{+2}} \quad (7)$$

$$\frac{v_i}{v'_i} = \frac{V}{V'} \cdot \frac{K'_m}{K_m} \quad (8)$$

Further, it follows from equation (6) that in a given enzyme reaction the isotope effect of $v_i$ is a function of the substrate concentration, and may be greater or less than 1.

For two-substrate reactions [including those of the NAD-dependent dehydrogenases (see Table 3), which are particularly interesting in connection with D and T isotope effects], most of the possible mechanisms lead to the same rate law, which is given by the Dalziel equation (9)[84]; this replaces equation (2).

$$\frac{E_0}{v_i} = \Phi_0 + \frac{\Phi_1}{[S_a]} + \frac{\Phi_2}{[S_b]} + \frac{\Phi_{1,2}}{[S_a]\,[S_b]} \quad (9)$$

$[S_a]$ and $[S_b]$ are the concentrations of the substrates or coenzymes. The $\Phi_i$ are the products of the rate constants of the individual steps; their connection with the mechanism is given by *Dalziel*[84], and their determination is also described in[83]. From the $\Phi$ of an overall reaction (forward and reverse reactions), it is possible, with the aid of the Haldane equation[85], the Dalziel equations[84], and equations for product inhibition[86,87], to derive quantities that characterize a mechanism. The enzyme mechanism can be derived in a similar and complementary manner from the isotope effects found for the quantities $\Phi$.

To illustrate the information obtainable from isotope effects, consider the liver alcohol dehydrogenase reaction (which was originally assumed to proceed by a simple Theorell-Chance mechanism[88]):

$$E + CoH \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} ECoH \underset{+SH;\ k_{-2}}{\overset{+S;\ k_{+2}}{\rightleftharpoons}} ECo \underset{k_{-3}}{\overset{k_{+3}}{\rightleftharpoons}} E + Co$$

(Co, CoH, S, and SH represent the coenzyme and the substrate and their reduced forms)

The parameters of the forward and the reverse reactions are

$$\Phi_0 = 1/k_{+3};\ \Phi_1 = 1/k_{+1};\ \Phi_2 = 1/k_{+2};\ \Phi_{1,2} = k_{-1}/k_2 k_{+1}$$

(forward reaction)

$$\Phi_{0r} = 1/k_{-1};\ \Phi_{1r} = 1/k_{-3};\ \Phi_{2r} = 1/k_{-2};\ \Phi_{1,2r} = k_{+3}/k_{-2}k_{-3}$$

(reverse reaction)

For the isotope effects $\Phi/\Phi' = \varphi$ we obtain the following conditions:

$$\varphi_{1r} = 1; \quad \varphi_0 = 1; \quad \varphi_{2r} = \varphi_{1,2r}; \quad \varphi_1\,\varphi_2/\varphi_{1,2} = \varphi_{0r}$$

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In *Baker*'s investigations [89] the second and fourth conditions were not satisfied, so that a simple Theorell-Chance mechanism probably is not involved. Other applications of the Dalziel equation are given in [50, 89–94].

### b) Competitive Measurements

#### α) [S] and [S'] are comparable

The overall rate $v_t$ for the transformation of an isotopic substrate mixture [94a] is

$$v_t = v_s + v'_s = \frac{V\,[S]}{[S] + K_m\,(1 + [S']/K'_m)} + \frac{V'\,[S']}{[S'] + K'_m\,(1 + [S]/K_m)} \quad (10)$$

where $v_s$ and $v'_s$ are the partial reaction rates of the labeled and non-labeled substrates, respectively. Since $K_m/K'_m$ may be greater or smaller than 1, each partial rate may also be greater or smaller than that at the corresponding substrate concentration in the absence of isotope effects. The rate equation (10) corresponds formally to that of a competitive inhibition, but it cannot be concluded that a labeled substrate acts as a competitive inhibitor.

Equation (10) shows that the ratio of the partial rates in the competitive experiment is always proportional to the ratio of the substrate concentrations [95].

$$\frac{v_s}{v'_s} = \frac{V}{V'} \cdot \frac{K'_m}{K_m} \cdot \frac{[S]}{[S']} \quad (11)$$

$V/V'$ and $K_m/K'_m$ can be determined by two methods in competitive experiments: by determination of $v_t$ and the ratio of the partial rates, or by determination of the dependence of $v_t$ on the ratio of the substrate concentrations [96].

#### β) [S] is much greater than [S'] (radioactive tracer)

In nearly all experiments with radioactively labeled substrates, $[S'] \ll [S]$ and $[S'] \ll K'_m$. The information obtainable from equation (10) is considerably restricted. $v_t$ practically corresponds to the partial rate $v_s$, so that the partial rate $v_s$ cannot be determined independently [*]. Thus equation (11) gives an isotope effect only for the ratio $VK'_m/V'K_m$.

If the specific activity of the substrate is $[S']/[S] = N_0$ and that of the product is $N_p$, the isotope effect at low conversion $f$ [3] is

$$\left(\frac{N_0}{N_p}\right)_{f\to 0} = \frac{k}{k'} = \frac{v_i}{v'_i} \cdot \frac{[S']}{[S]}.$$

Substitution in equation (11) gives (see also [97])

$$\left(\frac{N_0}{N_p}\right)_{f\to 0} = \frac{V}{V'} \cdot \frac{K'_m}{K_m} \quad (12)$$

### c) Comparison of Non-competitive and Competitive Experiments

The advantage of the use of highly or completely labeled substrates is that $K_m$, $V$, $K'_m$, and $V'$, as well as the kinetic quantities $\Phi$ and $\varphi$ (cf. Section V, 1a) can be determined directly in multi-substrate reactions [50, 89–94]. However, even if the reaction conditions are closely controlled, the errors in the individual measurements lead to large errors in the isotope effect [5]. This is shown by a comparison of the results obtained for alcohol dehydrogenase [50, 92] and the dependence of the isotope effect of the urease reaction on various enzyme preparations [97].

The competitive procedure has the following advantages: There are no errors due to the comparison of two sets of measurements, such as are necessary in non-competitive experiments. In the competitive method, the isotope effect can be determined with small errors by radioactive or mass-spectrometric analysis of the products. Labeling of the required substrates in trace amounts is generally easier than the preparation of isotopically pure substrates; *e.g.* also the preparation of stereospecifically labeled substrates is unnecessary (cf. notes to Table 4). The procedure is better suited to *in vivo* investigations. One disadvantage is the fact that tracer labeling generally gives only $VK'_m/V'K_m$ (cf. Section V, 1b).

## 2. Interpretation of the Isotope Effect in Biochemistry

Most publications on enzymatic isotope effects deal with deuterium isotope effects, and particularly with the study of hydrogen transfer by oxidoreductases and isomerases. Examples are given in Section V.3 and in Table 3. Although far less enzyme reactions than organic reactions have been studied with the aid of isotope effects, some general data on the magnitude of isotope effects in enzyme reactions and their interpretation can be given.

[*] This is most easily seen from the fact that for $[S'] \ll K'_m$, equation (2) simplifies to $v'_i = V'[S']/K'_m$. Consequently, only the ratio $V'/K'_m$ can be determined, and not the individual quantities.


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Table 3. Deuterium isotope effects in biochemical redox reactions.

| Enzyme and reaction | Substrate | $\frac{V}{V'}$ | $\frac{K_m}{K'_m}$ [a] | $\frac{v_i}{v'_i}$ etc. | Conditions and ref. |
|---|---|---|---|---|---|
| Alcohol dehydrogenase (yeast)<br>$CH_3CHO + NADH + H^+ \rightleftharpoons CH_3CH_2OH + NAD^+$ | $CH_3CD_2OH$<br>[A-4-D]-NADH | 1.75<br>1.75 | 2.3 [92]<br>1.39 | <br>1.31 [b] | pH = 7.45; 24 °C<br>[91] |
| Alcohol dehydrogenase (liver)<br>$CH_3CHO + NADH + H^+ \rightleftharpoons CH_3CH_2OH + NAD^+$ | [A-4-D]-NADH<br>[B-4-D]-NADH | 1.59<br>0.50 [d] | 1.31 | 1.6 [b] | pH = 8.8; 27 °C<br>[91] |
| Lactate dehydrogenase<br>Pyruvate + NADH + $H^+ \rightleftharpoons$ Lactate + $NAD^+$ | [A-4-D]-NADH<br>[B-4-D]-NADH | 1.41<br>0.81 [d] | 0.43<br>1.59 | 0.35 [b] | pH = 7.4; 25 °C<br>[93] |
| Lactate dehydrogenase (ox heart)<br>Pyruvate + NADH + $H^+ \rightleftharpoons$ Lactate + $NAD^+$ | [A-4-D]-NADH<br>[B-4-D]-NADH | 1.35<br>1.10 [d] | 0.69<br>2.02 | 0.92 [b] | pH = 7.4; 25 °C<br>[93a] |
| Lactate dehydrogenase (*Leuconostoc mesenteroides*)<br>Lactate + $NAD^+ \rightleftharpoons$ Pyruvate + NADH + $H^+$ | [2-D]-D-Lactate | | <br>1.86 | | pH = 8.6<br>[111a] |
| Malate dehydrogenase<br>Oxalacetate + NADH + $H^+ \rightleftharpoons$ Malate + $NAD^+$ | [A-4-D]-NADH<br>[B-4-D]-NADH | 1.85 | 1.70<br>0.82<br>1.51 | 1.09 [b] | pH = 7.4; 25 °C<br>[94] |
| Glucose-6-P dehydrogenase<br>Glucose-6-P + $NADP^+ \rightarrow$<br>Gluconic acid-6-P + NADPH + $H^+$ | | 2.0—2.4 | 1.3—1.6 | 1.3—1.6 | pH = 5.9—9.4<br>[107] |
| Formic dehydrogenase (pea)<br>$HCOOH + NAD^+ \rightarrow CO_2 + NADH + H^+$ | | | not significant | 3.0(16 °C)—2.0(37 °C)<br>$E_A(H) = 11700 \pm 150$ cal<br>$E_A(D) = 14935 \pm 170$ cal<br>[c] | pH = 6.8<br>[108] |
| Formic dehydrogenase (*E. coli*)<br>$HCOOH \rightarrow CO_2 + 2\,H^+ + 2e^-$ | | | | 1.0 | pH = 6.8; 32 °C<br>[108] |
| Catalase<br>$H_2O_2 + HCOOH \rightarrow CO_2 + 2\,H_2O$ | | | 1.0 | 1.5 | pH = 5.9; 27 °C<br>[108] |
| Glycolic oxidase<br>$HOCH_2COOH + NAD^+ \rightleftharpoons$<br>$OHCCOOH + NADH + H^+$ | | | | <br><br>2.5 | <br><br>[114] |
| Succinate dehydrogenase<br>$HOOCCH_2CH_2COOH \rightleftharpoons HOOCCH{=}CHCOOH$ | 77% D | | 0.69 | up to 5.9 [99]<br>$E_A(H) = 11250 \pm 150$ cal<br>$E_A(D) = 12700 \pm 300$ cal<br>[c] | [96] |
| Monoamino oxidase<br>Amine + $H_2O$ + $O_2$ --> aldehyde + $NH_3$ + $H_2O_2$ | | | | 2.3 | [110] |
| Sarcosine oxidase<br>Sarcosine --> $H_2CO$ + glycine → serine | | 1.5 | 0.5 | | [95] |
| Cytochrome-$b_5$ reductase<br>NADH + $H^+$ + 2 cytochrome-$b_5$ (oxidized)<br>→ $NAD^+$ + 2 cytochrome-$b_5$ (reduced) | [A-4-D]-NADH<br>acetyl analogue<br>pyridinaldehyde analogue | | 1.66[117] | 3.66<br>10.45<br>8.7 | pH = 8.1; 25 °C<br>[100] |
| NADH oxidase<br>Acceptor: $O_2$ | [B-4-D]-NADH | | | 4.5 | [116] |
| NADH-Dehydrogenase<br>Acceptor: 2,6-Dichloroindophenol and others | [B-4-D]-NADH | | | 1.66—1.1 | [116] |

[a] Isotope effects of the Michaelis constant or of equilibrium constants of the listed substrates in E3. $K_m/K'_m > 1$ indicates firmer bonding of the deuterated substrate [cf. eq. (5)].

[b] Isotope effects for the rate constants of the bonding of coenzymes.

[c] Activation energies ($E_A$) for rupture of the C—H and C—D bonds.

[d] Secondary isotope effects.

The deuterium isotope effects of $v_i$ and $V$ in enzyme reactions are comparable with those of ordinary organic reactions. Though a value of 6 to 7 is expected for a normal deuterium isotope effect between 20 and 35 °C[16], the observed effects of, on average 1.5 to 3 still fit into the same scheme if the transition state is similar to the reactants or to the products. The remarks in Section II.1 on the magnitude of the isotope effect as a function of the loosening of the bond along the reaction coordinate then apply. Moreover, there is often some compensation and hence reduction of the measurable isotope effect because, in the absence of substrate saturation, the ratio $v_i/v'_i$ depends on $VK'_m/V'K_m$ [eqs. (6), (8), and (11)]. Even when the rate-determining step is preceded by equilibration, effects of this type must be expected in the overall isotope effect[4]. Consequently, deuterium isotope effects of 6 or more are seldom attained (see Table 3 and [99, 100]).

The isotope effect of $K_m$ is often higher than that expected for equilibrium constants, even when it is known that $K_m$ actually does have the significance of a dissociation constant $K_s$. For this case *Mahler*[92] and *Shiner*[50] believe that there must be interaction between

[99] *J. F. Thomson* and *F. J. Klipfel*, Biochem. biophysica Acta *44*, 72 (1960).

[100] *P. Strittmatter*, J. biol. Chemistry *237*, 3250 (1962).

the enzyme and the isotope-substituted bond already during binding of the substrate to the enzyme. This interaction also explains the large isotope effects of $K_m$ found when the substrate contains an isotope-substituted bond that does not take part in the overall reaction, *e.g.* the 4-B position of NADH for A-specific enzymes [50,93,94, *].

An interaction between the substrate and the enzyme during the binding of the substrate is also indicated by the hydrogen exchange brought about in dihydroxyacetone phosphate by aldolase even in the absence of an acceptor [94b].

There are several examples of greater affinity of the deuterated substrate for the enzyme ($K_m/K'_m > 1$) (see Table 3). Lower affinity of the deuterated substrate has also been confirmed by stronger inhibition of the deuterated substrate by a competitive inhibitor [95].

While the isotope effect of $K_m$ can provide information about the binding of the substrate, and hence about the active site of the enzyme, the isotope effect *per se* can be used as evidence of changes in the active site. A good example is found in native and carboxypeptidase-treated aldolase [101]. While the native enzyme showed no isotope effect in the synthesis with labeled triose phosphates, a deuterium isotope effect of 6 and a tritium isotope effect of 20 were found for the treated enzyme [101].

## 3. Specific Examples

The examples described here are arranged in accordance with the enzyme list [98]. The importance of the isotope effect for the elucidation of enzyme mechanisms can be shown *inter alia* for the participation of an enzyme in a coupled system, stereospecificity of a Caabd molecule, intramolecular proton shift, and cleavage of a molecule into identical fragments.

### a) Hydrogen Isotope Effect

Measurements of the isotope effect in the alcohol dehydrogenase (yeast) reaction with [4-D]-NADH (chemically and enzymatically reduced) and [1,1-$D_2$]-ethanol have been reported [50,91,92,102]. The authors assume that the rate-determining step is the transformation of the ternary complex

$$ECoSH \underset{k_-}{\overset{k_+}{\rightleftharpoons}} ECoHS$$

the isotope effect of which is $k_+/k'_+ = k_-/k'_- = 1.75$ (Table 3).

This small isotope effect can be explained by only a partial rupture of the hydrogen bond in the transition state of the complex. Such loosening is in agreement with the unexpectedly high isotope effect of the substrate dissociation constants, which is explained by an interaction between the enzyme and the C—H bond involved in the hydrogen transfer. According to *Silverstein* and *Boyer* [103], the cleavage of the NAD or NADH product is the rate-determining step. In this case the above assignment of the isotope effect to the kinetic constants would be invalid. *Müller-Hill* and *Wallenfels* [104] concluded from the temperature dependence of the reaction that the first of these mechanisms applies below 20 °C, and the second above 20 °C.

We have studied the temperature dependence of the isotope effect of [1-T]ethanol and [A-4-T]NADH as substrates of alcohol dehydrogenase (from yeast) [105, 105a]. The increase in the isotope effect with rising temperature (Table 4) can be explained by a change in the rate-determining step.

Since alcohol dehydrogenase of yeast also catalyses the oxidation of the homologues of ethanol at comparable rates, we were able to use this enzyme to study the influence of various substrates on the isotope effect in an enzyme reaction [105] (see Table 4). The increase in the isotope effect from ethanol to propanol is much greater than the accompanying change in the reaction rate, which is only 34% [106].

Table 4. Comparison of the isotope effects ($k_H/k_T$) in the reaction of some alcohols with alcohol dehydrogenase (yeast) under various conditions [105].

| Conditions | [1-T]Ethanol [a] | [1-T]Propanol [a] | [1-T]Butanol [a] |
|---|---|---|---|
| pH 7.6<br>15 °C | 3.3 ± 0.1 | 6.4 ± 0.05 | 6.8 ± 0.2 |
| pH 7.6<br>25 °C | 4.1 ± 0.05 | 6.7 ± 0.2 | 6.8 ± 0.2 |

[a] Mixture of the two stereoisomers. With tracer amounts of the tritiated substance, there is no appreciable double labeling, so that there is no need to use stereospecifically labeled substrates when the isotope effect is measured on the [A-4-T]-NADH formed.

For the alcohol dehydrogenase of liver [91], an iterative method was used to find the 13 kinetic constants from the 12 independent equations obtained for the forward and reverse reactions. Isotope effects could then be calculated for each step of a complex mechanism. In addition to the values in Table 3, $k_H/k_D = 2.28$ was obtained for the hydrogen transfer from $CH_3CH_2OH$ to $NAD^+$, and $k_H/k_D = 3.11$ for the transfer from [A-4-D]NADH to $CH_3CHO$.

In the determination of the isotope effect of [A-4-T]-NADH in the alcohol dehydrogenase reaction with acetaldehyde, propionaldehyde, or butyraldehyde, a substrate dependence is observed with the enzyme from yeast [105a], but not with that from liver [105b]. This confirms that the rate-determining step in the reaction of the liver enzyme depends on the dissociation of the enzyme.

[*] $NAD^+$ ($NADP^+$) = nicotinamide adenine nucleotide (phosphate); NAD (NADPH) = reduced forms of $NAD^+$ and $NADP^+$; [A-4-D]NADH: in the nicotinamide portion of NADH, the 4-position facing forward when the atoms are numbered 1 to 6 in the anticlockwise direction is now labeled, *i.e.* [4*R*-4-D]-NADH [100a]. Similarly, [B-4-D]NADH is [4*S*-4-D]NADH. Depending on the stereospecificity of the hydrogen transfer, enzymes that transfer hydrogen to the A position of NADH are known as A-enzymes, and substrates of the type CHHbd are divided into A- and B-substrates.


[100a] *J. W. Cornforth, G. Ryback, G. Popjak, C. Donninger,* and *G. Schroepfer jr.*, Biochem. biophysic. Res. Commun. *9*, 371 (1962).

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[105a] *D. Palm*, Z. Naturforsch. *21b*, 547 (1966).

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[106] *J. van Eys* and *N. O. Kaplan*, J. Amer. chem. Soc. *79*, 2782 (1957).

*Thomson* [92,93a] studied isotope effects of [A-4-D]NADH and [B-4-D]NADH in the lactate dehydrogenase reaction. [B-4-D]NADH gives an inverse isotope effect in relation to the normal isotope effect of V due to [A-4-D]NADH (Table 3); this points at least to the interaction of both hydrogens in position 4 of the NADH with the enzyme in the course of the reaction.

From the isotope effect of the NADP-dependent glucose 6-phosphate dehydrogenase, it was possible to determine the rate-determining step for the formation of $CO_2$ from glucose in whole cells. This is a C–H cleavage, either during the H transfer from glucose to NADP or during the reoxidation of the NADP. The same was found for tumor cells [107].

Whereas various substrates have been studied with the one enzyme alcohol dehydrogenase, *Aebi* [108] has carried out comparative measurements with one substrate (formate) and various enzymes (Table 3).

The succinate dehydrogenase reaction on deuterated succinic acid is a classic example of enzymatic isotope effects [109]. With perdeuterated substrates, it was later found that $V/V' = 5.9$ [99]. However, secondary isotope effects must also be taken into account in the case of the [$D_4$]succinate. As a substrate of the respiratory chain, [$D_4$]succinate has no retarding effect on the oxidative phosphorylation.

The elucidation of a stereospecific reaction was achieved by *Belleau* [110] for the enzymatic decarboxylation of amino acids to amines and the dehydrogenation of the latter. The two enantiomeric [1-D]tyramines were prepared, and their isotope effects in the monoamine-oxidase reaction with the decarboxylation product obtained from tyrosine in $D_2O$ were compared.

An isotope effect was expected in the dehydration of malate (fumarase reaction), but none was found [111]. Since the rupture of the stereospecifically labeled carbon-hydrogen bond is not rate-determining, one must postulate a mechanism involving a malate-X complex that is as yet unknown.

$$\text{malate} + \text{E} \overset{\text{slow}}{\rightleftharpoons} \text{malate-E} \rightleftharpoons \text{malate-X} \rightleftharpoons \text{E–fumarate} \rightleftharpoons \text{E} + \text{fumarate}$$

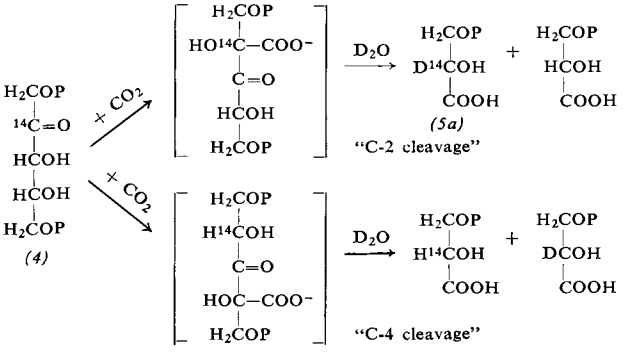
In the racemization of [2-D]lactate by an extract from *Clostridium butylicum*, an isotope effect of ${}_{\text{H}}k/k_{\text{D}} = 2.14$ was observed for both enantiomers. The fact that no deuterium was lost as a result of the racemization was shown by the fact that the rate of dehydrogenation by the lactate dehydrogenase both for the D- and for the L-form corresponded exactly to that of the deuterated lactic acids [111a].

Measurement of the deuterium isotope effect in the hexose isomerase reaction of [1-$^{14}$C-2-D]glucose 6-phosphate showed the occurrence of an intramolecular proton transfer [112]. In the substrate-enzyme complex, about 50% of the hydrogen is transferred as protons from C-2 into position 1 of the substrate (and *vice versa*) without exchange with the solvent.

An isotope effect of 2 was found for deuterium (about 3.2 for tritium) in both directions in the isomerase reaction. A similar isotope effect was found [113] for the triose phosphate isomerase. [3-D]1,3-Dihydroxyacetone-1-phosphate reacts 2.2 times more slowly than the unsubstituted substrate.

In the epimerization of uridine diphosphate galactose and glucose by an enzyme from yeast, an inverse isotope effect of $k_{\text{H}}/k_{\text{T}} = 0.66$ to 0.33 was found for the [4-T]labeled hexoses [113a]. The direction and magnitude of this isotope effect are in agreement with a mechanism in which the first step is a reversible hydrogen transfer from C-4 to the enzyme. Inverse isotope effects also have been found for an equilibrium of this type in the case of alcohol dehydrogenase (Table 3). This indicates a rearrangement of the enzyme complex, the hydrogen taking up the appropriate position for transfer to the epimeric position of the hexose. From the magnitude of the equilibrium isotope effect it is concluded that C, N, or O atoms are involved in the hydrogen transfer, and the participation of S can be excluded.

An interesting application of deuterium and tritium isotope effects was demonstrated [114,115] in the elucidation of various steps in the ribulose diphosphate carb-

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oxylase reaction (carboxydismutase). The object was to find whether the $CO_2$ is attached to C-2 or C-4 of the ribulose diphosphate *(4)* before cleavage into two molecules of 3-phosphoglyceric acid *(5)*. An intramolecularly doubly labeled [2-$^{14}$C-2-D]phosphoglyceric acid *(5a)* can be formed as well as the unlabeled acid only if the $CO_2$ is attached to C-2. Since the [$^{14}$C]glycolic acid obtained from the phosphoglyceric acid exhibited an isotope effect of 2.5 on oxidation with glycolic acid oxidase, this glycolic acid must have contained D as well as $^{14}$C, *i.e.* the $CO_2$ is attached to C-2 in *(4)*. 3-Tritiated *(4)* reacts four to six times more slowly than the H compound in the carboxylation at pH 8.1 and 25 °C. The release of the proton appears to be the limiting step of the overall reaction [115].

In the irreversible formation of a C–H bond by proton abstraction from a solvent in which the hydrogen is partially labeled, a much smaller content of the higher hydrogen isotopes is usually found in the product than in the solvent. This is a result of the isotope effect in the cleavage of an X–H bond, where X may be O, S, N, *etc.* A typical example, which has been studied both experimentally and theoretically, is the hydration of isobutylene in acidic media [121]. When this reaction is carried out in $H_2O/D_2O$ mixtures, the concentration of D in the t-butyl alcohol formed is 3.9 times lower than that in the water; the ratio for T is 7.1, and that for T in $D_2O$ is 1.9.

Corresponding biochemical examples are: In the enzymatic cleavage of citrate in HOT, T is incorporated into acetyl CoA. Hydrogen is incorporated preferentially, in the ratio $k_H/k_T = 6.7$ [122]. In the cleavage of *threo*-$D_S$-isocitrate to succinate and glyoxylate, an isotope effect of $k_H/k_T = 6.5$ to 13.9 is found, depending on the isocitrate concentration ($2\times10^{-3}$ to $4\times10^{-3}$ M), when the reaction is carried out in a buffer solution containing tritium [123]. In the cleavage of phosphoenol pyruvate by pyruvate kinase in HOT, T is incorporated with an isotope effect $k_H/k_T$ of 6.4 [124].

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### b) Isotope Effects of Carbon

*Lynn* and *Yankwich* [97] studied the isotope effect of the urease reaction (with urea having the natural $^{12}$C/$^{13}$C ratio) as a function of conversion, concentration, buffer, temperature, pH, and aging of the enzyme, and found a maximum value of 2.3%. The differences of the isotope effects found for various enzyme preparations were in some cases larger than the differences found for the above variables. The isotope effect of 5 to 10% found by other authors could not be confirmed.

A $^{14}$C isotope effect of an unusual magnitude was found [119] for the enzymatic oxidation of [$^{14}$C]formate by formic acid dehydrogenase. The value of 1.27 at 37 °C was independent of the substrate activity, which varied between 0.8 and 100 μCi/mmole.

The decarboxylation of oxalacetate to pyruvate by an enzyme from *Micrococcus lysodeikticus* shows no isotope effect with the $^{13}$C-labeled substrate. The Mn(II)-catalysed, non-enzymatic decarboxylation, on the other hand, gives an isotope effect of 1.06; solvent isotope effects in $D_2O$ indicate that the limiting step is not the actual decarboxylation [120].

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# Progress in the Chemistry of Allene

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*Considerable progress has been made in the past decade in the preparation and chemistry of allene. The present article is a critical review of this progress, and shows that owing to the particular structure of allene (two double bonds situated in mutually perpendicular planes), the chemistry of this compound is unique in many respects.*

## I. Introduction

The chemistry of acetylene and of butadiene, *i.e.* the smallest hydrocarbons containing a triple bond and two conjugated double bonds respectively, has been well known for a number of years, and both compounds are used as raw materials for huge industries [1]. On the other hand allene, *i.e.* the parent compound of the cumulenes, has found hardly any industrial use, and its chemistry, unlike that of acetylene and of butadiene, remained underdeveloped for a long time. Thus even a few years ago, little was known about such fundamental

[1] See, *e.g.*, *W. Reppe*: Neue Entwicklungen auf dem Gebiet der Chemie des Acetylens und Kohlenoxids. Springer, Heidelberg 1949; *Y. Mayor*, Ind. Petrole *32*, 62 (1964); *I. Kirshenbaum* and *R. P. Cahn* in: Encyclopedia of Chemical Technology. Interscience, New York 1964, Vol. III, p. 784.

aspects as the behavior of allene in free-radical reactions, the course of ionic additions, or the chemistry of organometallic compounds of allene.

This lack of interest is explained by the fact that for a long time no practically useful synthesis of allene was known, and the compound was regarded as a laboratory curiosity. However, modern petroleum chemistry has led to the development of economical processes for the synthesis of allene from petroleum fractions [2]. This, in turn, appears to have resulted in a growing interest in the chemistry of allene.

It was accepted for a long time that since the double bonds in allene are situated in mutually perpendicular planes, they react independently of each other, *i.e.* that allene may be regarded as a diene with isolated double bonds. However, the data available today show that this picture is oversimplified. Allene, which consists of two $sp^2$-hybridized carbon atoms and one sp-hybridized carbon atom, exhibits a combination of olefinic and acetylenic character. Thus a number of reactions of allene, such as its ease of hydration or its electrophilically induced cyclodimerization, are reminiscent of the behavior of acetylenes.

However, allene also differs from its own higher homologues. A typical example is the free-radical addition of thiols, which in the case of allene *(1)* proceeds predominantly by attack on one of the terminal carbon atoms, whereas in the case of 1,1-dimethylallene *(2)*, attack takes place preferentially at the central carbon atom [3,4].

$$H_2C{=}C{=}CH_2 + RSH \rightarrow RS\text{-}CH_2\text{-}CH{=}CH_2$$

*(1)*

$$\begin{matrix} H_3C \\ \diagdown \\ \quad C{=}C{=}CH_2 \\ \diagup \\ H_3C \end{matrix} + RSH \rightarrow \begin{matrix} H_3C \quad SR \\ \diagdown \quad | \\ \quad CH\text{-}C{=}CH_2 \\ \diagup \\ H_3C \end{matrix}$$

*(2)*

It follows that reactions observed with allene cannot be arbitrarily transposed to its homologues and that the validity of such generalizations must therefore always be checked experimentally. The present review is therefore confined to the chemistry of allene itself, in contrast to earlier reports on allenic hydrocarbons, which did not make such a clear distinction between the parent compound and its homologues [5].

## II. Synthesis and Occurrence of Allene

Most of the syntheses described below lead to mixtures of allene and its isomer, methylacetylene. These compounds exist in equilibrium with each other. At 300 °C in the gas phase, the equilibrium mixture consists of about 20% of allene and about 80% of methylacetylene [6].

$$H_2C{=}C{=}CH_2 \rightleftharpoons H_3C\text{-}C{\equiv}CH$$

However, this isomerization takes place only in the presence of catalysts. In the absence of catalysts allene is stable up to 400 °C [6]. Active charcoal is the most effective and most selective catalyst [7], whereas other substances, such as $Al_2O_3$ or $SiO_2$, lead to undesirable side reactions [6]. The use of active charcoal in combination with distillation at a low temperature or above atmospheric pressure is suitable for the quantitative conversion of allene into methylacetylene, and *vice versa* [7].

### A. Formation of Allene in Cracking Processes

Allene and methylacetylene are formed in a number of cracking processes, particularly in steam cracking, and are present to the extent of 1 to 1.5% in propylene obtained by the cracking of hydrocarbons [8]. The high consumption of propylene presents the possibility of the production of considerable quantities of allene. At present, however, the two isomers are usually removed from propylene by hydrogenation [8], and it is not clear whether this is due to lack of interest in allene or to lack of a separation process. Considerably better yields of allene are obtained in the cracking of pure hydrocarbons, *e.g.* propylene or isobutylene.

#### 1. Cracking of Propylene

The course of the pyrolysis of propylene is strongly dependent on the temperature and pressure. At high temperatures (above 750 °C) and reduced pressure, the reaction leads mainly to allene and methylacetylene, whereas at low temperatures and higher pressures, polymers are the main products [9]. These and similar earlier observations [10–13] were recently explained by the intermediate formation of allyl radicals *(3)*, which, depending on the reaction conditions, either lose hydrogen to form allene or add to the double bond of propylene to form oligomers and polymers [9].

$$H_3C\text{-}CH{=}CH_2 \xrightarrow{\Delta} \cdot CH_2\text{-}CH{=}CH_2 \quad (3) \quad \begin{cases} \rightarrow H_2C{=}C{=}CH_2 + H\cdot \\ \xrightarrow{+H_3C\text{-}CH{=}CH_2} \text{Polymers} \end{cases}$$

[2] Stabilized gas mixtures containing up to 60% of allene and methylacetylene (MAPP-Gas®) are marketed in the USA by the Dow Chemical Co. as a cutting and welding gas. See: *J. D. Hembree, R. W. Belfit, H. A. Reeves*, and *J. P. Baughman*, Welding Journal, *42*, 395 (1963); Iron Steel Eng. *41*, (5), 153 (1964).

[3] *T. L. Jacobs* and *G. E. Illingworth Jr.*, J. org. Chemistry *28*, 2692 (1963).

[4] A similar reversal of orientation has been observed in the ionic addition of HCl to allene and 1,1-dimethylallene (see [81]) and in the hydroboration of allene [125, 126] and 2,3-nonadiene [129].

[5] For a recent example, see *A. A. Petrov* and *A. V. Fedorova*, Usp. Chim. *33*, 3 (1964).

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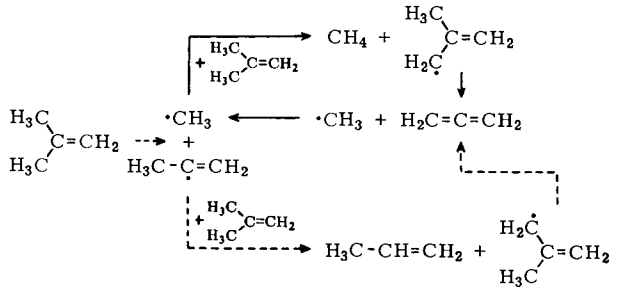
## 2. Cracking of Isobutylene

The preparation of allene by the pyrolysis of isobutylene has been known for some years [14], and several variants, such as steam cracking [15], cracking in the presence of inert diluent gases [16], or catalytic cracking [17], have been described. The course of the reaction again depends on pressure, temperature, and contact time. However, it can be directed to yield up to 60% of an allene/methylacetylene mixture [18]. The formation of methane and propylene as the principal by-products is understandable on the basis of Scheme 1.

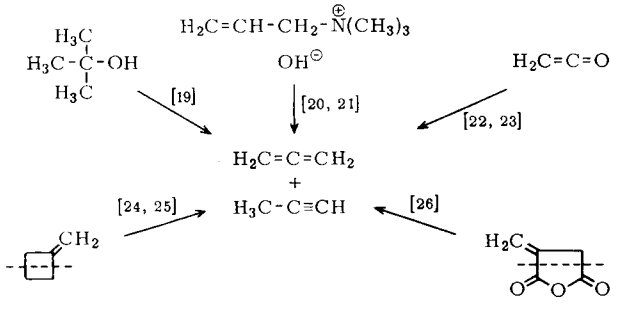


Scheme 1. Reaction steps in the pyrolysis of isobutylene.

Under conditions favoring long free-radical chains (full arrows), the reaction proceeds *via* methyl and methallyl radicals and yields methane as principal by-product. If the free-radical chain is shorter (broken arrows), the reaction *via* the 2-propenyl radical predominates. Since, in this case, half of the isobutylene is converted into propylene the conditions must be chosen such as to suppress the reaction by this second route.

## 3. Other Cracking Reactions

Allene and methylacetylene are formed also in other cracking reactions. Some typical examples are shown in Scheme 2.



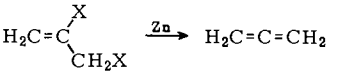
Scheme 2. Formation of allene and methylacetylene in cracking processes.

In most cases the starting material already contains the $C_3$ skeleton of allene, and the reactions are self-explanatory. An exception is the formation of allene in the pyrolysis of ketene, which contains only two carbon atoms.

### B. Formation of Allene from $C_3$ Halides

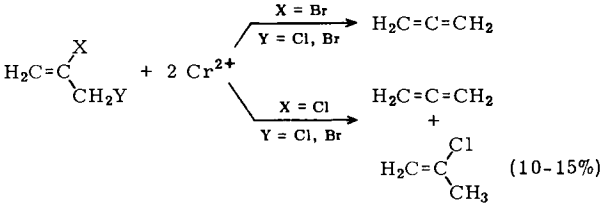
## 1. Dehalogenation of Vicinal $C_3$ Dihalides

Allene was first prepared by the debromination of 2,3-dibromopropene [27], and later by the dechlorination of 2,3-dichloropropene [28] with zinc dust in alcohol:



Both these methods have the disadvantage that the corresponding 2-halopropenes are also formed, and cannot be completely separated. This difficulty is avoided if the reaction is carried out in butyl or isoamyl acetate [29].

It was reported recently that chromium(II) sulfate is a suitable agent for the conversion of 2,3-dihalopropenes into allene [30]. To obtain optimum yields, it is necessary to use a starting material that contains a bromine (not chlorine) atom in the 2 position, and care must be taken to ensure that the allene formed is not reduced to propylene by excess of chromium(II) sulfate.



## 2. Reduction of Monohalides

The reduction of propargyl *(4)* or allenyl bromides *(5)* with zinc/copper leads to a 2:1 mixture of allene and methylacetylene [31].

[14] *F. O. Rice* and *L. A. Wall*, J. Amer. chem. Soc. *72*, 3967 (1950) and literature cited there: *F. O. Rice*, U.S.-Pat. 2429566 (1947); Chem. Abstr. *42*, 749 (1948).

[15] *J. Happel* and *C. J. Marsel*, U.S.-Pat. 2763703 (1956); Chem. Abstr. *51*, 8775 (1957).

[16] *H. G. Peer* and *O. E. Van Lohuizen*, Brit. Pat. 875195 (1959); Chem. Abstr. *56*, 8559 (1962).

[17] *J. Happel*, *H. Hudson*, and *C. J. Marsel*, U.S.-Pat. 3198848 (1965); Chem. Abstr. *63*, 13073 (1965).

[18] *F. O. Rice* and *W. S. Haynes*, J. Amer. chem. Soc. *70*, 964 (1948).

[19] *J. Happel* and *C. J. Marsel*, U.S.-Pat. 2752405 (1956); Chem. Abstr. *51*, 2015 (1957); U.S.-Pat. 2719872 (1955); Chem. Abstr. *50*, 7841 (1956).

[20] *R. Lukes* and *J. Trojanek*, Collect. czechoslov. chem. Commun. *14*, 688 (1949).

[21] *D. R. Howton*, J. org. Chemistry *14*, 1 (1949).

[22] *J. T. Fitzpatrick*, J. Amer. chem. Soc. *69*, 2236 (1947).

[23] *W. G. Guenther* and *W. D. Walters*, J. Amer. chem. Soc. *81*, 1310 (1959).

[24] *J. P. Chesick*, J. physic. Chem. *65*, 2170 (1961).

[25] *R. L. Brandauer*, *B. Short*, and *M. E. Kellner*, J. phys. Chem. *65*, 2269 (1961).

[26] *F. O. Rice* and *M. T. Murphy*, J. Amer. chem. Soc. *64*, 896 (1942).

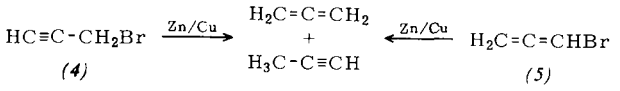
[27] *G. G. Gustavson*, Ž. russ. fiz.-chim. obšč. *20*, 615 (1888).

[28] Organic Syntheses *42*, 12.

[29] *Ya. M. Slobodin* and *A. P. Khitrov*, Ž. obšč. Chim. *31*, 3945 (1961).

[30] *W. C. Kray* and *C. E. Castro*, J. Amer. chem. Soc. *86*, 4603 (1964).

[31] *T. L. Jacobs*, *E. G. Teach*, and *D. Weiss*, J. Amer. chem. Soc. *77*, 6254 (1955).

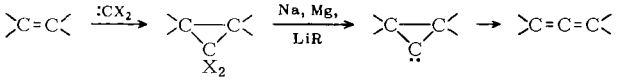


*(4)* *(5)*

The reduction of propargyl bromide *(4)* with magnesium *via* an intermediate Grignard compound also can be used for the synthesis of allene in the laboratory [32].

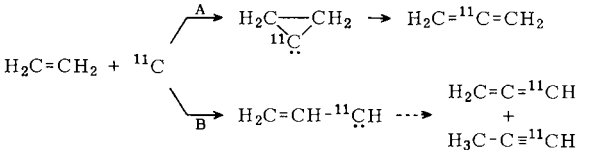
### C. Formation of Allene Via Intermediates Containing Bivalent Carbon (Cyclopropylidene)

After the discovery that halocarbenes can add to olefins to form geminal dihalocyclopropanes *(6)* [33], several substituted allenes were prepared by this reaction [34–37].

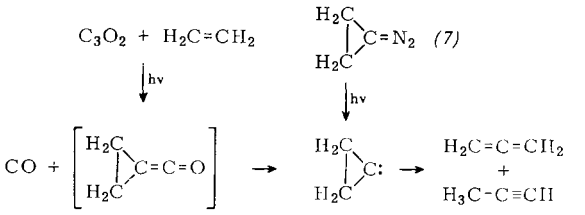


*(6)*

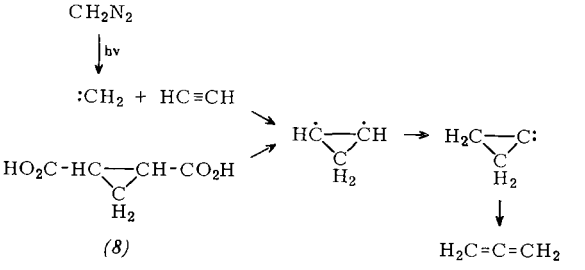
While this reaction has never been used for the synthesis of allene itself, the underlying principle of the insertion of carbon into a double bond has been utilized in a number of other reactions leading to allene. The direct routes, *i.e.* the insertion of atomic carbon into ethylene, has recently been studied thoroughly [38–42]. It was found with the aid of $^{11}C$ that this reaction proceeds mainly by insertion of a carbon atom into the $\pi$ bond (route A), and that insertion into a C–H bond (route B) occurs only to a minor extent.



Probably the same type of reaction is responsible for the formation of allene during photolysis of carbon suboxide, $C_3O_2$, in the presence of ethylene [43,44] and during that of diazocyclopropane *(7)* [45].



Allene (instead of cyclopropene) is obtained also in the reaction of methylene with acetylene, irrespective of whether the reaction is carried out in the gas phase [46] or in a solid argon matrix [47]. The mechanism proposed for this reaction could also explain the earlier observation that allene is formed in the Kolbe electrolysis of *cis*-cyclopropane-1,2-dicarboxylic acid *(8)* [48].



*(8)*

Allene is formed in many other reactions. However, since these do not represent a general synthetic principle (with the possible exception of the hydrolysis of carbides such as magnesium carbide [49] or calcium carbide [50]), they will not be discussed further.

### D. Deuterated Allenes

All the possible deuterated forms of allene, *i.e.* [D]-, [1,1-$D_2$]-, [1,3-$D_2$]-, [$D_3$]-, and [$D_4$]allene, have recently been synthesized and characterized [51]. They were all prepared by the dehalogenation of suitable halides with zinc.

## III. Physical Properties of Allene

Allene can be dangerous in the gaseous state (b.p. −34.5 °C), since its vapor can decompose exothermically and propagate a flame even in the absence of oxygen [52].

The classical physical data for allene are given elsewhere [5,53], and the present review will deal only with

[32] *M. Gaudemar*, Ann. Chimie (13) *1*, 161 (1956).

[33] *W. v. E. Doering* and *A. K. Hoffmann*, J. Amer. chem. Soc. *76*, 6162 (1954).

[34] *W. v. E. Doering* and *P. M. LaFlamme*, Tetrahedron *2*, 75 (1958).

[35] *W. R. Moore* and *H. R. Ward*, J. org. Chemistry *27*, 4179 (1962).

[36] *L. Skattebol*, Acta chem. scand. *17*, 1683 (1963).

[37] *T. J. Logan*, Tetrahedron Letters *1961*, No. 5, p. 173.

[38] *C. MacKay*, *P. Polak*, *H. E. Rosenberg*, and *R. Wolfgang*, J. Amer. chem. Soc. *84*, 308 (1962).

[39] *M. Marshall*, *R. Wolfgang*, and *C. MacKay*, Tetrahedron Letters *1963*, 2033.

[40] *M. Marshall*, *C. MacKay*, and *R. Wolfgang*, J. Amer. chem. Soc. *86*, 4741 (1964).

[41] *J. Dubrin*, *C. MacKay*, and *R. Wolfgang*, J. Amer. chem. Soc. *86*, 4747 (1964).

[42] *J. Nicholas*, *C. MacKay*, and *R. Wolfgang*, J. Amer. chem. Soc. *88*, 1610 (1966).

[43] *K. D. Bayes*, J. Amer. chem. Soc. *83*, 3712 (1961).

[44] *K. D. Bayes*, J. Amer. chem. Soc. *84*, 4077 (1962); *85*, 1730 (1963).

[45] *H. Shechter*, Abstracts of papers presented at the 141st meeting of the American Chemical Society, Washington, D. C., 1962, p. 15–O

[46] *H. M. Frey*, Chem. and Ind. *1960*, 1266

[47] *M. E. Jacox* and *D. E. Milligan*, J. Amer. chem. Soc. *85*, 278 (1963).

[48] *F. Fichter* and *H. Spiegelberg*, Helv. chim. Acta *12*, 1152 (1929).

[49] *J. F. Cordes*, *H. Luedemann*, and *K. Wintersberger*, Z. Naturforsch. *15b*, 677 (1960).

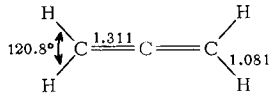
[50] *J. deVillelume*, Ann. Chimie 7, 265 (1952).

[51] *A. T. Morse* and *L. C. Leitch*, J. org. Chemistry *23*, 990 (1958).

[52] *J. M. Kuchta*, *I. Spolan*, and *M. G. Zabetakis*, J. chem. Engng. Data *9*, 467 (1964).

[53] See *e.g.* Beilstein: Organische Chemie. Springer, Heidelberg 1958, Vol. E III 1, p. 922.

more recent, mainly spectroscopic studies. Several papers have been concerned with the NMR spectrum of allene [54–56]. The IR spectra of gaseous and liquid allene and of a single crystal of allene have been recorded, and all the absorption bands have been assigned [57,58]. The Raman spectrum has also been studied in detail [58b,59]. Electron diffraction studies of gaseous allene gave the following parameters [60]:




The melting curve of allene between 0 and 9 kbar has recently been determined [61].

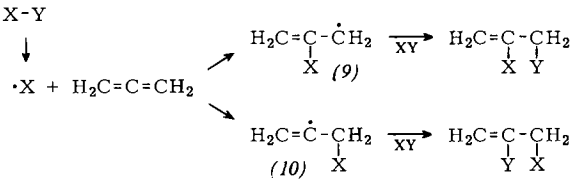
## IV. Reactions of Allene

### A. Additions to Allene

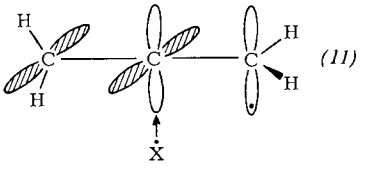
Addition reactions to allene were reported at the time of its first preparation [62] and soon afterwards [63], but only recently have such reactions been studied systematically. It was not until 1954 that the first definitely free-radical addition was described [64], and a number of entirely new aspects of electrophilic additions were discovered only two years ago [65].

#### 1. Free-Radical Additions

According to the classical views on free-radical additions, the mechanism of such a reaction of allene should depend on the point of attack of the chain-initiating radical. In the case of unsymmetrically substituted olefins, the preferred route is generally that involving the more stable of the possible free-radical intermediates [66]. It was therefore expected that free-radical attack on the center carbon atom of the allene molecule would be favored, since a resonance-stabilized allyl radical *(9)* can then be formulated as the intermediate, whereas terminal attack leads to a vinyl radical *(10)*.




In view of the special geometry of the allene molecule, however, these considerations are undoubtedly oversimplified. The radical *(11)* formed by attack on the center carbon atom resembles a radical on a primary carbon rather than an allyl radical, since the orbital of the odd electron does not overlap with the π-orbitals of the remaining double bond. This complication could increase the activation energy for an attack on the center carbon atom, and thus indirectly favor terminal attack. In other words, the course of such reactions cannot be predicted *a priori*.




*(11)*

During the past ten years, several free-radical additions to allene have been studied. The selectivities observed range from 100% terminal attack to 100% attack on the center carbon atom, depending on the nature of the compound added (Table 1) and on the reaction conditions.

Table 1. Selectivities of free-radical additions to allene.

| Reagent | Attacking radical | Attack on terminal C atom (%) | Attack on central C atom (%) | Ref. |
|---|---|---|---|---|
| $CF_3I$ | $CF_3$· | 100 | 0 | [64] |
| $H_2S$ | HS· | >95 | <5 | [67] |
| RSH | RS· | 80–95 [a] | 5–20 [a] | [3, 68] |
| $(CH_3)_3SnH$ | $(CH_3)_3Sn$· | 55 | 45 | [69] |
| HBr | Br· | 0–48 [b] | 52–100 [b] | [70–72] |

[a] Depends on the nature of R.

[b] Depends on the reaction temperature; low temperatures favor attack on the terminal C atom.


[54] *E. B. Whipple, J. E. Goldstein,* and *W. E. Stewart,* J. Amer. chem. Soc. *81,* 4761 (1959).

[55] *M. Karplus,* J. Amer. chem. Soc. *82,* 4431 (1960); J. chem. Physics *33,* 1842 (1960).

[56] *J. H. Goldstein* and *G. S. Reddy,* J. chem. Physics *36,* 2644 (1962).

[57] *J. Blanc, C. Brecher,* and *R. S. Halford,* J. chem. Physics *36,* 2654 (1962).

[58] For further IR investigations on allene, see a) *R. H. Pierson, A. N. Fletcher,* and *E. St. Clair Gantz,* Analytic. Chem. *28,* 1218 (1956); b) *M. G. Borisov* and *L. M. Sverdlov,* Optika i Spektroskopiya *15* (1), 37 (1963); c) *W. J. Jones* and *W. J. Orville-Thomas,* Proceedings of the 4th International Meeting on Molecular Spectroscopy, Bologna 1959. Pergamon Press, Oxford and New York (1962) *1,* 305; d) *A. G. Maki* and *R. A. Toth,* J. molecular Spectroscopy *17,* 136 (1965).

[59] *S. Brodersen* and *E. H. Richardson,* J. molecular Spectroscopy *4,* 439 (1960).

[60] *A. Almenningen, O. Bastiansen,* and *M. Traetteberg,* Acta chem. scand. *13,* 1699 (1959).

[61] *M. D. Boren, G. J. Scott,* and *S. E. Babb Jr.,* J. chem. Physics *43,* 1830 (1965).

[62] *G. Gustavson* and *N. Demjanoff,* J. prakt. Chem. (2) *38,* 202 (1888).

[63] *F. W. Smirnov,* J. Russ. Phys. Chem. Soc. *35,* 854 (1903); Chem. Zbl. *1904,* 575.

[64] *R. N. Haszeldine, K. Leedham,* and *B. R. Steele,* J. chem. Soc. (London) *1954,* 2040.

[65] *K. Griesbaum,* J. Amer. chem. Soc. *86,* 2301 (1964).

[66] *C. Walling*: Free Radicals in Solution. Wiley, New York 1957, p. 314.

[67] *K. Griesbaum, A. A. Oswald, E. R. Quiram,* and *P. E. Butler,* J. org. Chemistry *30,* 261 (1965).

[68] *K. Griesbaum, A. A. Oswald, E. R. Quiram,* and *W. Naegele,* J. org. Chemistry *28,* 1952 (1963).

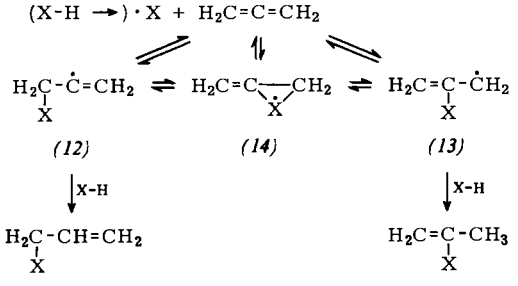
[69] *H. G. Kuivila, W. Rahman,* and *R. H. Fish,* J. Amer. chem. Soc. *87,* 2835 (1965).

[70] *D. Kovachic* and *L. C. Leitch,* Canad. J. Chem. *39,* 3636 (1961).

[71] *K. Griesbaum, A. A. Oswald,* and *D. N. Hall,* J. org. Chemistry *29,* 2404 (1964).

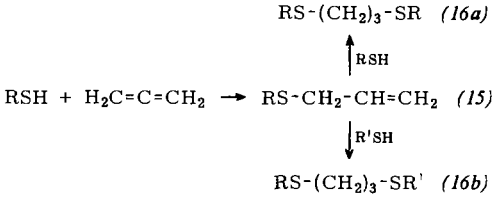
[72] *P. I. Abell* and *R. S. Anderson,* Tetrahedron Letters *1964,* 3727.

Numerous attempts have been made to explain the difference in the behavior of the various attacking reagents. It has been suggested that the point of attack may depend on the polarity of the attacking radical [73]. It was assumed that electrophilic radicals such as $\cdot CF_3$ would attack preferentially on the terminal carbon atom, while nucleophilic radicals such as $\cdot CH_3$ would tend to attack the center carbon atom. However, it can be seen from Table 1 that this assumption is not generally valid, since the nucleophilic trimethyltin radical yields only 45% of the center adduct, whereas the strongly electrophilic bromine atom gives 100% of the center adduct. It appears, therefore, that several factors are involved, *e.g.* the reversibility of the initial attack, the rate of the chain transfer, and the migratory aptitude and the steric requirements of the attacking radical. It is even possible [71], and this appears to be confirmed by more recent results [72], that the final product need not always reflect the site of the initial attack, since the radical formed first may rearrange [*e.g. (12)→(13)* or *vice versa*] before the chain transfer occurs, or it may be a bridged radical *(14)*, in which case any discussion of the point of initial attack would be meaningless.



However, whereas the orientation of free-radical additions to allene, and possibly also the cause of the orientation, may vary from one reagent to another, all these reactions appear to have certain features in common. Thus it has been repeatedly stated that allene is stable under the conditions of free-radical reactions, and does not isomerize to methylacetylene. Moreover, the reaction could generally be stopped at the monoadduct stage, provided that the monoadduct is stable under the conditions of the reaction and that allene is used in excess. Lower reaction temperatures have generally been found to give increased terminal attack and a decrease in the yield of the monoadduct, the diadduct being favored instead [68, 71].

The most thoroughly studied and most widely used of these reactions is the free-radical addition of thiol compounds, in the widest sense, to allene [3, 67, 68, 74, 75]. At temperatures up to 30 °C, these reactions exhibit high selectivity (at least 80%) for terminal attack, and apart from the addition of $H_2S$ [76], they can be directed to give either the monoadducts *(15)* or the diadducts *(16)*.



The formation of diadducts has been used for the synthesis of many symmetrical [75] (Table 2) and some unsymmetrical derivatives of propane-1,3-dithiol [77], which are not so readily obtained by other methods.

Table 2. Symmetrical thiol-allene diadducts.

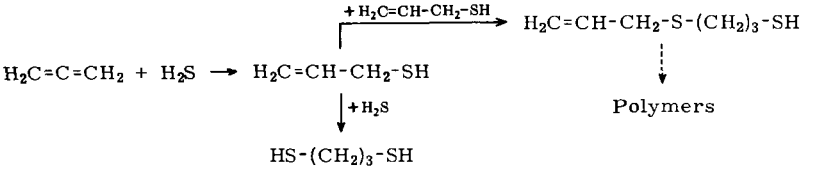
| Thiol | Diadduct | Selectivity (%) |
|---|---|---|
| $H_2S$ | $HS-(CH_2)_3-SH$ | 73 |
| $C_2H_5SH$ | $C_2H_5S-(CH_2)_3-SC_2H_5$ | 77 |
| $(CH_3)_3CSH$ | $(CH_3)_3CS-(CH_2)_3-SC(CH_3)_3$ | 80 |
| $C_6H_5CH_2SH$ | $C_6H_5CH_2S-(CH_2)_3-SCH_2C_6H_5$ | 90 |
| $C_6H_5SH$ | $C_6H_5S-(CH_2)_3-SC_6H_5$ | 57 |
| $CH_3COSH$ | $CH_3COS-(CH_2)_3-SCOCH_3$ | 90 |
| $(CH_3O)_2P(S)SH$ | $(CH_3O)_2P(S)S-(CH_2)_3-S(S)P(OCH_3)_2$ | 76 |
| $CH_3OCOCH_2SH$ | $CH_3OCOCH_2S-(CH_2)_3-SCH_2COCOCH_3$ | 95 |
| $HOCH_2CH_2SH$ | $HOCH_2CH_2S-(CH_2)_3-SCH_2CH_2OH$ | 84 |

[73] *A. P. Stefani, L. Herk,* and *M. Szwarc,* J. Amer. chem. Soc. *83*, 4732 (1961).

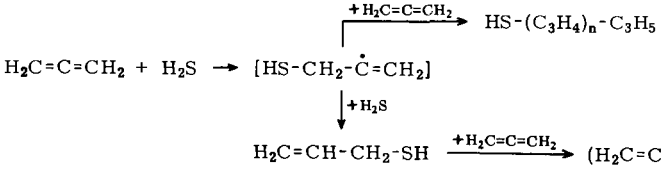
[74] *H. J. Van der Ploeg, J. Knotnerus,* and *A. F. Bickel,* Recueil Trav. chim. Pays-Bas *81*, 775 (1962).

[75] *A. A. Oswald, K. Griesbaum, D. N. Hall,* and *W. Naegele,* Preprints of Papers presented before the Division of Petroleum Chemistry, American Chemical Society Meeting, Chicago 1964, p. 29.

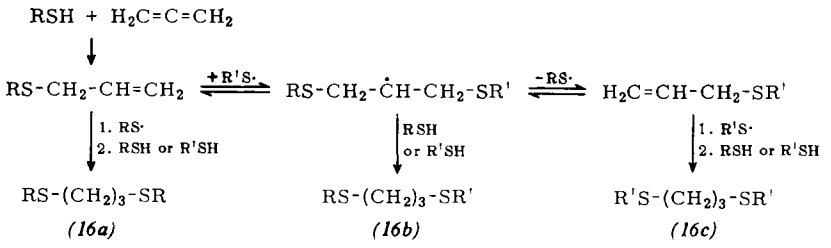
[76] The addition of $H_2S$ involves essentially two complications:
a) If $H_2S$ and allene are used in equimolar quantities, the principal side reactions are the dimerization of the initially-formed allylthiol and the further addition of $H_2S$:



b) If allene is used in excess it oligomerizes, and diallyl sulfide is also obtained:



[77] *D. N. Hall, A. A. Oswald,* and *K. Griesbaum,* J. org. Chemistry *30*, 3829 (1965).




However, while the formation of symmetrical diadducts *(16a)* normally proceeds without difficulties, the two-step addition of two different thiols is complicated sometimes by a reversal of the second addition step, in which the thiol added first is eliminated [77]. This effect leads then to three diadducts *(16a)–(16c)* instead of only the desired one *(16b)*. This difficulty can be avoided by suppression of the reversal of the second addition step (by use of the better hydrogen-releasing thiol in the second step instead of the first, or use of excess thiol, or both [77]). The success of such measures is shown in Table 3.

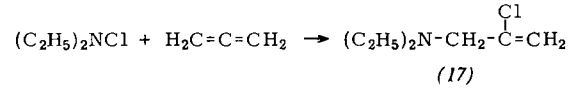
Table 3. Unsymmetrical thiol-allene diadducts.

| Starting materials | | Selectivity of formation of $RS-(CH_2)_3-SR'$ (mole-%) |
|---|---|---|
| $RS-CH_2-CH=CH_2$ R = | R'SH R' = | |
| $C_6H_5$ | $C_2H_5$ | 6 |
| $C_2H_5$ | $C_6H_5$ | 93 |
| $C_2H_5$ | $C_6H_5$ [a] | 100 |

[a] Fivefold excess.

The free-radical addition of hydrogen bromide to allene has been the subject of three recent studies [70–72]. In each case it was found that at ambient or higher temperatures, the product resulting from attack on the center carbon atom, *i.e.* 2-bromopropene, is formed with high selectivity. At lower temperatures the orientation of the addition changes, and at −80 °C the ratio of the products of center attack and terminal attack is almost 1:1 [71].

The free-radical addition of *N*-chlorodiethylamine to allene is reported to give the product *(17)* resulting from terminal attack [78]. However, the yields obtained

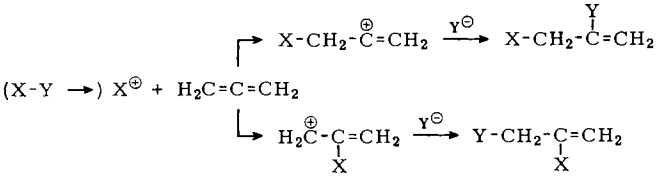



in this reaction were rather low, and the paper does not indicate whether it was ascertained that the center-attack product is not formed. The preferred course of the free-radical addition of $CCl_4$, $CCl_3Br$ [74], and $PH_3$ [79] also remains uncertain, since the yields were again very low. Although the products of terminal attack were detected in all three cases, they were evidently not the only compounds formed.

[78] *R. S. Neale*, J. Amer. chem. Soc. *86*, 5340 (1964).
[79] *H. Goldwhite*, J. chem. Soc. (London) *1965*, 3901.

## 2. Electrophilic Additions

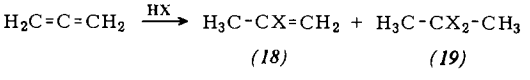
Electrophilic additions to allene can proceed in two ways (Scheme 3).



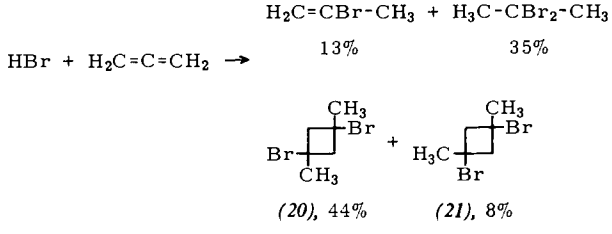

Scheme 3. Electrophilic additions to allene.

Both modes of reaction have been reported, and as in free-radical additions, the route followed appears to depend mainly on the nature of the compound being added.

Compounds of the form HX add in accordance with the Markovnikov rule. For a long time it was thought that 2-substituted propenes *(18)* and/or 2,2-disubstituted propanes *(19)* were the only products [80,81].



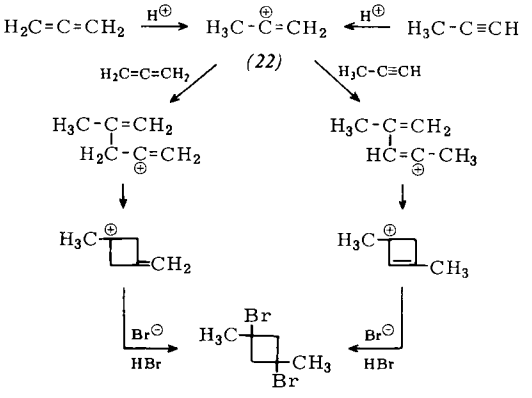

However, it was recently recognized that such reactions may be more complex. Thus in the electrophilic addition of hydrogen bromide to allene, it was found that considerable quantities of 1,3-dibromo-1,3-dimethylcyclobutane [two isomers, *(20)* and *(21)*] were formed as well as products of the type *(18)* and *(19)* [65].




Model experiments showed that these cyclic products do not result from a simple head-to-tail dimerization of 2-bromopropene. A mechanism was therefore proposed [82] for this novel electrophilically induced cyclodimerization, in which the cyclization is assumed to be

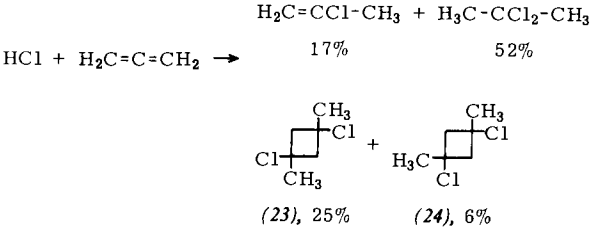
[80] *P. R. Austin*, U.S.-Pat. 2585529 (1952); Chem. Abstr. *46*, 3799 (1952).
[81] *T. L. Jacobs* and *R. N. Johnson*, J. Amer. chem. Soc. *82*, 6397 (1960).
[82] *K. Griesbaum*, Angew. Chem. *76*, 782 (1964); Angew. Chem. internat. Edit. *3*, 697 (1964).

brought about by a vinyl carbonium ion *(22)*. However, since the reaction of methylacetylene with HBr also leads to cyclodimerization [82], and since the rearrangement of allene to methylacetylene in the presence of HBr cannot be ruled out, it is not immediately possible to distinguish between the two routes given in Scheme 4.



Scheme 4. Cyclodimerization of allene and methylacetylene on addition of HBr.

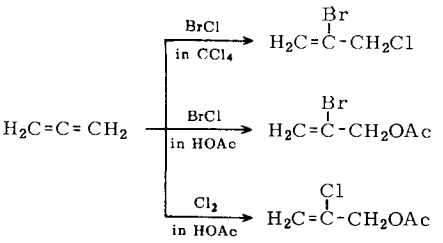
Preliminary studies of the scope of this cyclodimerization have shown that, contrary to previous results [81], considerable quantities of the cyclodimerization products *(23)* and *(24)* are also obtained in the hydrochlorination of allene [83].



No such cyclodimerization products were observed in the ionic addition of hydrogen fluoride [80], hydrogen iodide [83], phenol [84], and water [62] to allene. These reactions are all reported to lead to the conventional Markovnikov adducts. Apart from the addition of hydrogen iodide, however, all these reactions were studied before the occurrence of cyclodimerization was recognized, so that further studies will be necessary before a final conclusion can be reached. Nevertheless, all these reactions, irrespective of whether they give cyclic or linear products, evidently begin with the protonation of a terminal carbon atom.

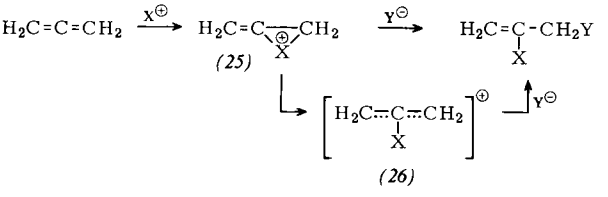
In the addition of halogens and interhalogen compounds [85], on the other hand, the opposite orientation was observed (Scheme 5).

In analogy to the bromonium complex formed in the addition of bromine to olefins [86], the first intermediate

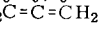


Scheme 5. Addition of halogens and interhalogen compounds to allene.

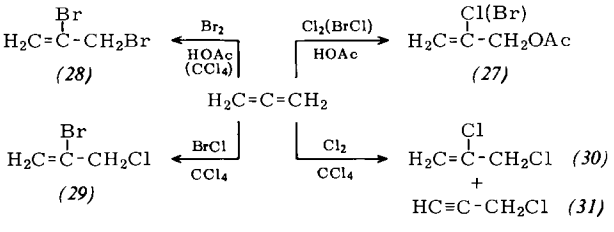
in these reactions may be a π-complex *(25)*, which rearranges to form the resonance-stabilized allyl carbonium ion *(26)*.



However, the observed orientation could also be explained by a direct attack of the nucleophile $Y^{\ominus}$ on *(25)*; in this case, the reaction on the terminal $sp^3$ carbon atom should be preferred to that on the center $sp^2$ carbon atom. It would then be unnecessary to assume the formation of the allyl carbonium ion *(26)*. In any case, the difference in orientation in the addition of HX compounds on the one hand and of $X_2$ and XY compounds on the other is understandable in view of the fact that protons cannot form bridged π-complexes with olefins [86]. The addition of HX compounds is probably influenced by the polarization of the allene molecule [5]:



All reported additions of compounds of the types $X_2$ and XY can be selectively directed so as to give the monoadduct. Sometimes, however, the nature of the adduct is strongly dependent on the solvent. For example, if the reaction is carried out in acetic acid with the chloride ion as the nucleophile, *i.e.* in the addition of $Cl_2$ or BrCl, the principal product is the haloacetate *(27)*, *i.e.* the acetate ion successfully competes with the chloride ion. This difficulty does not arise when the bromide ion is used as the nucleophile. Thus the addition of bromine to allene yields 2,3-dibromopropene *(28)*, no matter whether the reaction is carried out in acetic acid or in an inert solvent such as $CCl_4$ or $CH_2Cl_2$. The addition of BrCl in an inert solvent leads to the expected adduct *(29)*, whereas the addition of chlorine, also in an inert solvent, yields not only the adduct *(30)*, but also an equimolar quantity of the adduct *(31)*.



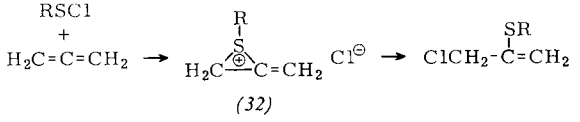
[83] *K. Griesbaum, W. Naegele,* and *G. C. Wanless,* J. Amer. chem. Soc. *87*, 3151 (1965).

[84] *H. G. Peer,* Dutch Pat. 101448 (1962); Chem. Abstr. *58*, 1404 (1963).

[85] *H. G. Peer,* Recueil Trav. chim. Pays-Bas *81*, 113 (1962).

[86] *N. C. Deno* in: Progress in Physical Organic Chemistry. Interscience, New York 1964, p. 145.

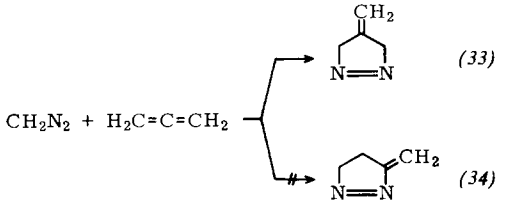
A predominantly anti-Markovnikov orientation was also observed in the addition of 2,4-dinitrophenylsulfenyl chloride [81] and in the reaction of dimethyl- [87] and diethylphosphorylsulfenyl chloride [88] with allene. Since these reactions also proceed *via* a bridged ion *(32)*, the orientation probably depends on the same factors as were indicated for the addition of halogens [89].



*(32)*

### 3. 1,3-Dipolar Additions

The only known example of this type of reaction with allene is the addition of diazomethane [90–92]; of the two possible products *(33)* and *(34)*, only the isomer *(33)* is obtained, *i.e.* the orientation is the same as in the addition of compounds of the type HX.



*(33)* *(34)*

### 4. Selective Reduction of Allene

The term "selective reduction" or "selective hydrogenation" of allene is used in the literature both for the reduction of allene to propylene and for the reductive removal of allene from mixtures of olefins without hydrogenation of the double bonds of these olefins [8,93]. Selective reduction of allene to propylene can be achieved either with chromium(II) sulfate or by catalytic hydrogenation [94]. Metals of group VIII, as well as noble metals, have been used as catalysts at relatively low hydrogen pressures and at temperatures between 20 and 120 °C. Some of these reactions are 100% selective [94].

[87] *W. H. Mueller, R. M. Rubin,* and *P. E. Butler,* J. org. Chemistry, in print.

[88] *Y. G. Gololobov, V. V. Semidetko,* and *L. Z. Soborovskii,* Russ. Pat. 166692 (1964); Chem. Abstr. *62,* 10461 (1965).

[89] The occurrence of episulfonium intermediates in such reactions was recently shown conclusively: (a) *G. H. Schmid* and *V. M. Csizmadia,* Canad. J. Chem. *44,* 1338 (1966); (b) *W. H. Mueller* and *P. E. Butler,* J. Amer. chem. Soc. *88,* 2866 (1966).

[90] *A. D'yakonov,* Ž. obšč. Chim. *1945,* 473; Chem. Abstr. *40,* 4718 (1946).

[91] *P. Dowd,* J. Amer. chem. Soc. *88,* 2587 (1966).

[92] *R. J. Crawford* and *D. M. Cameron,* J. Amer. chem. Soc. *88,* 2589 (1966).

[93] See, *e.g., M. Likins, J. F. Strotman,* and *D. O. McCarthy,* U.S.-Pat. 2946829 (1960); Chem. Abstr. *55,* 377 (1961).

[94] *G. C. Bond, G. Webb, P. E. Wells,* and *J. M. Winterbottom,* J. Catalysis *1,* 74 (1962) and literature cited there.

[95] *S. V. Lebedev,* Ž. russ. fiz.-chim. obsc. *45,* 1357 (1913).

[96] *A. T. Blomquist* and *J. A. Verdol,* J. Amer. chem. Soc. *78,* 109 (1956).

## B. Cyclization and Condensation Reactions of Allene

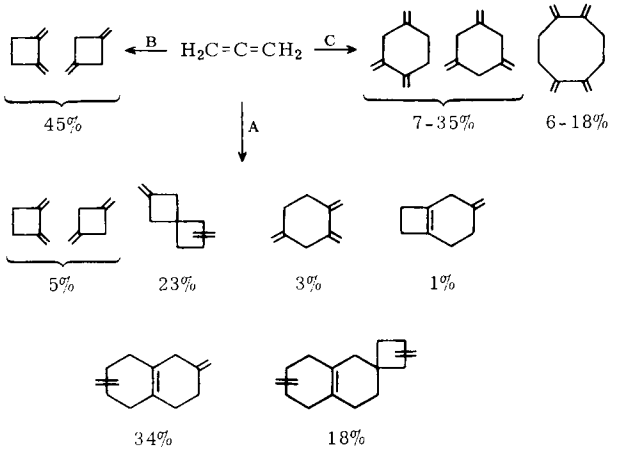
### 1. Homocyclization of Allene

The homocyclization or oligomerization of allene can be achieved by three methods: prolonged heating of liquid allene in a sealed tube at 110 to 160 °C, heating of gaseous allene at 400 to 600 °C for a short time in a flow apparatus, and cyclization in the presence of catalysts.

The oligomerization of liquid allene has been known for more than 50 years [95]. Though the impression has arisen over the years that this reaction is a convenient process for the synthesis of the allene dimer 1,2-dimethylenecyclobutane, more recent studies [96–99] have confirmed the original observation [95] that several compounds are formed and that the above dimer constitutes only a small part (about 5%) of the mixture of products. Other products are shown in Scheme 6 [97–99]

The pyrolysis of gaseous allene at 400 to 600 °C in a flow apparatus yields less of the higher oligomers [96–100], a mixture of 1,2- and 1,3-dimethylenecyclobutanes in a ratio of 3:1 to 4:1 being obtained in a yield of up to 45% [101,102].

Catalytic oligomerization with phosphorus-modified nickel carbonyl catalysts, on the other hand, leads to two trimers and a tetramer, whereas no dimer is formed (Scheme 6) [103–105].




Scheme 6. Products of the oligomerization of allene.
A: liquid phase, 110 to 160 °C; B: gas phase, 400 to 600 °C; C: in tetrahydrofuran at 110 °C with catalyst.

[97] *B. Weinstein* and *A. H. Fenselau,* Tetrahedron Letters *1963,* 1463; Abstracts of papers presented at the 148th meeting of the American Chemical Society, Chicago, Ill., 1964, p. 72-S.

[98] *A. H. Fenselau,* Dissertation, Stanford University, 1964.

[99] *Ya. M. Slobodin* and *A. P. Khitrov,* Ž. obsc. Chim. *33,* 2822 (1963).

[100] *R. N. Meinert* and *C. D. Hurd,* J. Amer. chem. Soc. *52,* 4540 (1930).

[101] *Y. M. Slobodin* and *A. P. Khitrov,* Ž. obsc. Chim. *33,* 153 (1963).

[102] See also *J. K. Williams* and *W. H. Sharkey,* J. Amer. chem. Soc. *81,* 4269 (1959).

[103] *R. E. Benson* and *R. V. Lindsey jr.,* J. Amer. chem. Soc. *81,* 4247 (1959).

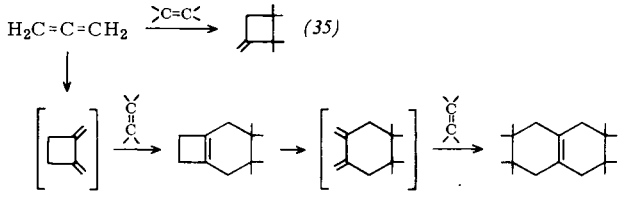
[104] *R. E. Benson,* U.S.-Pat. 2839510 (1958); Chem. Abstr. *52,* 18267 (1958); see also: Brit. Pat. 812902 (1959); Chem. Abstr. *54,* 7591 (1960).

[105] This ratio can be varied by the proper choice of catalyst.

## 2. Co-cyclization and Condensation of Allene with other Unsaturated Compounds

Allene can be co-cyclized with monoolefins containing an activated double bond, with conjugated diolefins, and with acetylene.

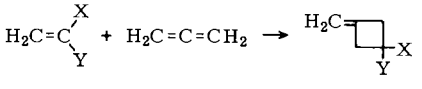
The thermal condensation of allene with activated monoolefins may proceed by one of the routes shown in Scheme 7. The product formed depends largely on the nature of the olefin, and sometimes also on the reaction conditions, particularly the ratio of the reactants.




Scheme 7. Reactions of allene with olefins containing an activated double bond.

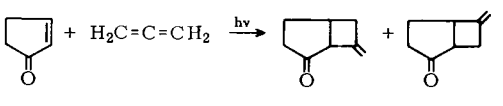
Tetrafluoroethylene [106] and some monosubstituted and unsymmetrically disubstituted ethylenes [107] react with preferential formation of derivatives of methylenecyclobutane *(35)* (Table 4), and this provides a particularly elegant one-step synthesis of 3-substituted methylenecyclobutanes [108].

Table 4. Examples of the one-step synthesis of 3-substituted methylenecyclobutanes [107].




| X | Y | Yield (%) |
|---|---|---|
| H | CN | 60 |
| $CH_3$ | CN | 62 |
| H | COOH | 21 |
| H | $COOCH_3$ | 25 |
| $CH_3$ | $COOCH_3$ | 25 |
| $CH_3$ | CH=O | 6.7 |
| H | $C_6H_5$ | 22 |
| $CH_3$ | $C_6H_5$ | 20 |

The photochemical reaction of cyclopentenone with allene leads to good yields of the two isomeric methylenecyclobutane adducts *(36)* and *(37)*, compound *(36)* being the major product [109].




*(36)* *(37)*

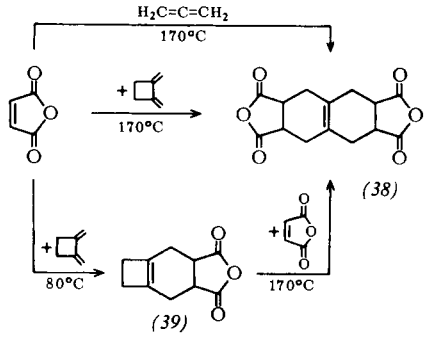
[106] *D. D. Coffman, P. L. Barrick, R. D. Cramer,* and *M. S. Raasch,* J. Amer. chem. Soc. *71,* 490 (1949).

[107] *H. N. Cripps, J. K. Williams,* and *W. H. Sharkey,* J. Amer. chem. Soc. *80,* 751 (1958); see also U.S.-Pat. 2914541 (1959); Chem. Abstr. *54,* 7588 (1960).

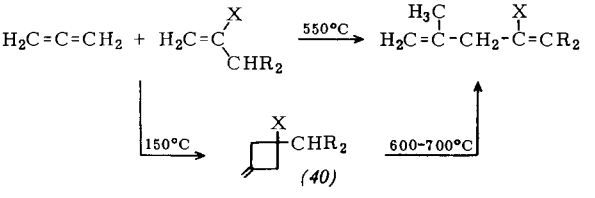
[108] *F. F. Caserio jr., S. H. Parker, R. Piccolini,* and *J. D. Roberts,* J. Amer. chem. Soc. *80,* 5507 (1958).

[109] *P. E. Eaton,* Tetrahedron Letters *1964,* 3695.

Heating with maleic anhydride, on the other hand, leads preferentially, but not exclusively [110], to the $\Delta^{4a,8a}$-octahydronaphthalene derivative *(38)* [96, 110, 111]. Model experiments with 1,2-dimethylenecyclobutane and maleic anhydride at different temperatures gave the strong indication that this reaction proceeds *via* 1,2-dimethylenecyclobutane and its subsequent Diels-Alder adduct *(39)* [96].



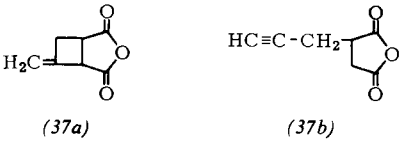

A reaction that does not at first sight appear to fit into either of these two categories is the condensation of allene with certain 2-substituted α-olefins to form open-chain 1,4-dienes [112]. However, when this reaction was carried out in steps at relatively low temperatures, it was found that it proceeds *via* a methylenecyclobutane intermediate *(40)*.




X: -CN, $-CO_2CH_3$, $-CH_3$, $-C_6H_5$

The co-cyclization of allene with conjugated dienes (Diels-Alder reaction) has been repeatedly described. Reliable data are available for the reactions of allene with cyclopentadiene and with hexachlorocyclopentadiene [113–115]. Both these reactions lead to the expected Diels-Alder adducts *(41)* having a methylenenorbornene structure.

[110] Small quantities of the compounds *(37a)* and *(37b)* were also formed: *K. Alder* and *O. Ackermann,* Chem. Ber. *90,* 1697 (1957).




*(37a)* *(37b)*

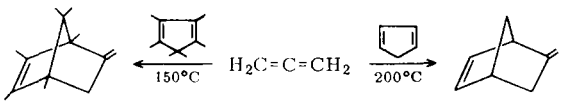
[111] *K. Alder* and *O. Ackermann,* Chem. Ber. *87,* 1567 (1954).

[112] *J. J. Drysdale,* U.S.-Pat. 2964505 (1960); Chem. Abstr. *55,* 10977 (1961).

[113] *E. U. Elam* and *R. H. Hasek,* U.S.-Pat. 2960541 (1960); Chem. Abstr. *55,* 7321 (1961).

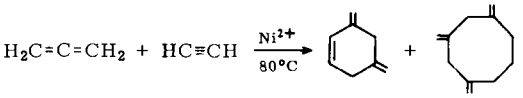
[114] *H. Pledger jr.,* J. org. Chemistry *25,* 278 (1960).

[115] *H. N. Cripps,* U.S.-Pat. 3214483 (1965); Chem. Abstr. *64,* 3380 (1966).




*(41b)*, 76% *(41a)*, 48%

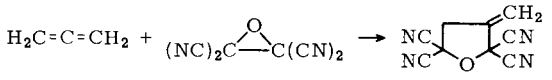
The reaction of allene with acetylene in the presence of nickel salts leads to a mixture of the 2:1 and 3:1 adducts *(42)* and *(43)*, but not to the acetylene tetramer, cyclooctatetraene, provided that allene is used in excess with respect to acetylene [116]. Similar results were obtained with substituted acetylenes [116].




*(42)*, 45% *(43)*, 5%

### 3. Addition of Allene to Saturated Systems

The reaction of allene with tetracyanoethylene oxide [117] yields the crystalline adduct *(44)* in a yield of more than 70%.

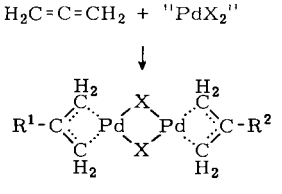



*(44)*

## C. Organometallic Chemistry of Allene [118]

Apart from a description of an $HgCl_2$ and an Na adduct [62] of doubtful structure, the organometallic chemistry of allene was virtually non-existent up to about 10 years ago. It is only recently that definite metal compounds of allene, the palladium $\pi$-allyl complexes, were prepared [119,120]. When gaseous allene is introduced into a solution of $(C_6H_5CN)_2PdCl_2$ in benzene or into a methanolic solution of $Na_2PdCl_4$ or $K_2PdBr_4$, complexes of the type *(45)* are formed in good yields.

On the other hand, when solid $(C_6H_5CN)_2PdCl$ is added to a solution of allene in benzene, the main product is the complex *(46)*. The reaction of allene with the same palladium reagent in benzonitrile yields the complex *(47)*, and in methanol the complexes *(47)* and *(48)* are formed in a ratio of almost 1:1.




*(45)*, $R^1 = R^2 = X = Cl, Br$

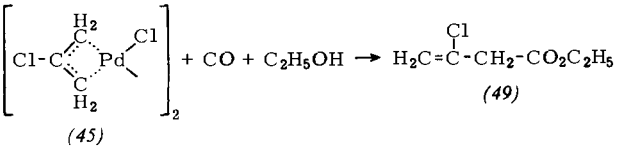
*(46)*, $R^1 = X = Cl$; $R^2 = -C(=CH_2)-CH_2Cl$

*(47)*, $R^1 = R^2 = -C(=CH_2)-CH_2Cl$; $X = Cl$

*(48)*, $R^1 = R^2 = -C(=CH_2)-CH_2OCH_3$; $X = Cl$

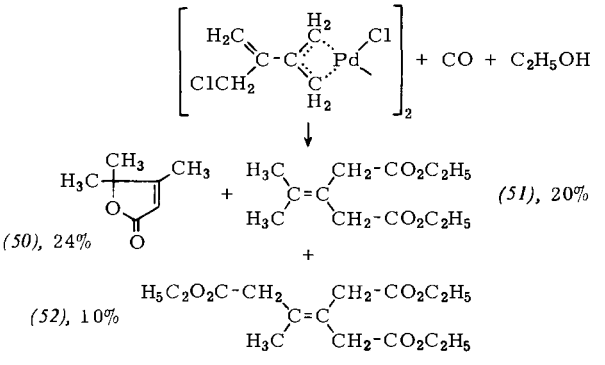
Preliminary studies showed that the bridging chlorine atoms in these compounds can be replaced by bromine, iodine, or thiocyanate, that the bridges can be cleaved by amines, and that the reaction with acetylacetone yields mononuclear complexes [120].

In analogy to the carbonylation of other Pd-allyl complexes [121], the carbonylation of the $PdCl_2$ complex *(45)* in ethanol leads to the ester *(49)* [122].

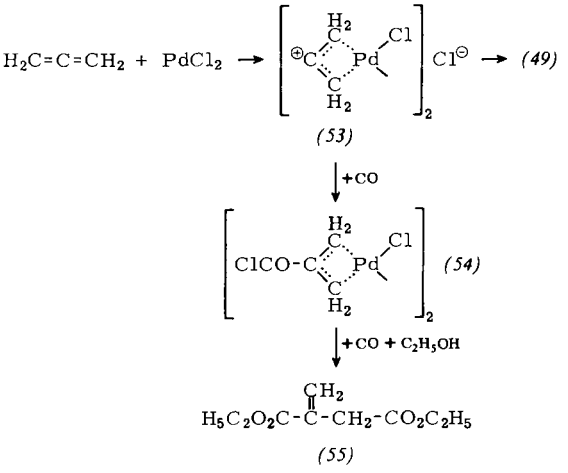



*(45)* *(49)*

The carbonylation of the $PdCl_2$ complex *(47)*, on the other hand, takes a more complicated course, and gives at least three products *(50)–(52)* in moderate yields [122].




Yet another route is followed by the direct carbonylation of allene in the presence of $PdCl_2$ [122]. Instead of a chlorination of the center carbon atom, such as occurs in the carbonylation of the $PdCl_2$ complex *(45)*, the $\pi$-complex *(53)* is chloroformylated to the intermediate complex *(54)*, which then yields the ester *(55)* in a normal carbonylation.




[116] *R. E. Benson* and *R. V. Lindsey jr.*, J. Amer. chem. Soc. *81*, 4250 (1959).

[117] *W. J. Linn* and *R. E. Benson*, J. Amer. chem. Soc. *87*, 3657 (1965).

[118] This section deals with reactions that could equally well be discussed as "Addition reactions".

[119] *R. G. Schultz*, Tetrahedron Letters *1964*, 301; Tetrahedron *20*, 2809 (1964).

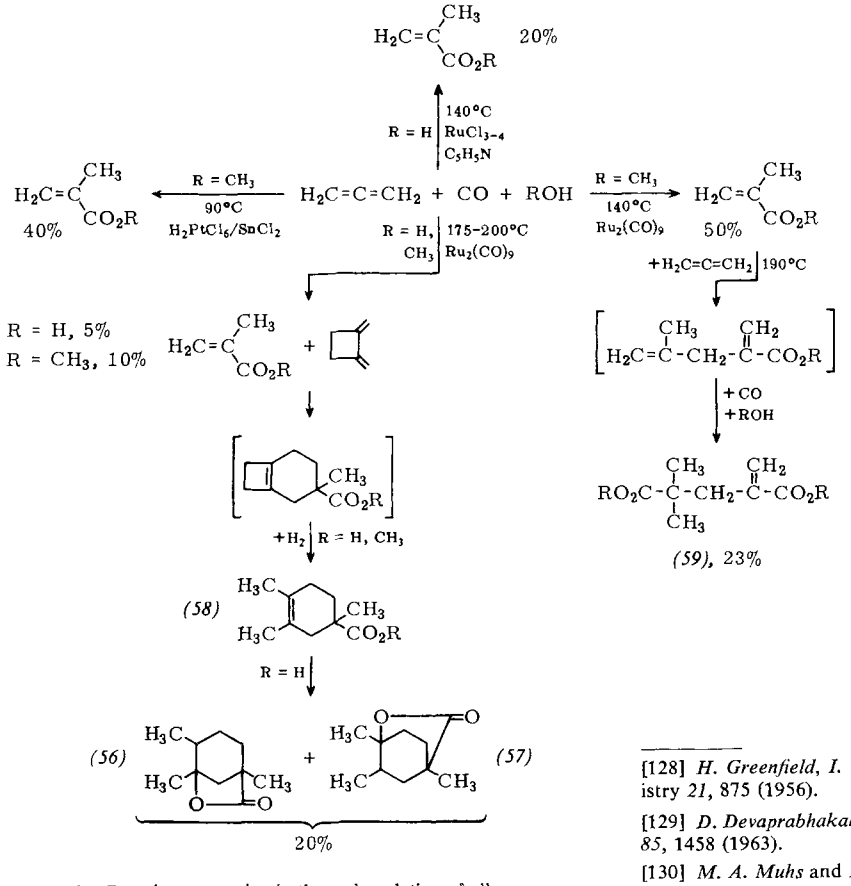
[120] *H. S. Lupin* and *B. L. Shaw*, Tetrahedron Letters *1964*, 883.

[121] *T. Tsuji, J. Kiji, S. Imamura*, and *M. Morikawa*, J. Amer. chem. Soc. *86*, 4350 (1964).

[122] *J. Tsuji* and *T. Susuki*, Tetrahedron Letters *1965*, 3027.

Interesting results were obtained also in the carbonylation of allene with $H_2PtCl_6/SnCl_2$ and particularly with $Ru_2(CO)_9$ as catalyst [123,124]. The reaction with $Ru_2(CO)_9$ between 90 and 140 °C leads to methacrylic acid when water is used as the solvent, and to methyl methacrylate when methanol is used. At 175 to 200 °C, on the other hand, only traces of these compounds are formed, and the main products isolated are the lactones *(56)* and *(57)* or the cyclic methyl ester *(58)*, depending on whether water or methanol is used as solvent. Finally, if the reaction is carried out in steps, first at 140 °C and then at 190 °C in methanol, dimethyl α,α-dimethyl-α'-methyleneglutarate *(59)* is formed together with methyl methacrylate. These results, which appear remarkable at first sight, are explained by Scheme 8 [124], from which it can be seen that some of the reactions resemble those discussed in the last section.

The hydroboration of allene is reported to yield a waxy organoborine polymer, from which 1,3-propanediol is obtained on treatment with hydrogen peroxide and base [125,126]. It was concluded, therefore, that the polymer has a 1,3-structure, *i.e.* that the electrophilic diborane [127] adds to the terminal carbon of allene.



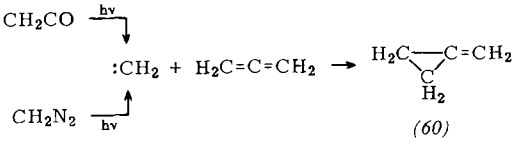

Scheme 8. Reactions occurring in the carbonylation of allene.

The reaction of allene with octacarbonyldicobalt leads to an ill-defined organocobalt compound, which catalyses the polymerization of allene [128]. A mercury(II) chloride adduct [129] and a silver nitrate complex [130] of allene have recently been described; however, no details were reported.

## D. Carbene Chemistry of Allene

### 1. Addition of Carbenes to Allene

The photolysis of ketene and of diazomethane in the presence of allene gives good yields of the expected methylenecyclopropane *(60)*, provided that the conditions are such that the initially highly excited adduct can be stabilized [131,132].




[123] *E. L. Jenner* and *R. V. Lindsey jr.*, U.S.-Pat. 2875254 (1959); Chem. Abstr. *53*, 14000 (1959).

[124] *T. J. Kealy* and *R. E. Benson*, J. org. Chemistry *26*, 3126 (1961); U.S.-Pat. 2871262 (1959); Chem. Abstr. *53*, 14008 (1959).

[125] *K. A. Saegebarth* and *C. Hundred*, U.S.-Pat. 3014075 (1961); Chem. Abstr. *56*, 13095 (1962).

[126] *S. Corsano*, Atti Accad. naz. Lincei, Rend., Cl. Sci. fisische mat. natur *34*, 430 (1963).

[127] *H. C. Brown*: Hydroboration. Benjamin, New York 1962.

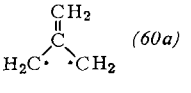
[128] *H. Greenfield*, *I. Wender*, and *J. H. Wotiz*, J. org. Chemistry *21*, 875 (1956).

[129] *D. Devaprabhakara* and *P. D. Gardner*, J. Amer. chem. Soc. *85*, 1458 (1963).

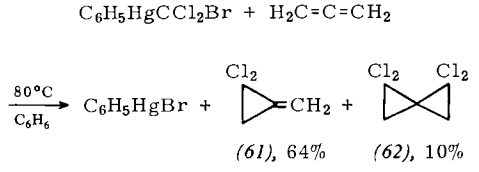
[130] *M. A. Muhs* and *F. T. Weiss*, J. Amer. Chem. Soc. *84*, 4697 (1962).

[131] *H. M. Frey*, Trans. Faraday Soc. *57*, 951 (1961).

[132] The pyrolysis of the diazomethane adduct *(33)* also yields methylenecyclopropane *(60)*; however, this reaction proceeds not *via* a carbene, but *via* trimethylenemethane *(60a)* [92]. Since trimethylenemethane is also formed in the photolysis of *(33)* at low temperatures, the formulation of this photolysis as a carbene reaction [131] became doubtful.



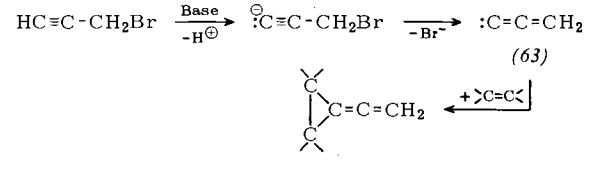
No additions of dihalocarbenes to allene were known until recently, probably because most syntheses of dihalocarbenes require strongly basic conditions, which lead to isomerization of allene. However, after introduction of the thermal preparation of dihalocarbenes from phenyltrihalomethylmercury compounds in the absence of bases, addition of dichlorocarbene to allene was recently achieved [133]. The product is a mixture of the adducts *(61)* and *(62)*.




*(61)*, 64% *(62)*, 10%

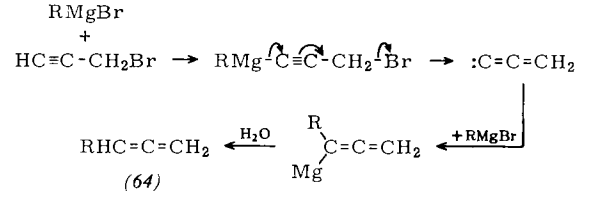
## 2. Allenyl Mono- and Dicarbenes

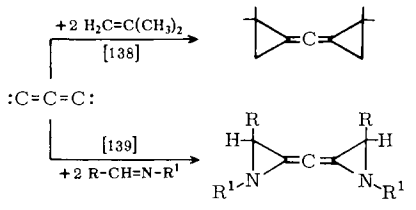
Whereas the existence of substituted alkenylidenes has been conclusively demonstrated [134], the evidence for the existence of allenylidene *(63)* was for a long time rather meager. The reaction of propargyl bromide with potassium t-butoxide in the presence of *cis*-2-butene leads to a mixture of hydrocarbons, whose infrared spectrum shows the presence of both allenic and acetylenic unsaturation. It was concluded that this reaction proceeds at least partly with the intermediate formation of allenylidene [135].




More convincing evidence has recently been discovered: The reaction of propargyl bromide with alkylmagnesium bromide in ether below 0 °C yields a substituted allene *(64)* as main product, and the following mechanism was proposed for this reaction [136]:

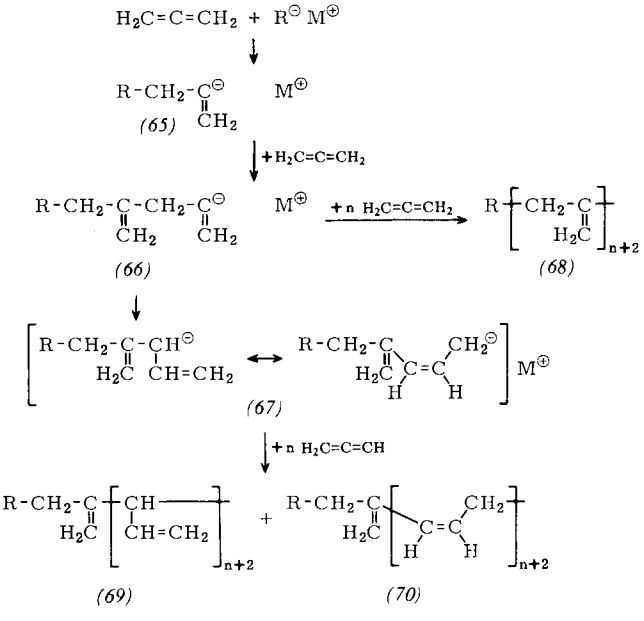
Allene dicarbene, which was first discovered in the atmosphere of a comet [137], was recently also detected on Earth. The dicarbene occurs in carbon vapor produced *in vacuo* from elementary carbon.




### E. Polymerization of Allene

Though a radon-initiated [140] and a photochemical [141] polymerization of allene had been reported earlier, no authentic high polymer of allene had been described up to 1963. The polymerization of allene by various transition-metal salts reduced with triisobutylaluminum (Ziegler catalysts) yields a linear polyallene of high molecular weight. The polymer is amorphous or crystalline (m.p. 122±3 °C), depending on the reaction conditions [142, 143]. Its structure is not uniform, but consists of blocks of vinylidene *(68)*, vinyl *(69)*, and *cis*-olefin structures *(70)*. This non-uniformity is thought to be due to the anionic reaction sequence in Scheme 9 [142], leading by a selective terminal attack on allene to the intermediates *(65)*–*(67)*, from which the observed structures *(68)*–*(70)* are derived.




Scheme 9. Polymerization of allene.
$R^{\ominus}M^{\oplus}$ *e.g.* = $VOCl_3/Al(i\text{-}C_4H_9)_3$

[133] *D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons jr., A. J. H. Treiber,* and *S. R. Dowd,* J. Amer. chem. Soc. *87*, 4259 (1965).

[134] *J. Hine*: Divalent Carbon. Ronald Press, New York 1964, p. 86.

[135] *H. D. Hartzler,* J. Amer. chem. Soc. *83*, 4990 (1961).

[136] *F. Serratosa,* Tetrahedron Letters *1964*, 895.

[137] *G. Herzberg,* Astrophys. J. *96*, 314 (1942).

[138] *P. S. Skell* and *L. D. Wescott,* J. Amer. chem. Soc. *85*, 1023 (1963).

[139] *I. E. Den Besten* and *C. R. Wenger,* J. Amer. chem. Soc. *87*, 5500 (1965).

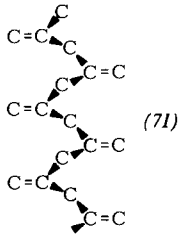
[140] *G. B. Heisig,* J. Amer. chem. Soc. *53*, 3245 (1931).

[141] *S. C. Lind* and *R. Livingston,* J. Amer. chem. Soc. *55*, 1036 (1933).

[142] *W. P. Baker jr.,* J. Polymer Sci. A, *1*, 655 (1963).

[143] *I. M. Robinson,* U.S.-Pat. 3151104 (1964); Chem. Abstr. *62*, 1760 (1965).

A largely uniform high molecular weight polyallene ($\overline{M}_n \approx 10^5$; m.p. 60 to 61 °C) with a vinylidene structure is obtained when π-complexes of nickel are used as catalysts. On the basis of X-ray analysis and because of the occurrence of dichroism in the IR spectrum, this polymer was assigned the helix structure *(71)* [144, 145].



*(71)*

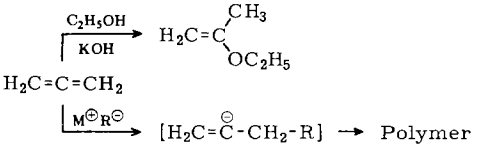
Experiments with other catalysts have so far had little success. For example, the polymerization of allene with octacarbonyldicobalt [124, 144], tri-(π-allyl)cobalt, or nickel(II) acetonylacetate reduced with triethylaluminum yielded only insoluble polymers, while nickel(II) complexes, pentacarbonyliron, and other iron complexes gave no polymer at all [144].

The copolymerization of allene with other olefins has been repeatedly described but no data have been given regarding the structures of the copolymers [146, 147]. The copolymerization of allene and ethylene in the presence of transition-metal salts reduced with aluminum alkyls is reported to yield a copolymer containing the allene in the form of vinyl, vinylidene, and *cis*-olefin structures [148], as in the products obtained by the homopolymerization of allene with Ziegler catalysts [142].

## V. Conclusion

This brief survey has shown that considerable progress has been made in the past ten years [149] in the preparation and in the chemistry of allene. However, it should not be assumed that the chemistry of allene is now known and understood in all its details. On the contrary, it is probable that allene will attract even more interest in the future for several reasons.

First, there are many questions mentioned in this report that still remain to be answered. Thus there is no general concept that permits an adequate description of the manner in which the course of ionic or free-radical additions depends on the nature of the addend. The explanations advanced so far are at best only working hypotheses. Further, there are a number of typical olefin reactions that have never been systematically investigated for allene. For example, only one publication describes a true anionic addition to allene [150], and the course of this reaction is opposite to that of the polymerization of allene, though the latter has also been described as an anionic reaction [142].



Secondly, any progress in the separation of allene, *i.e.*, in the direction of a more economical synthesis, could lead to industrial interest in the chemistry of this compound, *e.g.* in the use of some of the selective free-radical additions leading to 1,3-difunctional products, or in the use of organometallic reactions of allene. On the other hand, the discovery of reactions that utilize allene selectively, or give the same products from a mixture of allene and methylacetylene [151], would also be of interest.

Thirdly, the results of studies on the chemistry of allene may prove useful in other fields of chemistry. Thus the study of free-radical additions has thrown light on the relative availability of vinyl radicals in comparison with primary, secondary, and tertiary alkyl radicals, and the preferred addition of HX compounds to allene *via* a vinyl carbonium ion (propenylium ion) casts doubt on the reported instability of vinyl carbonium ions.

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German version: Angew. Chem. *78*, 953 (1966)
Translated by Express Translation Service, London

[144] *S. Otsuka, K. Mori,* and *F. Imaizumi,* J. Amer. chem. Soc. *87*, 3017 (1965).

[145] *H. Tadokoro, Y. Takahashi, S. Otsuka, K. Mori,* and *F. Imaizumi,* Polymer Letters *3*, 697 (1965).

[146] *S. Tocker,* U.S.-Pat. 3043818 (1962); Chem. Abstr. *57*, 12738 (1962); Ger. Pat. 1132334 (1962); Chem. Abstr. *59*, 4142 (1963).

[147] *C. Longiave, R. Castelli,* and *M. Ferraris,* Chim. e Ind. *44*, 725 (1962).

[148] *Y. Masuda,* Asashi Garasu Kenkyu Hokoku *15*, 73 (1965); Chem. Abstr. *63*, 14986 (1965).

[149] About 80% of the articles cited here appeared after 1956.

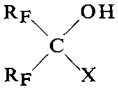
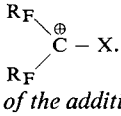
[150] *A. J. Faworski,* J. prakt. Chem. (2) *44*, 215 (1891).

[151] Examples of such reactions are the electrophilically induced cyclodimerizations described in [83].

# Reactions of the Carbonyl Group in Fluorinated Ketones

BY DR. N. P. GAMBARYAN, E. M. ROKHLIN, YU. V. ZEIFMAN, CHEN CHING-YUN, AND PROF. I. L. KNUNYANTS

INSTITUTE FOR ORGANO-ELEMENTAL COMPOUNDS, ACADEMY OF SCIENCES OF THE USSR, MOSCOW (USSR)

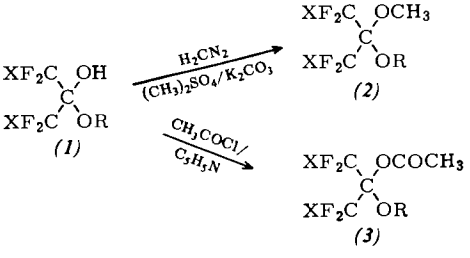
*The chemistry of polyfluorinated ketones has recently received a great deal of attention* [1,2] [a]. *The carbonyl and imino groups of the fluorinated ketones and their imines react in many different ways. In particular, the electron-attracting perfluoroalkyl groups intensify the electrophilic properties and weaken the nucleophilic properties of the carbonyl group. The perfluoroalkyl group also hinders the heterolytic removal of the hydroxyl group from adducts*  *by reducing the stability of the carbonium ion*  *. The increased electrophilicity of the carbonyl group and the increased stability of the addition products leads not only to a change in reactivity in the characteristic ketone reactions, but also to numerous new reactions which are not observed with non-fluorinated ketones. Thus it is possible to synthesize a wide variety of fluoroorganic compounds from perfluorinated ketones* [b].

## I. Reactions of Fluorinated Ketones with Nucleophiles

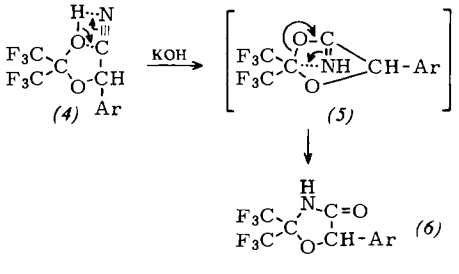
### 1. Alcohols and Amines

Hexafluoroacetone reacts vigorously with water [c] or alcohols, giving the "hydrate" or 2-alkoxyhexafluoropropan-2-ols *(1)*, with X = F, which decompose on heating to the starting materials [5,6] [d]. Alkylation of the compounds *(1)*, X = F, Cl, leads to fairly stable acetals *(2)* [5,6,8]; acylation yields *O*-acyl derivatives *(3)* [9].

Hexafluoroacetone and *gem*-hydroxynitriles (cyanohydrins) give unstable 2-(cyanoalkoxy)hexafluoro-2-propanols, *e.g. (4)*, which react with an excess of alkali



to form 5-substituted 4-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidines such as *(6)*, probably *via* unstable 4-imino-1,3-dioxolanes *(5)* [10,11].



Reactions with amines, amides, hydroxylamine, or semicarbazide lead to geminal amino alcohols *(7)* or to

[1] *A. Ya. Yakoubovich*, Usp. Chim. *25*, 3 (1956).

[2] *H. P. Braendlin* and *E. T. McBee* in: Advances in Fluorine Chemistry. Butterworths, London 1963, Vol. 3, p. 1.

[a] The review by *Braendlin* and *McBee* [2] does not deal only with perfluorinated ketones; moreover, though published in 1963, it is already outdated. The papers discussed in [1,2] will not be reviewed in the present article.

[b] We have been concerned mainly with hexafluoroacetone, since in addition to being the most readily available and simplest perfluorinated ketone, this is also a typical representative of this class of compounds.

[c] Similarly, geminal mercapto alcohols are formed from fluorinated ketones with $H_2S$ [3,4].

[3] *J. F. Harris*, J. org. Chemistry *30*, 2190 (1965).

[4] *A. V. Fokin, V. A. Komarov, A. A. Skladnev*, and *S. M. Davydova*, Ž. vses. chim. Obšč. im D. I. Mendeleeva *9*, 710 (1964).

[5] *Chen Ching-yun*, Dissertation, Akademy Institute for Organo-Elemental Compounds, Moscow 1960.

[6] *I. L. Knunyants, Chen Ching-yun*, and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1960*, 686.

[d] 2-Alkoxynitropentafluoro-2-propanols, prepared from perfluoronitroacetone, are more stable [7].

[7] *I. L. Knunyants, A. V. Fokin*, and *V. A. Komarov*, Izvest. Akad. Nauk SSSR, Ser. chim. *1966*, 466.

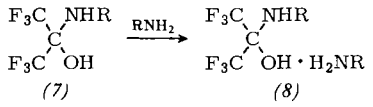
[8] *H. E. Simmons* and *D. W. Wiley*, J. Amer. chem. Soc. *82*, 2288 (1960).

[9] *P. E. Newallis* and *P. Lombardo*, J. org. Chemistry *30*, 3834 (1965).

[10] *Yu. V. Zeifman* and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Ser. chim. *1964*, 1687.

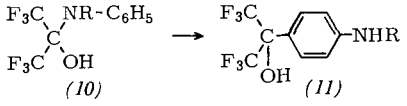
[11] *Yu. V. Zeifman* and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Ser. chim. *1964*, 1622.

the adducts *(8)* [12–18] [e]. A compound previously [2] thought to be the semicarbazone of hexafluoroacetone was identified by us as *(7)*, R = $NHCONH_2$ [14].



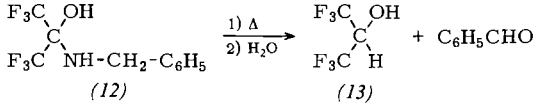
*(7)* *(8)*

The further reaction of geminal amino alcohols depends on the reaction partner RR'NH, and can lead to products of rearrangement, redox reactions, or cleavage. Geminal amino alcohols containing an *N*-aryl group, *e.g. (10)*, rearrange to carbinols such as *(11)* [18, 23, 24] [f].



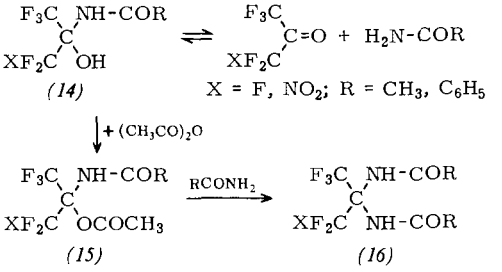
*(10)* *(11)*

Geminal amino alcohols containing an *N*-benzyl group, *e.g. (12)*, undergo a redox reaction on heating to give benzaldehyde derivatives and a fluorinated alcohol [26] (cf. Section I.6).



*(12)* *(13)*

When heated with acetic anhydride, geminal amino alcohols containing an *N*-acyl group, *e.g. (14)*, are converted into *O*-acetyl compounds *(15)* or 2,2-bis-(acylamino)pentafluoropropanes *(16)* [17, 27] [g].

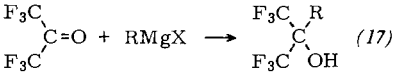


*(14)* X = F, $NO_2$; R = $CH_3$, $C_6H_5$

*(15)* *(16)*

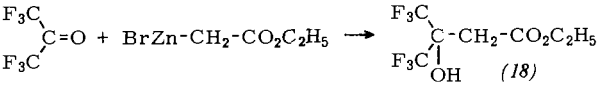
## 2. Organometallic Compounds

Like all ketones, hexafluoroacetone reacts with organometallic compounds, *i.e.* Grignard, Iozič [h], and Reformatsky compounds, to give derivatives of the types *(17)* and *(18)* [6, 18] [i].



*(17)*

R = $CH_3$, $C_2H_5$, $C_6H_5$, $HC{\equiv}C$, $C_6H_5{-}C{\equiv}C$, $CH_2{=}CH{-}C{\equiv}C$, $(CH_3)_2C(OH){-}C{\equiv}C$, $(CF_3)_2C(OH){-}C{\equiv}C$



*(18)*

The reaction with organometallic compounds is well suited to the experimental confirmation of the stronger electrophilic activity of fluorinated as compared with non-fluorinated ketones, owing to its irreversibility and the stability of the products. Thus a mixture of acetone, hexafluoroacetone, and phenylmagnesium bromide gives only bis(trifluoromethyl)phenylmethanol, *(17)* with R = $C_6H_5$, the yield being unaffected by the amount of acetone present [18].

## 3. Aliphatic Diazo Compounds

In reactions with diazoacetic ester, non-fluorinated ketones are generally nucleophilic, since they react with the electrophilic ethoxycarbonylcarbene to form enol ethers [28]. Unlike non-fluorinated ketones, hexafluoroacetone reacts with the weakly nucleophilic diazoacetic ester *(19)* to form ethyl 2,3-epoxy-4,4,4-trifluoro-3-

[12] *R. G. Kostyanovsky*, Doklady Akad. Nauk SSSR *139*, 877 (1961).

[13] *Yu. V. Zeifman, N. P. Gambaryan*, and *I. L. Knunyants*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 450.

[14] *Yu. V. Zeifman, N. P. Gambaryan*, and *I. L. Knunyants*, Ž. vses. chim. Obsc. im D. I. Mendeleeva *10*, 235 (1965).

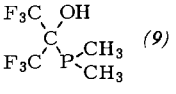
[15] *H. Newman* and *E. L. Moon*, J. org. Chemistry *29*, 2061 (1964).

[16] *P. E. Newallis* and *E. J. Rumanowski*, J. org. Chemistry *29*, 3114 (1964).

[17] *Yu. W. Zeifman, N. P. Gambaryan*, and *I. L. Knunyants*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 2046.

[18] *I. L. Knunyants, N. P. Gambaryan, Chen Ching-yun*, and *E. M. Rokhlin*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1962*, 684.

[e] Fluorinated ketones also react with phosphines and arsines to form *gem*-substituted alcohols, *e.g. (9)* [19–22].



*(9)*

[19] *E. I. Grinstein, A. B. Bruker*, and *L. Z. Soborovsky*, author's certificate (USSR) No. 170498.

[20] *A. B. Bruker, E. I. Grinstein*, and *L. Z. Soborovsky*, author's certificate (USSR) No. 169117.

[21] *G. W. Parshall*, Inorg. Chem. *4*, 52 (1965).

[22] *W. R. Cullen* and *G. E. Styan*, J. organomet. Chemistry *4*, 151 (1965).

[23] *I. L. Knunyants, Chen Ching-yun, N. P. Gambaryan*, and *E. M. Rokhlin*, Ž. vses. chim. Obšč. im D. I. Mendeleeva *5*, 114 (1960).

[24] *E. E. Gilbert, E. S. Jones*, and *J. P. Sibilia*, J. org. Chemistry *30*, 1001 (1965).

[f] *p*-Aminophenyl-bis(trifluoromethyl)methanol, *(11)* with R = H, is strongly antispasmodic [5, 25].

[25] *K. S. Raevski*, Farmakol. i. Toxikol. *24*, 495 (1961).

[26] *N. P. Gambaryan* and *I. L. Knunyants*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 722.

[27] *I. L. Knunyants, Yu. V. Zeifman*, and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Ser. chim. *1966*, 1108.

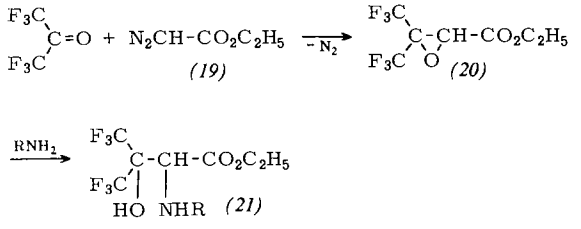
[g] Geminal amino alcohols, *(7)* with R = alkyl or aryl, are decomposed to hexafluoroacetone and *N*-alkyl- (or aryl)acetamide by acetic anhydride [13].

[h] Iozič compounds are alkynylmagnesium bromides.

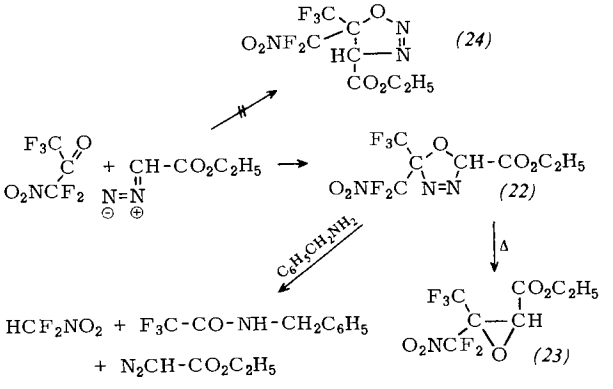
[i] Isopropylmagnesium bromide gives only hexafluoroisopropanol (80% yield) [18].

[28] *I. L. Knunyants, N. P. Gambaryan*, and *E. M. Rokhlin*, Usp. Chim. *27*, 1361 (1958).

trifluoromethylbutyrate *(20)* [29] [k]. As can be seen by comparison with the non-fluorinated analogue, cleavage of the oxirane ring in *(20)* by nucleophiles proceeds more readily and in another direction. Thus, with amines racemic ethyl 2-alkylamino-4,4,4-trifluoro-3-hydroxy-3-trifluoromethylbutyrates *(21)* are formed [30].



Pentafluoronitroacetone, which is even more electrophilic than hexafluoroacetone, reacts very vigorously with diazoacetic ester, even at −40 °C, to give a stable adduct *(22)*, which liberates nitrogen only on prolonged heating at 165 °C to give ethyl 2,3-epoxy-4,4-difluoro-4-nitro-3-trifluoromethylbutyrate *(23)* [29]. The fragments formed by the reaction of the primary adduct with benzylamine are compatible only with structure *(22)*; the isomer *(24)* may be ruled out.

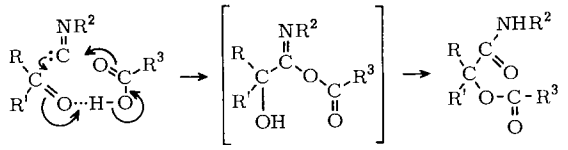


It is of interest to establish the direction of addition of the diazoacetic ester to polar multiple bonds. Since the carbonyl double bond in perfluoroketones is polarized (see Section I.4), the direction of addition is determined by the electronic structure of the diazoacetic ester. Our results, which indicate a nucleophilic attack by the terminal nitrogen atom on the carbonyl carbon, show that a considerable contribution is made by canonical structures such as

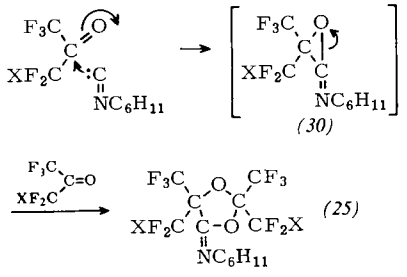
$\overset{\ominus}{N}{=}\overset{\oplus}{N}\text{–}CH\text{–}CO_2R$ and $\overset{\ominus}{N}{=}N\text{–}\overset{\oplus}{C}H\text{–}CO_2R$.

### 4. Isocyanides and Trialkyl Phosphites

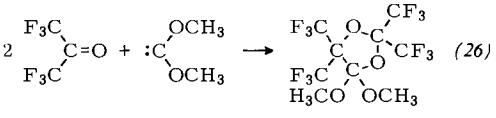
Isocyanides generally are regarded as weak nucleophiles, or to some extent as nucleophilic carbenes. However, the nucleophilicity of isocyanides is insufficient for reaction with ordinary carbonyl compounds in the absence of a third component. Non-fluorinated ketones react with isocyanides only in the presence of acids, which increase the positive charge on the carbonyl carbon (Passerini and Ugi reactions) [31, 32].



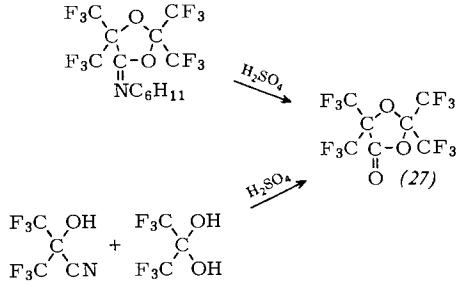
The electrophilicity of fluorinated ketones, on the other hand, is so high that they react vigorously with cyclohexyl isocyanide without a catalyst, to form cyclohexyl-



iminodioxolanes *(25)*, X = F or $NO_2$ [33]. A similar reaction of fluorinated ketones with dialkoxycarbenes, which leads to dialkoxydioxolanes such as *(26)*, has recently been described [34, 35] [l].



The iminodioxolane *(25)*, X = F does not decompose at 200 °C, and is hydrolysed only slowly by concentrated sulfuric acid at 100 °C to the dioxolanone *(27)*, the structure of which is confirmed by its chemical properties and by independent synthesis [33, 36].



[29] *N. P. Gambaryan, L. A. Simonyan,* and *I. L. Knunyants,* Doklady Akad. Nauk SSSR *155*, 833 (1964).

[k] In a similar reaction, diphenyldiazomethane gives 1,1-bis(trifluoromethyl)-2,2-diphenylethylene oxide [18].

[30] *N. P. Gambaryan* and *L. A. Simonyan,* Izvest. Akad. Nauk SSSR, Ser. chim. *1964*, 1529.

[31] *M. Passerini,* Gazz. chim. ital. *61*, 964 (1931).

[32] *I. Ugi,* Angew. Chem. *74*, 9 (1962); Angew. Chem. internat. Edit. *1*, 8 (1962).

[33] *N. P. Gambaryan, E. M. Rokhlin, Yu. V. Zeifman, L. A. Simonyan,* and *I. L. Knunyants,* Doklady Akad. Nauk SSSR *166*, 864 (1966).

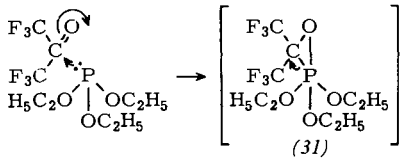
[34] *R. A. Braun,* J. Amer. chem. Soc. *87*, 5516 (1965).

[35] *R. A. Braun,* J. org. Chemistry *31*, 1147 (1966).

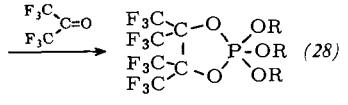
[l] A similar cyclic adduct (2:1) is formed with dimethylsilene $(CH_3)_2Si$ [34].

[36] *I. L. Knunyants, E. M. Rokhlin, N. P. Gambaryan, Yu. A. Cheburkov,* and *Chen Ching-yun,* Chim. Nauka i Prom. *4*, 802 (1959).

The characteristic ability of isocyanides to undergo α-additions is due to the fact that the "carbene" carbon has a lone pair of electrons as well as an empty orbital. Tervalent phosphorus, whose compounds are also characterized by α-additions, has a similar dual character. Thus hexafluoroacetone reacts with triethyl phosphite under mild conditions to form an adduct of two molecules of hexafluoroacetone and one of triethyl phosphite. The properties of this adduct indicate a cyclic phosphorane structure *(28)*, R = $C_2H_5$. In contrast to the reaction with isocyanides, two fluoroketones are attached *via* C–C bridges in this case [37].

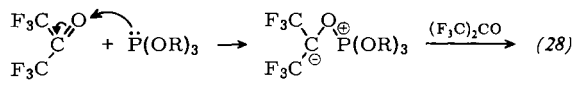


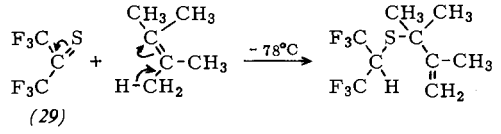
*(31)*



*(28)*

It is possible to explain the formation of the cyclic phosphorane *(28)*, R = $C_2H_5$, by an "inverse" polarization of the carbonyl group in hexafluoroacetone, similar to that of the thiocarbonyl group in perfluorothioacetone *(29)* [38]. Many authors believe that the Perkov reaction starts with an attack on the oxygen of the carbonyl group [39]. *Ramirez* [40]



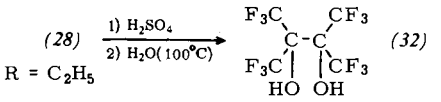


*(29)*

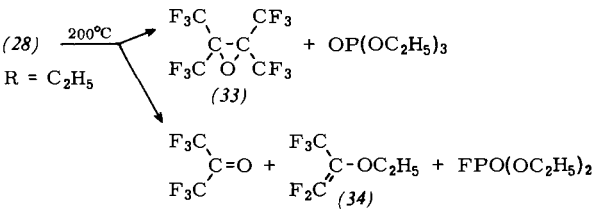
postulated a similar mechanism for the reaction of trialkyl phosphites with 1,2-dicarbonyl compounds. The first step in the reactions is assumed to be the attack of the nucleophilic trialkyl phosphite on the carbonyl oxygen. However, since the electronegativity of carbon is so much smaller than that of oxygen, "inverse" polarization of the carbonyl group is unlikely.

It may be assumed that the reaction of perfluoroketones both with isocyanides and with trialkyl phosphites begins with a nucleophilic attack on the carbonyl carbon and formation of a particularly reactive 1:1 adduct *(30)* or *(31)* containing a strained three-membered ring. The structure of the final product, *i.e.* the 2:1 adduct, will then depend on where the ring of the original 1:1 adduct opens. The iminooxirane *(30)* reacts by cleavage of a C–O bond, and not of a C–C bond as in most reactions of oxiranes. The phosphorane *(31)*, on the other hand, adds the second molecule of hexafluoroacetone by cleavage not of the P–O bond of the three-membered ring, but of the P–C bond, just as in the decomposition of the phosphorane containing a four-membered ring, which is formed as an intermediate in the Wittig reaction of carbonyl compounds with phosphorylides.

Hydrolysis of *(28)* yields perfluoro-2,3-dimethylbutane-2,3-diol (dodecafluoropinacol) *(32)* [37,41]. Thermal decomposition of *(28)* leads to perfluoro-2,3-dimethyl-2-butene oxide *(33)* [m] and 2-ethoxyperfluoropropene



*(32)*



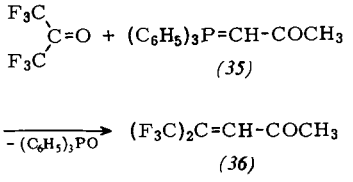
*(33)*

*(34)*

*(34)* [41]. Thus *(34)* is not a direct product of the reaction of hexafluoroacetone with triethyl phosphite, as was assumed by *Wiley* and *Simmons* [43], but is the result of further transformation of the stable adduct *(28)*.

## 5. Wittig-Staudinger Reactions

Unlike non-fluorinated ketones, hexafluoroacetone reacts even with very inactive "phosphorylides"; thus the reaction with acetylmethylenetriphenylphosphorane *(35)* leads to perfluoro(isopropylidene)acetone *(36)* [44,n].



*(35)*

*(36)*

Tetraphenyl(phosphine imide) *(37)* also reacts readily with carbonyl compounds of the type *(38)* [13,18] [o]. However, hexafluoro-*N*-phenylpropane-2-imine *(39)*, R =

[37] *N. P. Gambaryan, Yu. A. Cheburkov*, and *I. L. Knunyants*, Izvest. Akad. Nauk SSSR, Ser. chim. *1964*, 1526.

[38] *W. J. Middleton, E. G. Howard*, and *W. H. Sharkey*, J. Amer. chem. Soc. *83*, 2589 (1961).

[39] *F. W. Lichtenthaler*, Chem. Reviews *61*, 607 (1961); *I. L. Knunyants*, Ž. vses. chim. Obšč. im D. I. Mendeleeva *7*, 281 (1962).

[40] *F. Ramirez*, Pure appl. Chem. *9*, 337 (1964); *F. Ramirez, N. Ramanathan*, and *N. B. Desai*, J. Amer. chem. Soc. *85*, 3465 (1963).

[41] *E. M. Rokhlin, Yu. V. Zeifman, Yu. A. Cheburkov, N. P. Gambaryan*, and *I. L. Knunyants*, Doklady Akad. Nauk SSSR *161*, 1356 (1965).

[m] The structure of *(33)* has been confirmed by independent syntheses from dodecafluoropinacol *(32)* with $P_2O_5$ and from bis(trifluoromethyl)diazirine with hexafluoroacetone [41,42].

[42] *R. B. Minasyan, E. M. Rokhlin, N. P. Gambaryan, Yu. V. Zeifman*, and *I. L. Knunyants*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 761.

[43] *D. W. Wiley* and *H. E. Simmons*, J. org. Chemistry *29*, 1876 (1964).

[44] *V. F. Plakhova* and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1962*, 681.

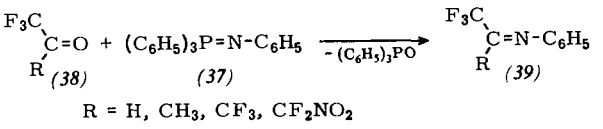
[n] Acetone does not react with *(35)* or with ethoxycarbonylmethylenetriphenylphosphorane *(35a)* even under severe conditions [44,45]. Monofluoroacetone, on the other hand, reacts with *(35a)* at 90 °C [45].

[45] *H. Machleidt, V. Hartmann*, and *H. Bünger*, Liebigs Ann. Chem. *667*, 35 (1963).

[o] *P,P,P*-triphenylphosphine imine reacts with hexafluoroacetone in the same way to give hexafluoropropan-2-imine [46].

[46] *Yu. V. Zeifman, N. P. Gambaryan*, and *I. L. Knunyants*, Doklady Akad. Nauk SSSR *153*, 1334 (1963).

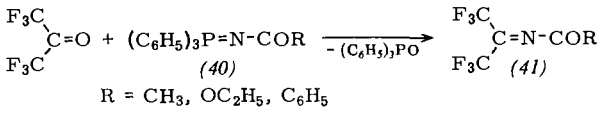
$CF_3$, is more conveniently prepared by heating hexafluoroacetone with phenyl isocyanate and a catalytic



*(38)* *(37)* *(39)*

R = H, $CH_3$, $CF_3$, $CF_2NO_2$

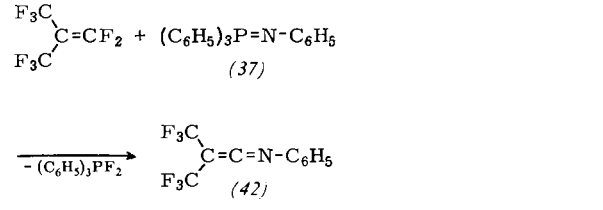
amount of triphenylphosphine oxide[46]; evidently *(37)* is an intermediate in this reaction[47]. Hexafluoroacetone reacts readily even with *N*-acyltriphenyl(phosphine imides) *(40)* to form *N*-acylimines *(41)*[17].



*(40)* *(41)*

R = $CH_3$, $OC_2H_5$, $C_6H_5$

Interestingly, tetraphenyl(phosphine imide) also reacts readily with perfluoroisobutene to give difluorotriphenylphosphorane and the anil *(42)* of bis(trifluoromethyl)ketene[48].

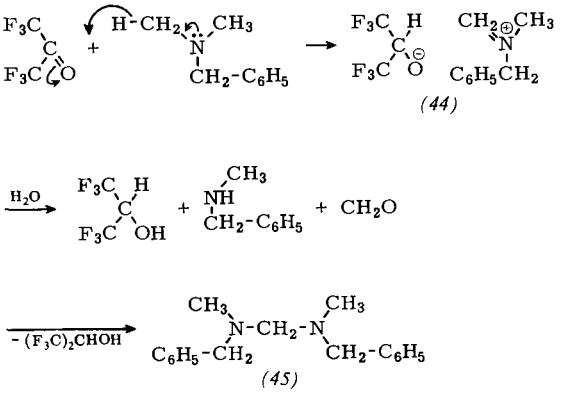


*(37)* *(42)*

### 6. Hydride Transfer

Hexafluoroacetone is readily reduced to 1,1,1,3,3,3-hexafluoro-2-propanol by $H^{\ominus}$ donors such as $Na[BH_4]$, $Li[AlH_4]$[49,50], or isopropylmagnesium bromide[18] (see also[51])[p].

However, the ease with which hexafluoroacetone abstracts protons from amines is unexpected. Hexafluoroacetone reacts exothermically with *N*-benzyldimethylamine to form an iminium salt *(44)*[26]. Surprisingly, the hydride ion is not removed from the methylene, but from the methyl group, evidently because of steric factors. The structure of *(44)* is inferred from the NMR spectrum and the chemical properties. Hydrolysis of *(44)* yields 1,1,1,3,3,3-hexafluoro-2-propanol and *N,N'*-dibenzyl-*N,N'*-dimethylmethylenediamine *(45)*, the latter being formed by condensation of formaldehyde and *N*-benzylmethylamine[26].



*(44)*

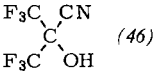
*(45)*

The fluorinated isopropyl alcohol is also obtained from hexafluoroacetone with benzylamine, triethylamine, and *N*-isopropyldimethylamine[26]. *N*-Benzyldiethyl- and tribenzylamines, on the other hand, do not react even when heated.

## II. Acid- and Base-Catalysed Reactions of Fluorinated Ketones

Many reactions of carbonyl compounds proceed only in the presence of acids or bases, and fluorinated ketones are fundamentally no exception in this respect. Basic catalysts liberate the conjugate base, *i.e.* the anion, from weak acids such as HCN or ethyl malonate, and this can then add on to carbonyl compound[54].

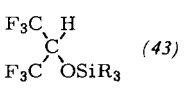
Like non-fluorinated carbonyl compounds, hexafluoroacetone reacts with HCN[q] only in the presence of a catalyst (*e.g.* a little piperidine) to form the *gem*-hydroxycyanide *(46)*, which can be converted readily into perfluoro-α-hydroxyisobutyric acid or its derivatives[36].



*(46)*

Perfluoronitroacetone reacts with HCN at 100 °C in the absence of catalysts[7]. Fluorinated ketones react also with KCN or NaCN to form the corresponding "cyanohydrin" salts[56].

Hexafluoroacetone in pyridine reacts readily with compounds such as *(47)* or *(48)* containing reactive methyl-



*(43)*

[47] *J. J. Monagle, T. W. Campbell,* and *H. F. McShane,* J. Amer. chem. Soc. *84,* 4288 (1962).

[48] *N. P. Gambaryan, E. M. Rokhlin, Yu. V. Zeifman,* and *I. L. Knunyants,* Izvest. Akad. Nauk SSSR, Ser. chim. *1965,* 749.

[49] *I. L. Knunyants* and *M. P. Krasuskaya,* authors' certificate (USSR) No. 138604.

[50] *W. J. Middleton* and *R. V. Lindsey,* J. Amer. chem Soc *86,* 4948 (1964).

[51] *H. J. Kötzsch,* Chem. Ber. *99,* 1143 (1966).

[p] As a result of the hydride transfer, the reaction of fluorinated ketones with trialkylsilanes leads to trialkylsilyloxy-1,1,1,3,3,3-hexafluoropropanes *(43)* [21,52,53]; hydrides of other group IV elements react similarly [52].

[52] *W. R. Cullen* and *G. E. Styan,* Inorg. Chem. *4,* 1437 (1965).

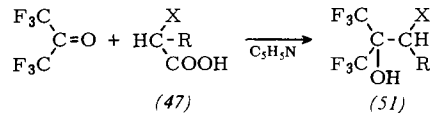
[53] *A. F. Yanzen* and *C. J. Willis,* Canad. J. Chem. *43,* 3063 (1965).

[54] *H. Felkin,* Bull. Soc. chim. France *1956,* 1510.

[q] Hexafluoroacetone reacts with isocyanic acid to give the relatively stable 2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)-ethyl isocyanate (decomposes above 0 °C) [55].

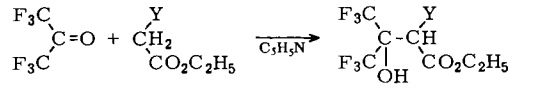
[55] *F. W. Hoover, H. B. Stevenson,* and *H. S. Rothrook,* J. org. Chemistry *28,* 1825 (1963).

[56] *T. Mill, J. O. Rodin, R. M. Silverstein,* and *C. Woolf,* J. org. Chemistry *29,* 3715 (1964).



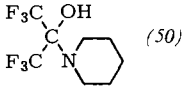
(47) (51)

| X | COOH | COOH | CN | $CO_2C_2H_5$ | $CO_2C_2H_5$ |
|---|---|---|---|---|---|
| R | H | $C_6H_5CH_2$ | H | $CH_3CONH$ | $C_6H_5CONH$ |



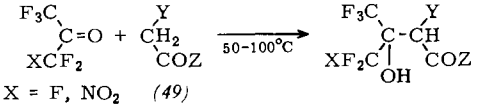
(48) Y = $CO_2C_2H_5$, $COCH_3$

ene [5,6,10,18,57,58] [r]. For reaction with non-fluorinated carbonyl compounds, the methylene groups must be activated with the stronger base piperidine [60]. In the reaction of hexafluoroacetone with malonic acid, more than two equivalents of piperidine even interfere due to formation of the adduct *(50)*, which cannot form the compound corresponding to *(51)* with malonic acid by the Knoevenagel mechanism [5].



*(50)*

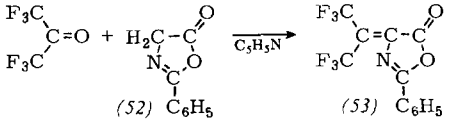
In some cases the condensation of fluorinated ketones with compounds containing active methylene groups *(49)* proceeds at 50–100 °C *without* catalysts [61,61a].[1]



X = F, $NO_2$ *(49)*

| Y | H | H | COOR |
|---|---|---|---|
| Z | $CH_3$ | $C_6H_5$ | OR |

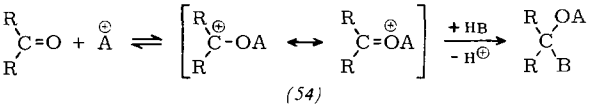
The behavior of hexafluoroacetone confirms the general rule that *the hydroxy compounds obtained from fluorinated ketones and compounds containing active methylene groups can be converted only with difficulty into the corresponding unsaturated compounds* [2].



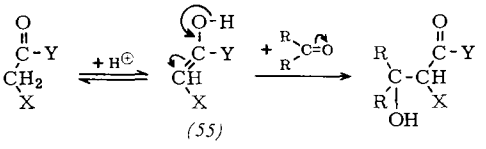
*(52)* *(53)*

An exception to this rule is the conjugated unsaturated derivative *(53)* obtained from hexafluoroacetone and 2-phenyl-$\Delta^2$-1,3-oxazolidin-5-one *(52)* in pyridine at room temperature [62] (but cf. [63]) [s].

An acid used as catalyst in reactions of carbonyl compounds can play a dual role: it activates the carbonyl compound, *i.e.* converts it into a carboxonium ion *(54)*, which is sufficiently electrophilic to interact with the weak nucleophile HB; in reactions with pseudo-acids, the catalyst favors the conversion of the pseudo-acid, which has no nucleophilic properties, into a sufficiently nucleophilic enol *(55)* [54].

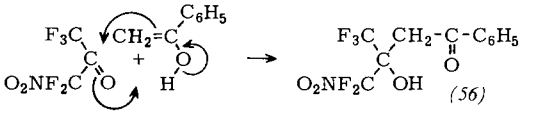


*(54)*



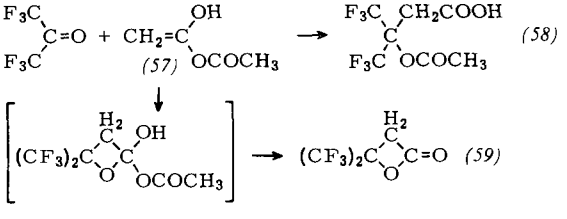
*(55)*

The second type of activation apparently occurs in the reaction of perfluoronitroacetone with acetophenone in the presence of a catalytic quantity of $H_2SO_4$, which leads at about 20 °C to the hydroxy ketone *(56)* [65].



*(56)*

The participation of the enol form of the compounds with active CH groups has been confirmed in the reaction of hexafluoroacetone with acetic anhydride in the presence of a catalytic amount of $H_2SO_4$ [66]. Thus the enol form *(57)* of acetic anhydride reacts in two ways, giving both an acetoxy acid *(58)* and a β-lactone *(59)*.



*(57)* *(58)* *(59)*

In this second type of activation, the fluorinated ketones react more readily than their non-fluorinated analogues. However, in reactions in which the catalytic action of the

[57] *I. L. Knunyants, Chen Ching-yun,* and *N. P. Gambaryan,* Ž. vses. chim. Obsc. im D. I. Mendeleeva *5*, 112 (1960).

[58] *E. M. Rokhlin,* Dissertation, Academy Institute for Organo-Elemental Compounds, Moscow 1962.

[r] Nitromethane reacts with hexafluoroacetone on heating in the presence of catalytic quantities of $K_2CO_3$ to form 1,1,1-trifluoro-3-nitro-2-trifluoromethyl-2-propanol [57, 59].

[59] *Chen Ching-yun, N. P. Gambaryan,* and *I. L. Knunyants,* Doklady Akad. Nauk SSSR *133*, 1113 (1960).

[60] *W. J. Gensler* and *E. Berman,* J. Amer. chem. Soc. *80*, 4949 (1958).

[61] *L. A. Simonyan, N. P. Gambaryan,* and *I. L. Knunyants,* Ž. vses. chim. Obšč. im. D. I. Mendeleeva *11*, 467 (1966).

[61a] *I. A. Dyatshenko, B. R. Livshits, N. P. Gambaryan, V. A. Komarov,* and *Kh. A. Abdulganieva,* Ž. vses. chim. Obsc. im. D. I. Mendeleeva, in press.

[62] *E. M. Rokhlin, N. P. Gambaryan, Chen Ching-yun,* and *I. L. Knunyants,* Doklady Akad. Nauk SSSR *134*, 1367 (1960).

[63] *E. M. Rokhlin, N. P. Gambaryan,* and *I. L. Knunyants,* Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1962*, 927.

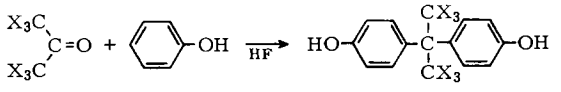
[s] 1,1,1-Trifluoroacetone and ethyl cyanoacetate also form the unsaturated ethyl α-cyano-β-trifluoromethyl-2-butenoate [64] under mild conditions.

[64] *E. B. Davidson* and *C. G. Overnerger,* J. org. Chemistry *27*, 2267 (1962).

[65] *L. A. Simonyan,* unpublished.

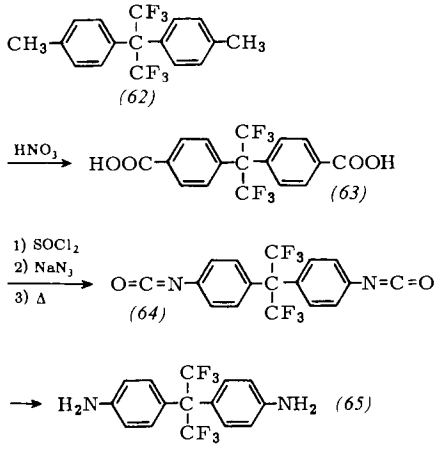
[66] *Yu. V. Zeifman* and *I. L. Knunyants,* Izvest. Akad. Nauk SSSR, Ser. chim. *1966*, 1661.

acid is based simply on activation of the carbonyl group, the reaction of the fluorinated ketones becomes more difficult owing to the lower basicity of the oxygen atom[t]. Thus acetone reacts with phenol in anhydrous hydrogen fluoride at room temperature to form 2,2-bis-(*p*-hydroxyphenyl)propane *(60)*[23], whereas hexafluoroacetone reacts only at about 100 °C to form the analogous compound *(61)*[u][6,23].



X = H : 20°C — *(60)*, X = H
X = F : 100°C — *(61)*, X = F

Toluene reacts with hexafluoroacetone in the presence of HF in the same way as phenols, but under somewhat more vigorous conditions[v]. The reaction yields hexafluoro-2,2-bis(*p*-tolyl)propane *(62)*, which is used for the synthesis of the dicarboxylic acid *(63)*, the diisocyanate *(64)*, and the diamine *(65)*[73–76].



*(62)*

*(63)*

*(64)*

*(65)*

[t] Accordingly, non-fluorinated ketones dissolve in concentrated $H_2SO_4$, whereas fluorinated ketones do not [67]. Hexafluoroacetone reacts with $PCl_5$ only at 275–300 °C, giving 2,2-dichlorohexafluoropropane [68]. Concerning the reaction of perfluorocyclobutanone with boron chlorides, see [21].

[67] *R. N. Haszeldine*, J. chem. Soc. (London) *1953*, 1748.

[68] *B. S. Farah* and *E. E. Gilbert*, J. org. Chemistry *30*, 1241 (1965).

[u] The diphenol *(61)* is a starting material for the preparation of polymers [69–72].

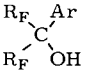
[69] *A. Ya. Yakoubovich, I. L. Knunyants, E. M. Grobman, L. I. Maslennikova*, and *G. Ya. Gordon*, author's certificate (USSR) No 132403.

[70] *M. D. Bargamova, Yu. A. Cheburkov*, and *I. L. Knunyants*, author's certificate (USSR) No. 138037.

[71] *N. P. Gambaryan, G. S. Nesmeyanova*, and *I. L. Knunyants*, Ž. vses. chim. Obšč. im. D. I. Mendeleeva *7*, 231 (1962).

[72] *V. V. Korshak, S. V. Vinogradova*, and *V. A. Pankratov*, Doklady Akad. Nauk SSSR *156*, 880 (1964).

[v] In this case it was possible to isolate the intermediate *(66)*.



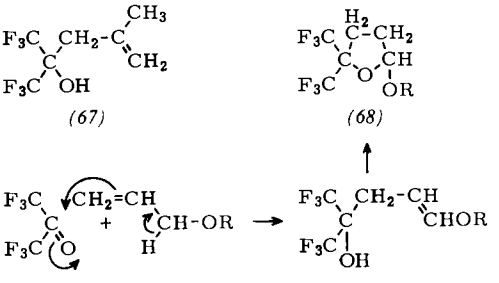
*(66)*

[73] *B. R. Livshits, I. A. Dyatshenko, V. P. Paliy*, and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Ser. chim., in press.

The condensation of fluorinated ketones with aromatic compounds and with compounds containing active methylene groups is also catalysed by Lewis acids[6,73,77–81].

The electrophilicity of fluorinated ketones is so high that they can react sometimes without prior activation of the carbonyl group, even with very weak nucleophiles which react with non-fluorinated ketones only in the presence of catalysts. For example, hexafluoroacetone reacts with isobutene at room temperature[82]; with less nucleophilic olefins, it reacts only on heating or in the presence of $AlCl_3$[82,83]. Perfluoronitroacetone[82] and perfluorocyclobutanone[78], which is further activated as a result of the ring strain, react even more readily with olefins.

Fluorinated ketones react with olefins containing allylic hydrogen by a six-membered cyclic transfer, *i.e.* with allyl rearrangement[w], resulting in the formation of unsaturated alcohols such as *(67)* or of products such as *(68)*[78,82].



*(67)*

*(68)*

With olefins containing no allylic hydrogen (*e.g.* styrene or vinyl ethers)[61a,65,85] and with 1,3-dienes[78,86,87], fluorinated ketones react under very mild conditions to

[74] *B. R. Livshits, T. Ch. Dymshits, N. P. Cambaryan*, and *I. L. Knunyants*, Ž. vses. chim. Obšč. im. D. I. Mendeleeva *11*, 469 (1966).

[75] Dutch Pat. Appl. 6406896 (Dec. 18th, 1964), du Pont; Chem. Abstr. *62*, 14585 (1965).

[76] *I. L. Knunyants, N. P. Gambaryan, B. R. Livshits*, and *L. A. Simonyan*, authors' certificate (USSR) No. 179764.

[77] *W. Y. Middleton*, J. org. Chemistry *30*, 1402 (1965).

[78] *D. C. England*, J. Amer. chem. Soc. *83*, 2205 (1961).

[79] *D. C. England*, French Pat. 1325204 (April 26th, 1963); Chem. Abstr. *59*, 11339 (1963).

[80] *B. S. Farah, E. E. Gilbert*, and *Y. P. Sibilia*, J. org. Chemistry *30*, 998 (1965).

[81] *B. S. Farah, E. E. Gilbert, M. Litt, Y. A. Otto*, and *Y. P. Sibilia*, J. org. Chemistry *30*, 1003 (1965).

[82] *Yu. V. Zeifman, El. M. Rokhlina*, and *N. P Gambaryan*, Izvest. Akad. Nauk. SSSR, Ser. chim *1965*, 1466.

[83] *I. L. Knunyants* and *B L. Dyatkin*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1962*, 355.

[w] Ethyl pyruvate reacts with asymmetrically substituted olefins only under more vigorous conditions, but in accordance with the same scheme [84].

[84] *R. T. Arnold* and *P. Veeravagu*, J. Amer. chem. Soc. *82*, 5411 (1960).

[85] *H. R. Davis*, US.-Pat. 3164610 (1965); Chem. Abstr. *62*, 7727 (1965).

[86] *Yu. V. Zeifman, N. P. Gambaryan*, and *I. L. Knunyants*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 1472.

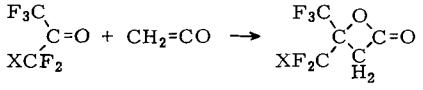
[87] *W. J. Linn*, J. org. Chemistry *29*, 3111 (1964).

give four-membered *(69)* [x] or six-membered cycloadducts *(70)* [y].

*(69)* *(70)*

X = F, $NO_2$; Y = $C_6H_5$, OAlk

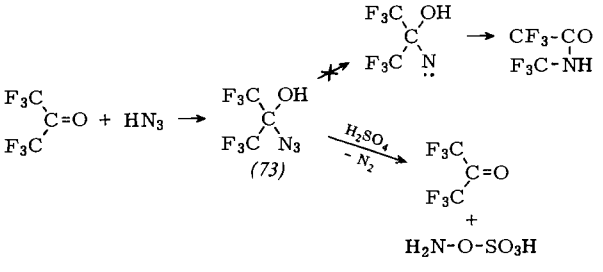
Hexafluoroacetone [90] and perfluoronitroacetone [7] react still more readily, and in the absence of catalysts, with ketene to form the β-lactone *(72)*, whereas a Lewis acid, *e.g.* $BF_3$, is required to activate acetone [91]. It is worth noting that the reaction of trifluoroacetone with



X = F, $NO_2$ *(72)*

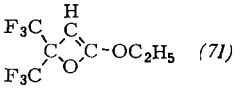
ketene proceeds only in the presence of a catalyst and under more vigorous conditions than are required for acetone. The electrophilicity of trifluoroacetone, which hinders catalytic activation, is apparently not high enough to enable this ketone to react without additives [92].

Perfluoroketones are also electrophiles in relation to hydrazoic acid, whereas non-fluorinated ketones behave as nucleophiles. With non-fluorinated ketones, the reaction begins with an attack by the acid catalyst on the carbonyl oxygen atom; the *gem*-hydroxyazide formed as an intermediate, which normally cannot be isolated, loses $N_2$ and undergoes a Schmidt rearrangement [93]. Hexafluoroacetone reacts with $HN_3$ without catalysts to form 2-azido-1,1,1,3,3,3-hexafluoro-2-propanol



*(73)*

[x] Hexafluoroacetone reacts with ethoxyacetylene to give the adduct *(71)* [88].



*(71)*

[88] *W. J. Middleton*, J. org. Chemistry *30*, 1307 (1965).

[y] Non-fluorinated ketones do not enter into this diene synthesis. Even the reactive ethyl mesoxalate reacts only at 100 to 135 °C; only carbonyl dicyanide reacts at 20 °C to give a 5,6-dihydro-2*H*-pyran [89].

[89] *O. Achmatowicz* and *A. Zamojski*, Bull. Akad. Sci. polon. Cl. III *5*, 927 (1957).

[90] *I. L. Knunyants* and *Yu. A. Cheburkov*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk, *1960*, 678.

[91] *H. E. Zaugg*, Org. Reactions *8*, 305 (1954).

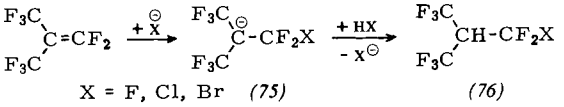
[92] *I. L. Knunyants* and *Yu. A. Cheburkov*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1961*, 808.

[93] *H. Wolf*, Org. Reactions *3*, 307 (1946).

*(73)* [z]. Conversion into *N*-trifluoromethyltrifluoroacetamide could not be achieved; instead of the Schmidt rearrangement, the *gem*-hydroxyazide decomposed and hexafluoroacetone was liberated [18].

Perfluoronitroacetone [7] and perfluorocyclobutanone [94,95] give stable adducts even with hydrogen halides, FNO, and $FNO_2$ (probably as with nucleophilic reagents). Although hexafluoroacetone forms a fairly stable adduct with FNO [95], it does not react with hydrogen halides; with KF in diglyme, however, it gives potassium heptafluoro-2-propanolate [96] [A].

A change in reaction mechanism is observed also in the hydrohalogenation of perfluoroisobutene to *(76)*, which unlike that of non-fluorinated olefins, proceeds readily only in the presence of catalytic quantities of halogen anions [98,99] [B].



X = F, Cl, Br *(75)* *(76)*

Thus in reactions of fluorinated ketones (as well as of other compounds containing π-bonds of low electron density) with weak nucleophiles, a peculiar "reversal" of the reaction mechanism is observed in some cases:

*Electrophilic addition in non-fluorinated ketones becomes nucleophilic addition in fluorinated ketones.*

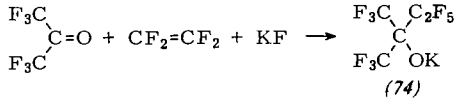
[z] A *gem*-hydroxyazide of this type was also obtained [78] from perfluorocyclobutanone and $HN_3$.

[94] *S. Andreades* and *D. C. England*, J. Amer. chem. Soc. *83*, 4670 (1961).

[95] *S. Andreades*, J. org. Chemistry *27*, 4157 (1962).

[96] *A. G. Pittman* and *D. L. Sharp*, Polymer Letters *3*, 379 (1965).

[A] The reaction of perfluorinated ketones, KF, and tetrafluoroethylene in diglyme leads to t-alkoxides, *e.g. (74)*, as a result of addition of the anion $CF_3CF_2^{\ominus}$ to the fluorinated ketone [97].



*(74)*

[97] *D. P. Graham* and *V. Weinmayr*, J. org. Chemistry *31*, 957 (1966).

[98] *I. L. Knunyants, M. P. Krasuskaya*, and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 723.

[99] *I. L. Knunyants, S. T. Kocharyan, Yu. A. Cheburkov, M. D. Bargamova*, and *E. M. Rokhlin*, Doklady Akad. Nauk SSSR *165*, 827 (1965).

[B] Similar effects have been observed in other reactions of fluorinated olefins [100–104] and polycyanoethylenes [105,106].

[100] *W. T. Miller, J. H. Fried*, and *H. Goldwhite*, J. Amer. chem. Soc. *82*, 3091 (1960).

[101] *R. E. Banks, R. N. Haszeldine*, and *D. R. Taylor*, Proc. chem. Soc. (London) *1964*, 121.

[102] *F. S. Fawcet, C. W. Tullock*, and *D. D. Coffmann*, J. Amer. chem. Soc. *84*, 4275 (1962).

[103] *S. Andreades*, J. org. Chemistry *27*, 4163 (1962).

[104] *C. G. Krespan*, J. org. Chemistry *27*, 1813 (1962).

[105] *C. L. Dickinson, D. W. Wiley*, and *B. C. McKusick*, J. Amer. chem. Soc. *82*, 6132 (1960).

[106] *C. L. Dickinson* and *B. C. McKusick*, J. org. Chemistry *29*, 3087 (1964).

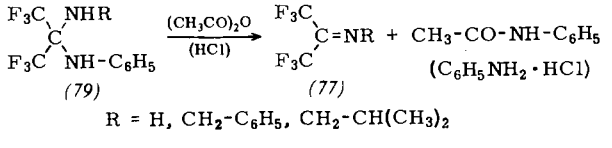
## III. Peculiarities in the Formation and Chemical Properties of Fluorinated Imines

A characteristic feature of perfluoroketones is that reactions with ammonia, amines, hydrazine, hydroxylamine, and other compounds containing amino groups do not lead to substitution of the carbonyl oxygen and formation of a C=N grouping. They lead instead to geminal amino alcohols[C], which do not lose water spontaneously, and which usually cannot be dehydrated even with reagents such as acetic anhydride[13].

When the carbonyl group carries only *one* perfluoroalkyl substituent, the usual derivatives of carbonyl compounds are still obtained. Thus benzyl trifluoromethyl ketone[108] and 1,1,1-trifluoroacetone[109,110] give oximes and hydrazones in the usual manner.

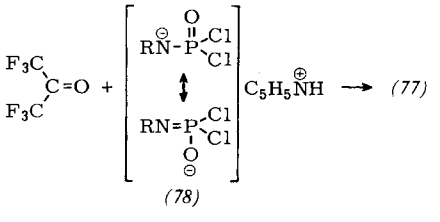
We have also obtained the anil 1,1,1-trifluoro-*N*-phenylpropane-2-imine directly from 1,1,1-trifluoroacetone and aniline[13], whereas hexafluoropropane-2-imines *(77)* could only be obtained by special methods (see also Section I.5). For example, the reaction of hexafluoroacetone with $NH_3$ followed by treatment with $POCl_3$ in pyridine yields imines *(77)*, R = H or $CH_3$[111] [D].

The most remarkable imine synthesis is based on the decomposition of *N*-alkyl-*N'*-phenylhexafluoropropane-2,2-diamines *(79)* in the presence of electrophilic reagents[13,46]. The route of decomposition of the diamine *(79)* depends on the relative basicities of the two amine residues: If the difference in the basicities of the amine residues (and hence the stability of the cations *(80)* resulting from the cleavage) is very large (several powers of ten), the route of decomposition is determined by the stability of the cation *(80)* and the less basic amine is split off (route A); if the difference in basicity is not large (not more than one power of ten), as in the diamine *(81)*, the predominant point of attack for the electrophile is the deciding factor, with the result that the more basic amine is split off (route B)[112].

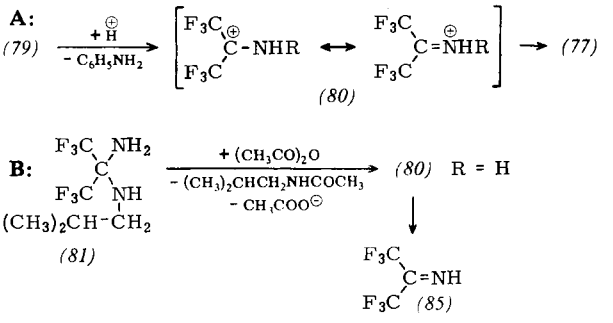



*(79)* *(77)*

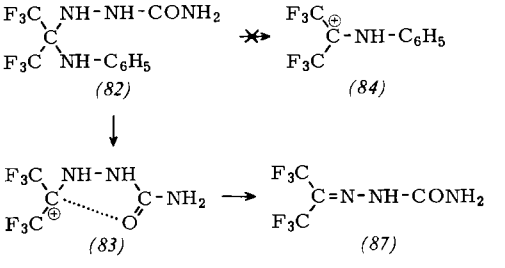
R = H, $CH_2$-$C_6H_5$, $CH_2$-$CH(CH_3)_2$



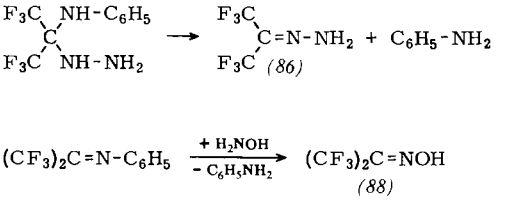

*(78)*




In the HCl-catalysed decomposition of 1-(1-anilino-2,2,2-trifluoro-1-trifluoromethylethyl)semicarbazide *(82)*[14], the elimination of aniline is due to the greater basicity of the latter as well as to the greater stability of the carbonium ion *(83)* in comparison with the carbonium ion *(84)*.




The unsubstituted hexafluoropropane-2-imine *(85)* [= *(77)*, R = H] is most easily obtained by thermal elimination of aniline (180 °C) from hexafluoro-*N*-phenylpropane-2,2-diamine *(79)*, R = H[46]. Thermal decomposition has also been used for the preparation of the hydrazone *(86)*, the semicarbazone *(87)*, and the oxime *(88)*[E] of hexafluoroacetone[13,14]; the oxime *(88)* can be prepared by other methods as well[113–115].




[C] Perfluoro-4-heptanone [107] and perfluoronitroacetone [7, 13] undergo haloform cleavage on reaction with amines.

[107] *M. Hauptstein* and *R. A. Braun*, J. Amer. chem. Soc. *77*, 4930 (1955).

[108] *W. R. Nes* and *A. Burger*, J. Amer. chem. Soc. *72*, 5412 (1950).

[109] *F. Swarts*, Bull. Akad. roy. Belg. *13*, 175 (1927).

[110] *A. L. Henne, M. S. Newman, L. L. Quill*, and *R. A. Staniforth*, J. Amer. chem. Soc. *69*, 1819 (1947).

[111] *W. J. Middleton* and *C. G. Krespan*, J. org. Chemistry *30*, 1398 (1965).

[D] This probably involves not a dehydration of a geminal amino alcohol, but a reaction of the Wittig-Staudinger type between hexafluoroacetone and the pyridinium salt *(78)*, R = H or $CH_3$ [112].

[112] *N. P. Gambaryan*, Dissertation, Institute for Organo-Elemental Compounds, Moscow 1965.

[E] The oxime of hexafluoroacetone and hexafluoro-2-(hydroxylamino)-2-propanol does not undergo the Beckmann rearrangement; sulfuric acid regenerates hexafluoroacetone [13,18].

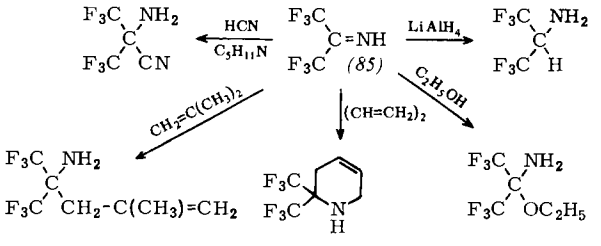
[113] *I. L. Knunyants, B. L. Dyatkin, L. S. German, I. N. Rozhkov*, and *V. A. Komarov*, Ž. vses. chim. Obšč. im. D. I. Mendeleeva *8*, 709 (1963).

[114] *B. L. Dyatkin, E. P. Mochalina, L. T. Lanceva*, and *I. L. Knunyants*, Ž. vses. chim. Obšč. im. D. I. Mendeleeva *10*, 469 (1965).

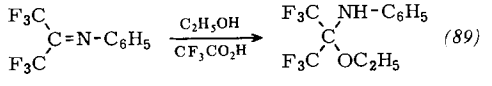
[115] *I. L. Knunyants, L. S. German, I. N. Rozhkov*, and *B. L. Dyatkin*, Izvest. Akad. Nauk SSSR, Ser. chim. *1966*, 250.

The trifluoromethyl groups considerably increase the electrophilicity of the azomethine bond in hexafluoropropane-2-imine *(85)*. This is shown particularly by the ease of reaction with ammonia and with amines [F]. In contrast to the non-fluorinated azomethines [116], adducts can be isolated in this case [13,46]; thus hexafluoropropane-2,2-diamine can be distilled at 91–92 °C/760 mm without decomposition [46].

Unlike the other known aliphatic imines [117], hexafluoropropane-2-imine *(85)* is stable up to 250 °C. It gives many of the characteristic reactions of azomethines, such as reduction with lithium tetrahydridoaluminate or addition of HCN [G]. Unlike azomethines, *(85)* reacts smoothly with ethanol at 100 °C [46]. The diene synthesis and the reaction of hexafluoropropane-2-imine *(85)* with isobutene [86] are also novel.

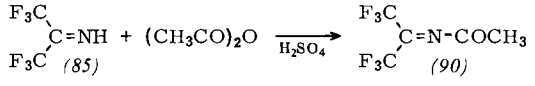


Hexafluoro-*N*-phenylpropane-2-imine is less reactive than *(85)*. However, the geminal ethoxy amine *(89)* can be obtained with ethanol and a little trifluoroacetic acid [46].

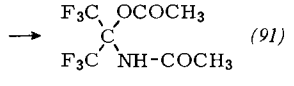


*(89)*

This reaction shows that catalysis by electrophiles is more important with hexafluoropropane-2-imines than with hexafluoroacetone itself, since the imine nitrogen is more nucleophilic than the carbonyl oxygen. Thus the imine *(85)* is acylated by ketene only in the presence of $BF_3$, the product being the *N*-acetyl derivative *(90)* [111]. Compound *(85)* does not react with acetic anhydride in the absence of catalysts, even at 100 °C, but in the presence of $H_2SO_4$ at 0 °C it gives the adduct *(91)*, probably *via (90)* [27].

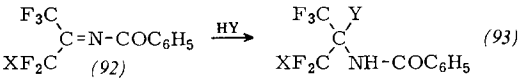


*(85)* *(90)*



*(91)*

The azomethine linkage in imines of fluorinated ketones can be activated not only by acids, but also by replacement of the hydrogen in the imino group by electron-attracting substituents. Thus *N*-acylimines of fluorinated ketones, *e.g. (92)*, react readily with water, alcohols, amines, amides, phenylacetylene, and acetophenone to give the corresponding adducts *(93)* [17,118].

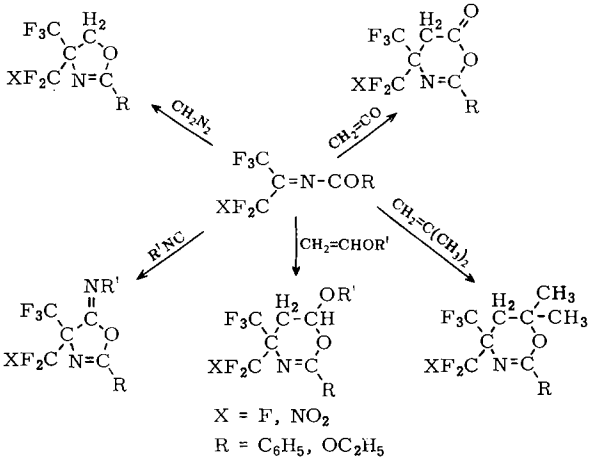


*(92)* *(93)*

X = F, $NO_2$

Y = OH, OR, NHR, $C{\equiv}C\text{-}C_6H_5$, $NH\text{-}COC_6H_5$, $CH_2\text{-}COC_6H_5$

*N*-Acylimines of hexafluoroacetone and pentafluoronitroacetone also enter into 1,4-additions with diazomethane, isonitriles, ketene [H], vinyl ethers, and olefins, which had previously been unknown for acylimines [33,



X = F, $NO_2$

R = $C_6H_5$, $OC_2H_5$

118,121]. Nevertheless, the activities of the *N*-acylimines of perfluorinated ketones are lower than those of hexafluoroacetone and perfluoronitroacetone. This is due to the lower polarity of the C=N bond as compared with the C=O bond.

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Translated by Express Translation Service, London

[F] 1,1,3,3,3-Pentafluoro-1-nitro-*N*-phenylpropane-2-imine undergoes haloform cleavage with ammonia or amines [13].

[116] *R. W. Layer*, Chem. Reviews *63*, 489 (1963).

[117] *P. L. Pickard* and *T. L. Tolbert*, J. org. Chemistry *26*, 4886 (1961).

[G] The imine *(85)* readily adds $HN_3$ and HNCO to form 1-amino-2,2,2-trifluoro-1-trifluoromethylethyl azide and isocyanate, respectively [111].

[118] *N. P. Gambaryan*, unpublished.

[H] A similar 1,4-addition of ketene is possible in the case of 4-hexafluoroisopropylidene-2-phenyl-$\Delta^2$-1,3-oxazolidin-5-one *(53)*, but only in the presence of pyridine [119,120].

[119] *E. M. Rokhlin* and *N. P. Gambaryan*, Izvest Akad Nauk SSSR, Otdel. chim. Nauk *1963*, 1952.

[120] *E. M. Rokhlin* and *N. P. Gambaryan*, Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1963*, 1959.

[121] *Yu. V. Zeifman*, *N. P. Gambaryan*, and *R. B. Minasyan*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 1910.

## Quaternary Structure and Color of Crustacyanin

By Prof. R. Kuhn and H. Kühn

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Institut für Chemie, Heidelberg (Germany)

From lobster shells a blue chromoprotein (crustacyanin) can be isolated [1], whose prosthetic group is astaxanthin (3,3'-dihydroxy-4,4'-dioxo-β-carotene [2]). We used Calgon® to decalcify the shells, from which the chromoprotein could then be extracted readily with a phosphate buffer (pH 7). Purification was effected by salting out with ammonium sulfate and by preparative ultracentrifugation.

α-Crustacyanin, the native chromoprotein ($\lambda_{max}$ = 632 mμ in water), is stable for months in 0.2 M phosphate buffer (pH 7). It behaves as a single substance in the analytical ultracentrifuge, on fractional salting out with ammonium sulfate, and on electrophoresis. Extinction coefficients of 1% aqueous solutions (1 cm path) are: $E_{278\ m\mu} = 19.4 \pm 0.4$ and $E_{632\ m\mu} = 65 \pm 2$. One mole of astaxanthin is present in 19000 ± 1000 g of chromoprotein. α-Crustacyanin contains 15.7% of N (Dumas method) and the following amino acids [3] (g of anhydro amino acid per 100 g of chromoprotein): Lys 6.86; His 1.99; Arg 4.37; Asp 12.95; Thr 5.71; Ser 5.58; Glu 8.41; Pro 4.69; Gly 2.61; Ala 5.58; Val 6.64; Ileu 3.82; Leu 4.20; Phe 8.67; Tyr 9.76; Cys 1.39; Try 2.5.

α-Crustacyanin has a molecular weight of *ca.* 310000; it contains 16 molecules of bound astaxanthin. The intrinsic viscosity at 20 °C is $[\eta] \approx 0.09$ dl/g, corresponding to an axial ratio of about 10:1 if an ellipsoid of revolution [4] is assumed.

Subunits of molecular weight *ca.* 38000 (= β-crustacyanin, $\lambda_{max}$ = 585 mμ in water) are formed from α-crustacyanin in neutral phosphate buffers of low ionic strength; β-crustacyanin contains two molecules of bound astaxanthin per protein molecule.

In acidic solution (pH 3.7 to 3.0) and in neutral 0.15% sodium dodecyl sulfate solution α- and β-crustacyanin dissociate to subunits of molecular weight *ca.* 20000; the absorption maximum is shifted to 440 mμ (acidic solution) or 482 mμ (dodecyl sulfate solution). These subunits contain one molecule of bound astaxanthin each.

α- and β-Crustacyanin can be further dissociated by the action of alkali (pH ≥ 11) or urea (≥ 4 M), yielding smaller, colorless subunits, which sediment at only 1.2 S, and a colored component which sediments faster ($\lambda_{max}$ of the whole solution = 400 mμ).

Like α-crustacyanin, β-crustacyanin and the fragments of molecular weight *ca.* 20000 also behave homogeneously in the ultracentrifuge.

The changes in quaternary structure of α- and β-crustacyanin under the influence of acids, bases, or urea are reversible: neutralization or dialysis against phosphate buffer regenerates α-crustacyanin from the solutions of the subunits, and this product cannot be differentiated from native α-crustacyanin in the ultracentrifuge. Treatment of β-crustacyanin with acids, bases, urea, or detergents yields subunits having the same $\lambda_{max}$ values and molecular weights as those from α-crustacyanin. Neutralization or dialysis of solutions of these subunits, however, regenerates only β-crustacyanin and no α-crustacyanin, whence it follows that the formation of β-crustacyanin from α-crustacyanin is not reversible.

| Substance | $\lambda_{max}$ [mμ] | Mol. wt. at 20 °C | Method |
|---|---|---|---|
| α-Crustacyanin | 632 | 320000 | Ultracentrifuge |
| | | 307000 | Light scattering [5] |
| β-Crustacyanin | 585 | 36000 | Ultracentrifuge |
| | | 39500 | Osmometry [6] |
| α- or β-Crust. after treatment with 0.15% Na dodecyl sulfate | 482 | 19600 | Ultracentrifuge |
| α- or β-Crust. at pH 3.5 | 440 | 19800 | Ultracentrifuge |
| α- or β-Crust. at pH 13 | 400 | ≤10000 | Ultracentrifuge |
| α- or β-Crust. in 8 M urea soln. | 400 | ≤10000 | Ultracentrifuge |
| Equiv. wt. of α- and β-crust. (calc. per mole of astaxanthin) | | 19000 | Photometry, dry wt. |

Received: August 9th, 1966 [Z 310 IE]
German version: Angew. Chem. *78*, 979 (1966)

[1] *G. Wald, N. Nathanson, W. P. Jencks*, and *E. Tarr*, The Biological Bulletin *95*, 249 (1948); *W. P. Jencks* and *B. Buten*, Arch. Biochem. Biophysics *107*, 511 (1964); *D. F. Cheesman, P. F. Zagalsky*, and *H. J. Ceccaldi*, Proc. Roy. Soc. (London) *164 B*, 130 (1966).

[2] *R. Kuhn* and *N. A. Sörensen*, Ber. dtsch. chem. Ges. *71 B*, 1879 (1938); Angew. Chem. *51*, 465 (1938).

[3] Measurements by Dr. *E. Schweizer*, Max-Planck-Institut für Zellchemie, Munich.

[4] *H. A. Scheraga* and *L. Mandelkern*, J. Amer. chem. Soc. *75*, 179 (1953).

[5] Measurements by Dr. *E. Schuch*, BASF, Ludwigshafen.

[6] Measurements by *S. Knof*, Institut für physikalische Biochemie und Kolloidchemie, Frankfurt/Main.

## Synthesis of the Central Octacyclic Structure of the Principal Calebash Curare Alkaloid, C-Curarine-I [1]

By Prof. H. Fritz and R. Oehl

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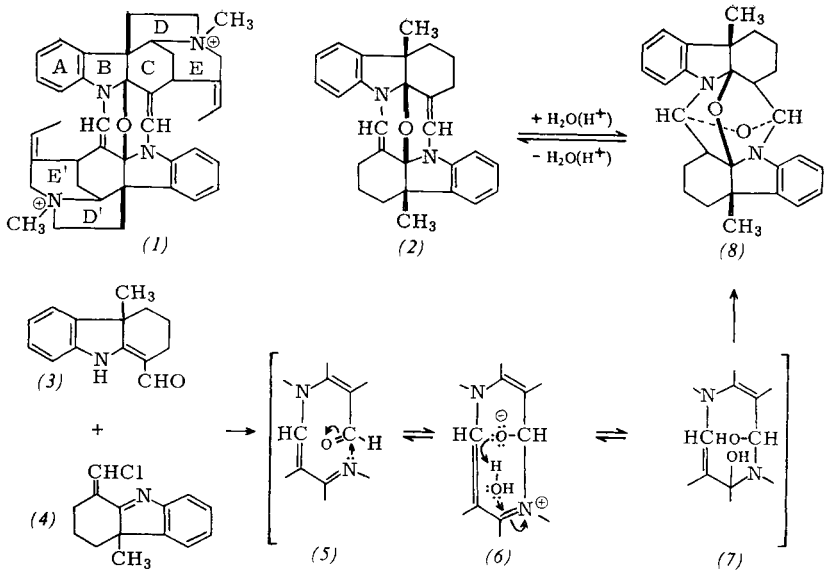
If from C-curarine-I [2] *(1)* one formally eliminates the rings D,E,D', and E' fused around the periphery, one obtains an octacyclic ring system *(2)* which constitutes the chromophore of the alkaloid. We have succeeded in synthesizing this long sought chromophore [3], whose structural peculiarity is the central diazacyclooctadiene system bridged by an oxygen atom.

If an equimolar mixture of the compounds *(3)* [4] and *(4)* [5] in moist ether is kept for about 18 hr at 20 °C, the racemate (m.p. 216 °C) of the indoline derivative *(8)* is first formed, in about 20% yield, in a stereospecific reaction [5].

The structure *(8)* is proved by elemental analysis, UV spectrum (indoline absorption), IR spectrum (ether band at 8.38 μ; no OH or NH band), and mass spectrum ($M^+ = 426$). In particular, the NMR spectrum (in $CDCl_3$) shows the presence of two equivalent *C*-methyl groups (6H singlet at $\tau = 8.93$; TMS as internal standard) and two equivalent amino-acetal protons (2H singlet [6] at $\tau = 4.63$). The $C_2$ symmetry required for formula *(8)* follows from the equivalence of these groups. The central tricyclic system of structure *(8)* — which is almost strain-free in the model — is isosteric with that of adamantane, and in fact is that of 2,6-dioxa-4,8-diazaadamantane. The "indoline base VII" of unknown constitution [7] obtained from C-curarine-I is very probably identical with compound *(8)* in its central nonacyclic structure.

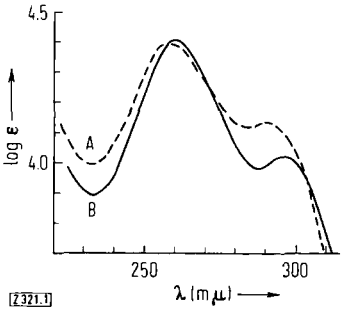
Formation of compound *(8)* from *(3)* and *(4)* and one molecule of water presumably proceeds by way of *(5)*, *(6)*, and *(7)*.

Acid catalysed dehydration (methanolic 1 N HCl; 20 °C; 24 hr) leads to equilibration of *(8)* with *(2)* (m.p. 205 °C), which is also formed in a sterically pure form. An approxi-



mately equimolar mixture of *(8)* and *(2)* results, independently of which of them is the starting material. These substances can be easily separated by preparative chromatography on silica gel G with benzene; they crystallize readily.

The structure *(2)* is in agreement with elemental analyses, the molecular weight (408) determined by mass spectrometry, and the IR spectrum (no OH or NH band). The NMR spectrum shows that like *(8)*, compound *(2)* has $C_2$ symmetry, since the six protons of the two *C*-methyl groups give a sharp singlet at $\tau = 8.87$ (in $CDCl_3$; TMS as internal standard). The two protons attached to enamine C atoms give a signal at $\tau = 3.30$ slightly split by allylic coupling, *i.e.* at the same position as that of the corresponding protons of nor-C-curarine-I [2b]. This result definitely excludes one alternative structure to *(2)* for our synthesis product (O bridge between the two CH groups and correspondingly different positions of the double bonds) because in that case the two protons in question would be attached to amino-acetal C atoms and their resonance signals would appear at appreciably higher field.




UV spectra.

A: Synthetic C-curarine derivative *(2)*, 0.390 mg in 25 ml of methanol.

B: C-curarine-I dichloride *(1)* + $2Cl^{\ominus}$, 0.507 mg in 25 ml of methanol.

Finally, the UV spectrum of compound *(2)* (see Figure) agrees as well with that of C-curarine-I *(1)* as is possible in view of the simplified structure of the former. The higher alkyl substitution of the alkaloid *(1)* than of compound *(2)* is weakly discernable in that the spectrum of the former has the short-wavelength and the long-wavelength maxima shifted bathochromically by 2 and 7 mμ, respectively, in comparison with that of the latter.

Our synthetic C-curarine-I derivative *(2)* also gives the intense blue color with ceric sulfate/sulfuric acid [8] that is typical of C-curarine-I, the shades and the intensities being identical.

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German version: Angew. Chem. *78*, 978 (1966)

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[1] Presented at the *Westdeutsche Chemiedozententagung* in Würzburg (Germany), April 1966. Synthetic Experiments in the Indole Alkaloid Series, Part V. – Part IV: *H. Fritz* and *O. Fischer*, Tetrahedron *20*, 2047 (1964).

[2a] *H. Wieland*, *W. Konz*, and *R. Sonderhoff*, Liebigs Ann. Chem. *527*, 160 (1937); *H. Wieland* and *H. J. Pistor*, *ibid. 536*, 68 (1938).

[2b] *J. Nagyvàry*, *W. Arnold*, *W. v. Philipsborn*, *H. Schmid*, and *P. Karrer*, Tetrahedron *14*, 138 (1961).

[3] *K. Bernauer*, Fortschr. Chem. org. Naturstoffe *17*, 183 (1959).

[4] *H. Fritz*, Chem. Ber. *92*, 1809 (1959).

[5] *H. Fritz*, *A. Krekel*, and *H. Meyer*, Liebigs Ann. Chem. *664*, 188 (1963).

[6] Splitting of this signal by coupling with the neighboring proton is difficult to detect because of the 60–70 ° dihedral angle.

[7] *W. v. Philipsborn*, *W. Arnold*, *J. Nagyvàry*, *K. Bernauer*, *H. Schmid*, and *P. Karrer*, Helv. chim. Acta *43*, 141 (1960).

[8] *J. Kebrle*, *H. Schmid*, *P. Waser*, and *P. Karrer*, Helv. chim. Acta *36*, 102 (1953).

## Synthesis of Derivatives of Benzo[*b*]thiepin and Benzo[*b*]thiepin 1,1-Dioxide [1]

By Dr. Hans Hofmann and H. Westernacher

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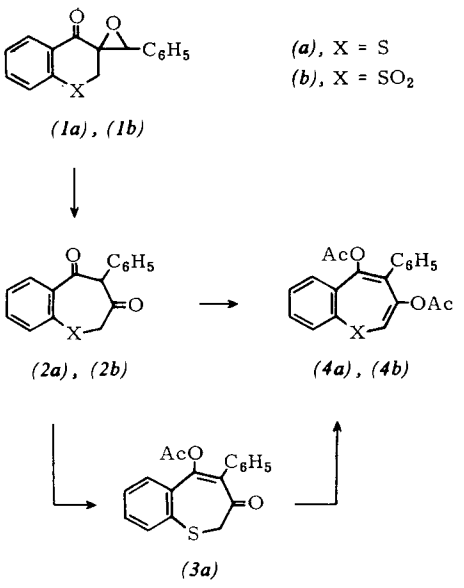
der Universität Erlangen-Nürnberg (Germany)

Treatment of spiro[1-thio-4-chromanone-3,2′-(3′-phenyloxirane)] *(1a)* or spiro[(1-thio-4-chromanone 1,1-dioxide)-3,2′-(3′-phenyloxirane)] *(1b)* [2] with concentrated sulfuric acid or boron trifluoride-ether affords 2,3,4,5-tetrahydro-4-phenylbenzo[*b*]thiepin-3,5-dione *(2a)*, m.p. 93 to 94 °C, yield 70 %, or its dioxide *(2b)*, m.p. 162–163 °C, yield 90 %. The compounds *(2a)* and *(2b)* were isolated in the same way as the analogous benzo[*b*]oxepins [3].

The IR spectrum (in KBr; C=O stretching vibrations at 1732 and 1673 $cm^{-1}$) and the $^1$H-NMR spectrum [in $CDCl_3$; $\tau = 6.5$ (2 H), $\tau = 3.65$ (1 H)] show that compound *(2a)* exists exclusively as diketone in the solid state and in slightly polar solvents. However, the IR spectrum (in KBr, OH stretching vibration at 3550 $cm^{-1}$, C=O stretching vibrations at 1735, 1698, and 1636 $cm^{-1}$, S=O stretching vibrations at 1321 and 1160 $cm^{-1}$) of compound *(2b)* indicates an enolized molecule.



*(1a), (1b)* *(a)*, X = S; *(b)*, X = $SO_2$

*(2a), (2b)* *(4a), (4b)* *(3a)*

Treatment of compound *(2a)* with acetic anhydride in pyridine for 45 min at room temperature gives 5-acetoxy-2,3-dihydro-4-phenylbenzo[*b*]thiepin-3-one *(3a)*, m.p. 124 to 125 °C, in 65 % yield, but after 15 hr at room temperature only 3,5-diacetoxy-4-phenylbenzo[*b*]thiepin *(4a)*, m.p. 86 to 87 °C, was obtained (yield 98 %). To the best of our knowledge this is the first compound containing a benzo[*b*]thiepin skeleton.

The compound *(2b)* with acetic anhydride in pyridine (10 min, room temperature) affords directly 3,5-diacetoxy-4-phenylbenzo[*b*]thiepin 1,1-dioxide *(4b)*, m.p. 140–141 °C (yield 98 %).

The structures of compounds *(4a)* and *(4b)* follow from the IR and NMR spectra:

*(4a)*: IR (in KBr): enol acetate C=O at 1768 $cm^{-1}$.
NMR (in $CDCl_3$): non-aromatic protons at $\tau$ = 8.35 and 8.15 (each 3 H of the two acetate groups) and at $\tau$ = 4.0 (1 H).

*(4b)*: IR (in KBr): enol acetate C=O at 1775 $cm^{-1}$; S=O stretching vibration at 1324 $cm^{-1}$ (the asymmetric S=O stretching vibration is overlapped by the C–O vibration).
NMR (in $CDCl_3$): non-aromatic protons at $\tau$ = 8.28 and 8.20 (each 3 H of the two acetate groups) and at $\tau$ = 3.25 (1 H).

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[1] We thank the Deutsche Forschungsgemeinschaft for financial assistance.

[2] *O. Dann* and *H. Hofmann*, Chem. Ber. *95*, 1446 (1962).

[3] *H. Hofmann*, Angew. Chem. *77*, 864 (1965); Angew. Chem. internat. Edit. *4*, 872 (1965).

## 3,4-Diazanorcaradiene [1]

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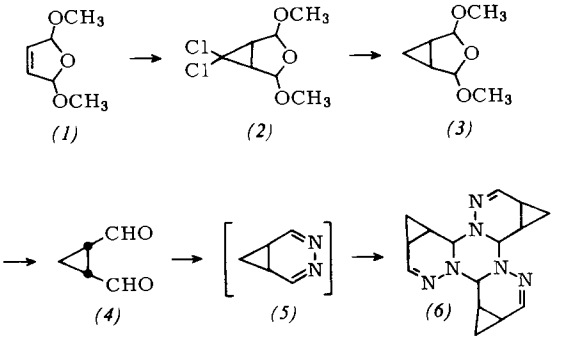
The valence-tautomeric equilibrium between diphenyldiazanorcaradiene and diphenyldiazacycloheptatriene lies entirely on the side of the norcaradiene form [2]. It was hoped that synthesis of the unsubstituted diazanorcaradiene would provide information whether, and to what degree, the nitrogen atoms or the phenyl substituents are responsible for the greater stability of the bicyclic tautomer.

When treated with ethyl trichloroacetate/$CH_3ONa$, the *cis-trans* mixture of 2,5-dihydro-2,5-dimethoxyfurans *(1)* obtained from furan on treatment with $Br_2$ in $CH_3OH$ gives *(2)*, m.p. 40 °C; yield 11 %. Probably only the *cis*-isomer takes part in this reaction since the product *(2)* is homogeneous on gas chromatography and its NMR spectrum ($CCl_4$) shows only three sharp singlets at $\tau$ = 4.94, 6.57, and 7.42 in the ratio 1:3:1. Reduction of compound *(2)* with Li/t-butyl alcohol affords a product *(3)*, b.p. 65–67 °C/14 mm, $n_D^{20}$ = 1.4352; yield 67 %, whose NMR spectrum (without a solvent) shows an $AMX_2$ system (three ring protons: $\tau_A$ = 10.04, $\tau_M$ = 9.44, $\tau_X$ = 8.32; $J_{gem.}$ = 4.7, $J_{cis}$ = 8.0, $J_{trans}$ = 4.0 Hz) and two singlets at $\tau$ = 6.69 and 5.22 in the ratio 1:1:2:6:2. In contrast to *(2)*, the product *(3)* gives an immediate precipitate with dinitrophenylhydrazine solution.

When heated with 0.1 N sulfuric acid (13 min at 100 °C) the ether *(3)* gives *cis*-1,2-cyclopropanedicarbaldehyde *(4)*, which can be extracted from the aqueous solution with chloroform and purified, though with great loss, by gas chromatography. The dialdehyde is stable in chloroform at −78 °C; its IR spectrum ($CCl_4$) contains the bands expected for an aldehyde (1710, 2730, and 2830 $cm^{-1}$), and its NMR spectrum ($CDCl_3$) shows aldehyde protons at $\tau$ = 0.5 as well as the cyclopropane protons (multiplet at $\tau$ = 7.4 to 8.5). Oxidation with $KMnO_4$ gives *cis*-1,2-cyclopropanedicarboxylic acid.



*(1)* *(2)* *(3)* *(4)* *(5)* *(6)*

Condensation of the dialdehyde *(4)* with hydrazine affords three substances which, according to their elemental composition and molecular weights, must be trimers of *(5)*. These three components can be separated chromatographically ($Al_2O_3$, ether). Each of them yields the original mixture of three components when treated with acid. Presumably these isomers are compounds of type *(6)*. This structure is supported by the IR spectrum (KBr; C=N bands at 1615 $cm^{-1}$), the UV spectrum [$CH_3OH$; *(6a)*, m.p. 211 °C, $\lambda_{max}$ = 252.5 mμ (ε = 11500); *(6b)*, m.p. 184 °C, $\lambda_{max}$ = 256 mμ (10600); *(6c)*, decomp. 232 °C, λmax = 262.5 mμ (8300)], and the NMR spectra [$CDCl_3$; 12 cyclopropane protons as a multiplet at $\tau$ = 7 to 9.5; 3 protons as a multiplet centered at $\tau$ = 2.88; *(6a)*, 1 proton each as singlet at $\tau$ = 5,82. 6.33, and 6.62; *(6b)*, analogously at $\tau$ = 5.65, 5.87, and 6.27; *(6c)*, 3 protons as singlet at $\tau$ = 5.43]. Oxidation of the mixture of isomers with $KMnO_4$ in 2 N hydrochloric acid again affords *cis*-cyclopropanedicarboxylic acid.

The formation of compound *(6)* from *(4)* and hydrazine indicates that the bicyclic diazanorcaradiene *(5)* which can be assumed to be an intermediate also is more stable than its monocyclic valence tautomer.

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German version: Angew. Chem. *78*, 981 (1966)

[1] Valence Tautomerism of Heterocycles, Part 8.– Part 7: *G. Maier* and *F. Seidler*, Chem. Ber. *99*, 1236 (1966).

[2] *G. Maier*, Chem. Ber. *98*, 2438, 2446 (1965).

## Ring Closure Reactions of *N*-(α-Chloroalkylidene)carbamoyl Chlorides

By Dr. E. Degener, Dr. H.-G. Schmelzer, and Dr. H. Holtschmidt

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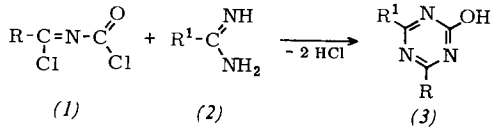
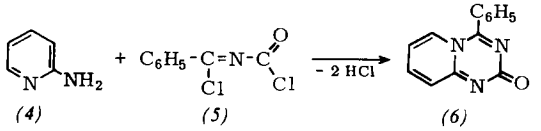
IR spectra of aliphatic isocyanates that are perchlorinated in the α-position indicate that in many cases these compounds exist partly or wholly as *N*-(α-chloroalkylidene)carbamoyl chlorides *(1)* [1]. With compounds of amidine structure *(2)* they react under the conditions of the Schotten-Baumann reaction to give almost quantitatively 2-hydroxy-*s*-triazines *(3)* [2]. 2-Hydroxy-*s*-triazines with two different hydrocarbon radicals in the 4- and the 6-position can also be prepared in this way.



*(1)* *(2)* *(3)*

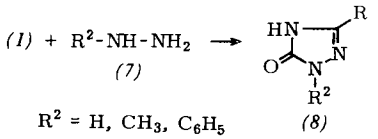
| R | $R^1$ | Yield of *(3)* (%) | M.p. of *(3)* (°C) |
|---|---|---|---|
| $CCl_3$ | $C_6H_5$ | 92 | 254—255 |
| $C_6H_5$ | $C_6H_5$ | 95 | 295 |
| $C_6H_5$ | 2-Cl—$C_6H_4$ | 71 | 228—229 |
| $C_6H_5$ | 4-Cl—$C_6H_4$ | 95 | 287—288 |
| $C_6H_5$ | 4-$CH_3$—$C_6H_4$ | 95 | 284 |
| $C_6H_5$ | 2-$CH_3$—O—$C_6H_4$ | 90 | 288 |
| $C_6H_5$ | $CH_3$ | 73 | 238 |
| $C_6H_5$ | $C_2H_5$ | 60 | 230 |
| $C_6H_5$ | 3-Cyclohexenyl | 80 | 264 |
| $C_6H_5$ | $C_6H_5$—$CH_2$ | 95 | 223—224 |
| $C_6H_5$ | $CH_3$—S | 95 | 275—276 |
| $C_6H_5$ | 4-Cl—$C_6H_4$—NH | 94 | 352—354 |
| $C_6H_5$ | $C_6H_5$—CH=N—NH | 90 | 262 |

Reaction of *N*-(α-chloroalkylidene)carbamoyl chlorides *(1)* with nitrogen heterocycles carrying a 2-amino substituent affords condensed heterocycles [3]. For example, 2-aminopyridine *(4)* and *N*-(α-chlorobenzylidene)carbamoyl chloride *(5)* give the dihydropyridotriazinone *(6)*, m. p. 179—181 °C [4].



*(4)* *(5)* *(6)*

1,2,4-Triazolin-3-ones *(8)* are obtained by treatment of *N*-(α-chloroalkylidene)carbamoyl chlorides *(1)* with hydrazines *(7)*.



$R^2$ = H, $CH_3$, $C_6H_5$ *(8)*

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[1] *H. Holtschmidt*, Angew. Chem. *74*, 848 (1962); Angew. Chem. internat. Edit. *1*, 632 (1962).

[2] *E. Degener, H. Holtschmidt*, and *H.-G. Schmelzer*, German published Pat. appl. 1193057 (Dec. 14th, 1962), Farbenfabriken Bayer AG.

[3] *E. Degener, H. Holtschmidt*, and *K. Swincicki*, Ger. Pat. 1167848 (June 5th, 1962), Farbenfabriken Bayer AG.

[4] The position of the substituents in compound *(6)* is not yet certain.

## Ring Closure Reactions of Polychloroazaalkenes

By Dr. H.-G. Schmelzer, Dr. E. Degener, and Dr. H. Holtschmidt

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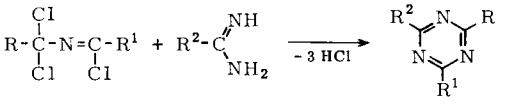
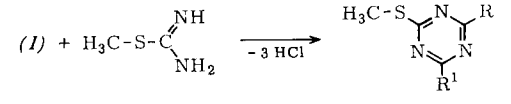
Polychloroazaalkenes *(1)* containing the structural unit of 1,1,3-trichloro-2-azapropene can be obtained by high-temperature chlorination of amines [1]. They afford *s*-triazines *(3)* on reaction with amidines *(2)* or their salts [2, 3]. In particular, trichloromethyl isocyanide dichloride gives 2,4-dichloro-*s*-triazines. Methylthio-*s*-triazines *(5)* are obtained when *S*-methylisothioureas *(4)* are used as amidine component. Use of guanidines *(6)* leads to amino-*s*-triazines *(7)*.

The ring closures can be effected under the conditions of the Schotten-Baumann reaction. A two-phase system, *e.g.* methylene chloride/water, is used as reaction medium in the preparation of 2,4-dichloro-*s*-triazines. The ring closure provides the first one-stage preparation of *s*-triazines with three different hydrocarbon substituents [3] and of 2-chloro-*s*-triazines with two different hydrocarbon substituents in the 4- and the 6-position [2].



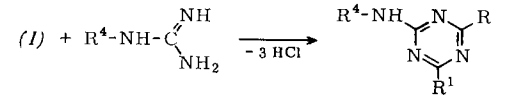
*(1)* *(2)* *(3)*

| R | $R^1$ | $R^2$ | *(3)*, yield (%) | *(3)*, m.p. (°C) |
|---|---|---|---|---|
| $CCl_3$ | Cl | $C_6H_5$ | 85 | 125—126 |
| $CCl_3$ | $CCl_3$ | H | 51 | 39.5 |
| $CCl_3$ | $CCl_3$ | $C_2H_5$ | 73 | 36 |
| $CCl_3$ | $CCl_3$ | 3-$O_2N$—$C_6H_4$ | 94 | 103 |
| $CCl_3$ | $CCl_3$ | 4-$CH_3O$—$C_6H_4$ | 84 | 144 |
| $CCl_3$ | $CCl_3$ | 4-Pyridyl | 64 | 114.5 |
| $CCl_2$=CCl | $CCl_3$ | $CH_3$ | 74 | 76—78 |
| $C_6H_5$ | Cl | $C_2H_5$ | 80 | 30—32 |
| $C_6H_5$ | Cl | $C_6H_5$ | 95 | 138—139 |
| $C_6H_5$ | Cl | 2-Cl—$C_6H_4$ | 95 | 115—116 |
| 3-$CF_3$—$C_6H_4$ | Cl | 4-Cl—$C_6H_4$ | 91 | 139—139.5 |
| 4-Cl—$C_6H_4$ | Cl | $CH_3$ | 95 | 140—141 |
| 3,4-$Cl_2$—$C_6H_3$ | Cl | 4-Cl—$C_6H_4$ | 95 | 227.5—228.5 |
| 4-Cl—$C_6H_4$ | $CCl_3$ | $C_2H_5$ | 89 | 82 |
| 2,4-$Cl_2$—$C_6H_3$ | $CCl_3$ | 4-Cl—$C_6H_4$ | 86 | 143.5—144.5 |
| Cl | Cl | $CH_3$ | 83 | 98—99 |
| Cl | Cl | n-$C_{17}H_{35}$ | 62 | 32—33.5 |
| Cl | Cl | $C_6H_5$ | 95 | 118—119 |
| Cl | Cl | 4-Cl—$C_6H_4$ | 95 | 148 |



*(4)* *(5)*

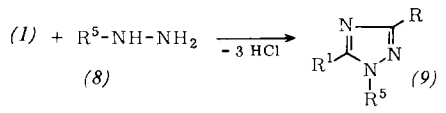
| R | $R^1$ | *(5)*, yield (%) | *(5)*, m.p. (°C) |
|---|---|---|---|
| Cl | Cl | 85 | 55—56.5 |
| $CCl_3$ | $CCl_3$ | 83 | 69 |
| $C_6H_5$ | Cl | 95 | 90—91 |
| $C_6H_5$ | $CCl_3$ | 66 | 134 |
| $CCl_3$ | Cl | 85 | b.p. 118—120/0.2 mm |



*(6)* *(7)*

R = $C_6H_5$, $CCl_3$; $R^1$ = $CCl_3$; $R^4$ = 4-Cl-$C_6H_4$

Reaction of the polychloroazaalkenes *(1)* with monosubstituted hydrazines *(8)* affords 1,2,4-triazoles *(9)* [4].



| R | $R^1$ | $R^5$ | *(9)*, yield (%) | *(9)*, m.p. (°C) |
|---|---|---|---|---|
| Cl | Cl | $C_6H_5$ | 60 | 97–98 |
| $CCl_3$ | $CCl_3$ | $C_6H_5$ | 92 | 154–155 |
| $C_6H_5$ | Cl | $C_6H_5$ [a] | 49 | 68–70 |
| Cl | Cl | $CH_3$ | 26 | 26 |
| $CCl_3$ | $CCl_3$ | $CH_3$ | 95 | 125–126.5 |
| Cl | Cl | 4-Cl–$C_6H_4$ | 66 | 103–104.5 |
| Cl | Cl | | 79 | 148–149.5 |

[a] The positions of the substituents are not yet certain.

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[1] *H. Holtschmidt*, Angew. Chem. *74*, 848 (1962); Angew. Chem. internat. Edit. *1*, 632 (1962); *H. Holtschmidt, E. Degener*, and *H.-G. Schmelzer*, Liebigs Ann. Chem., in press.

[2] *H.-G. Schmelzer* and *E. Degener*, German published Pat. appl. 1178437 (Dec. 22nd, 1962), Farbenfabriken Bayer AG.

[3] *H.-G. Schmelzer, E. Degener, G. Dankert*, and *H. Holtschmidt*, German published Pat. appl. 1200314 (Oct. 26th, 1963), Farbenfabriken Bayer AG.

[4] *H.-G. Schmelzer, E. Degener*, and *H. Holtschmidt*, German published Pat. appl. 1215164 (Jan. 25th, 1964), Farbenfabriken Bayer AG.

## Reactions of 4,5-Dimethyl-*cis*-1,*cis*-4,*trans*-7-cyclodecatriene

By Dr. P. Heimbach [*]

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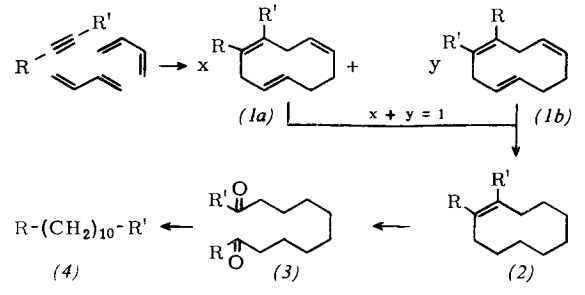
4- or 5-Mono- or 4,5-disubstituted *cis*-1, *cis*-4, *trans*-7-cyclodecatrienes can be prepared in good yield from butadiene and mono- or di-substituted acetylenes by means of catalysts containing zerovalent nickel [1]. These products can serve as starting material for syntheses illustrated below for 4,5-dimethyl-*cis*-1,*cis*-4,*trans*-7-cyclodecatriene *(1)*, R = R′ = $CH_3$.

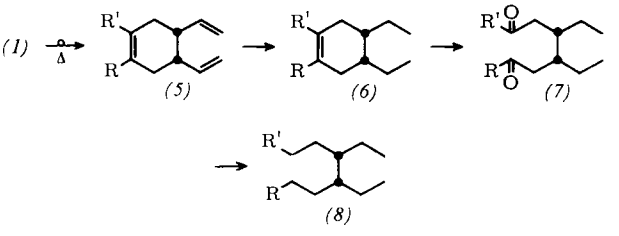


| | $n_D^{20}$ | | Yield (%) |
|---|---|---|---|
| *(1a)* + *(1b)* | 1.5141 | B.p. 30–35 °C/$10^{-4}$ mm | 95 [a] |
| *(2)* | 1.4940 | B.p. 112 °C/20 mm | 94 |
| *(3)* | | M.p. 67–67.5 °C [3] | 68 |

[a] Calculated on converted 2-butyne; 75% of the 2-butyne was consumed; 80% of the butadiene converted gave cyclooctadiene. Catalyst: Ni(0) + tri-(2-biphenyiyl) phosphite in the molar ratio 1:1. Temperature: 40 °C.

1,2-Dimethyl-*cis*-cyclodecene *(2)* can be prepared in 94% yield by partial hydrogenation of the triene *(1)* over Raney nickel under pressure (30 atm, 20 °C). Ozonization of compound *(2)* in methanol at −40 to −80 °C and subsequent hydrogenation of the hydroperoxy hemiketal formed [2] over $Pd/CaCO_3$ at 1 atm and 20 °C leads to 2,11-dodecanedione *(3)*, which is converted by Wolff-Kishner reduction into n-dodecane *(4)* in 85% yield. This reaction sequence makes possible the junction of R and R′ by ten methylene groups with the intermediacy of a disubstituted acetylene.

The stereospecific valence isomerization [4] of compound *(1)* to 1,2-dimethyl-*cis*-4,5-divinylcyclohexene *(5)*, R = R′ = $CH_3$, is about 25 times faster than the Cope rearrangement of *cis*-1, *trans*-5-cyclodecadiene to *cis*-divinylcyclohexane. The compound *(5)* can be hydrogenated over Raney nickel in hexane at 20 °C and atmospheric pressure to *cis*-4,5-diethyl-1,2-dimethylcyclohexene *(6)* in almost 100% yield. Oxidative fission of this product *(6)* by the method used for *(2)* gives good yields of *meso*-4,5-diethyl-2,7-octanedione *(7)*, Wolff-Kishner reduction of which affords *meso*-4,5-diethyloctane *(8)*.



| | $n_D^{20}$ | B.p. (°C/mm) | Yield (%) |
|---|---|---|---|
| *(5)* | 1.4869 | 92/20 | 100 |
| *(6)* | 1.4639 | 96/20 | 99 |
| *meso-(7)* [a] | 1.4505 | 133–134/10 | 72 |
| *meso-(8)* | 1.4276 | 73/10 | 70 |

[a] Purity 96%.

In the Wurtz synthesis of 4,5-diethyloctane from 3-bromohexane both the *meso*- and the racemic form are obtained; these can be separated by gas chromatography (50-m $V_2A$ capillary column, squalane, 100 °C, 0.7 atm of argon; retention time for the *meso*-form 24.6 min and for the racemic form 25.0 min).

The reaction sequence *(1)* → *(4)* is a general route for the preparation of 1-mono- or 1,2-di-substituted cyclodecenes *(2)*, 1,10-diketones *(3)*, and 1,10-substituted decanes *(4)*. The reaction *(7)* → *(8)* gives the *meso*-form when R = R′, but the pairs of diastereoisomers of *(7)* and *(8)* when R ≠ R′.

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German version: Angew. Chem. *78*, 983 (1966)

[*] Lecture at the *Nordwestdeutsche Chemiedozententagung* in Clausthal-Zellerfeld on June 12th, 1965.

[1] *G. Wilke*, Angew. Chem. *75*, 10 (1963), cited p. 19; Angew. Chem. internat. Edit. *2*, 105 (1963), cited p. 114.

[2] *R. Criegee* and *G. Wenner*, Liebigs Ann. Chem. *564*, 9 (1949).

[3] *J. Cason* and *F. S. Prout*, J. Amer. chem. Soc. *66*, 48 (1944).

[4] *P. Heimbach*, Angew. Chem. *76*, 859 (1964); Angew. Chem. internat. Edit. *3*, 702 (1964).

## A New Synthesis of Large Rings

By Dr. P. Heimbach [*] and W. Brenner

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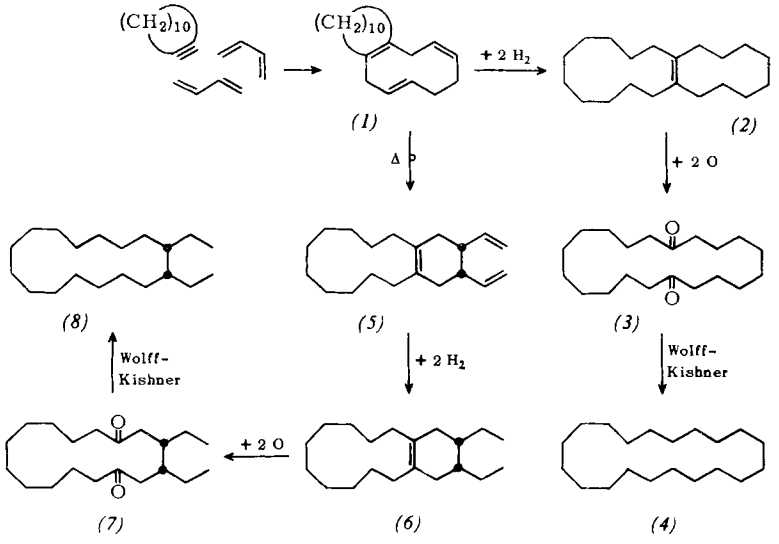
Like acyclic acetylenes [1], cycloalkynes such as cyclodecyne and 1,8-cyclotetradecadiyne [2] react with butadiene in the presence of catalysts containing zerovalent




| | $n_D^{20}$ | | Yield (%) |
|---|---|---|---|
| *(1)* | | M.p. 85—93 °C [d] | 95 [e] |
| *(2)* | | M.p. 63.5—64 °C | 96 |
| *(3)* | | M.p. 53—54 °C | 87 |
| *(4)* | | M.p. 60.5—61.5 °C [4] | 79 |
| *(5)* [a] | 1.5205 | B.p. 123—125 °C/0.2 mm | 98 |
| *(6)* [b] | 1.5405 | B.p. 100—107 °C/$10^{-4}$ mm | 97 |
| *(7)* | | M.p. 39 °C | 86 |
| *(8)* [c] | 1.4752 | B.p. 149—151 °C/0.8 mm | 90 |

[a] Purity 98.7%. [b] 98.6%. [c] 95%.

[d] Dependent on the rate of heating, since *(1)* rearranges to *(5)*.

[e] Calculated on the cyclodecyne converted (70%); 95% of the butadiene converted gives cyclooctadiene. Catalyst: Ni(0) + tri-(2-biphenylyl) phosphite in the molar ratio 1:1. Temperature: 40 °C.

The IR, $^1$H—NMR, and mass spectra of the products agree with the structures assigned. In the Raman spectra some of the bands for the tetrasubstituted double bonds lie at unexpectedly high wavelengths, *e.g.* for *(1)* at 1633 $cm^{-1}$, for *(2)* at 1631 $cm^{-1}$, for *(11)* at 1640 $cm^{-1}$, and for *(13)* at 1640 $cm^{-1}$.

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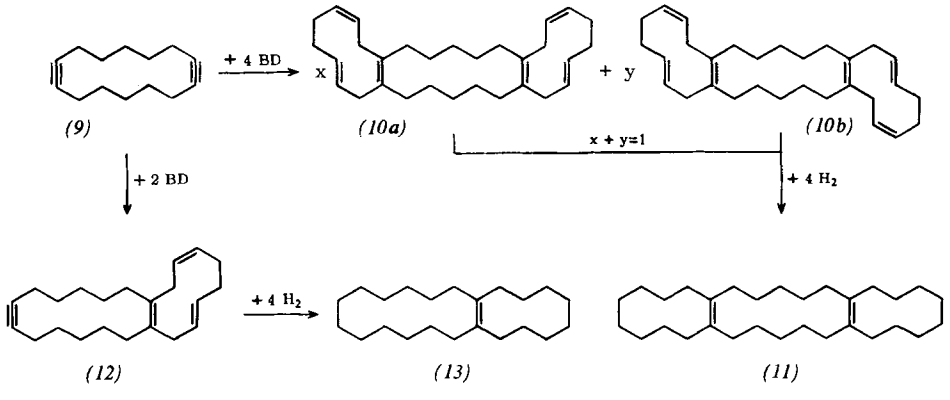
[*] Read in part by *P. Heimbach* at the *Nordwestdeutsche Chemiedozententagung* in Clausthal-Zellerfeld on June 12th, 1965.

[1] *G. Wilke*, Angew. Chem. *75*, 10 (1963), cited p. 19; Angew. Chem. internat. Edit. *2*, 105 (1963), cited p. 114.

[2] *J. Dale, H. Hubert*, and *G. S. D. King*, J. chem. Soc. (London) *1963*, 73.

[3] *P. Heimbach*, Angew. Chem. *78*, 983 (1966); Angew. Chem. internat. Edit. *5*, 961 (1966).

[4] *F. Sondheimer, Y. Amiel*, and *R. Wolovsky*, J. Amer. chem. Soc. *81*, 4600 (1959).




| | M.p. (°C) | Yield (%) |
|---|---|---|
| *(10a)* + *(10b)* | 160—164 [a] | 40 [b] |
| *(11)* | 200 | 90 |
| *(12)* | 98—101 [a] | 55 [b] |
| *(13)* | 84—85 | 95 |

[a] Dependent on the rate of heating.
[b] Calculated on the cyclotetradecadiyne consumed (45%).

nickel to give 4,5-oligomethylene-*cis*-1,*cis*-4,*trans*-7-cyclodecatrienes such as *(1)* in high yields. Reactions analogous to those described for 4,5-dimethyl-*cis*-1,*cis*-4,*trans*-7-cyclodecatriene[3] lead in good yields from *(1)* and related compounds to products containing large rings. Of the compounds *(1)* to *(8)*, only *(4)* was previously known.

After reaction of the cyclotetradecadiyne *(9)* with butadiene, a bicyclic hydrocarbon *(12)* and the tricyclic hydrocarbons *(10a)* and *(10b)* were isolated.

## Chloro(dicyclopentadienyl)ethylzirconium and its Reaction with Triethylaluminum

By Prof. H. Sinn and G. Oppermann

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Dichloro(dicyclopentadienyl)zirconium reacts with triethylaluminum or with ethylaluminum chlorides with removal of ethane, but, unlike the corresponding titanium compound (which is of interest as a catalyst for the low-pressure polymerization of ethylene), without formation of a compound containing zirconium in a lower oxidation state[1].

We have now prepared chloro(dicyclopentadienyl)ethylzirconium(IV), analogous to the titanium compound[2], by a Grignard reaction of $Cp_2ZrCl_2$ in $CH_2Cl_2$ at 0 °C. The bright yellow compound is extracted from the reaction

mixture with heptane, from which it is crystallized at −80 °C. The yield was 27 % calculated on the total amount of starting material, and 54 % on the amount consumed.

$C_2H_5Cp_2ZrCl$ is a crystalline, intensely yellow, diamagnetic compound [$\chi_g = -(0.44 \pm 0.04) \times 10^{-6}$ E.M.U./g], which is decomposed by light, air, or water. It is stable under nitrogen at 0 °C.

$C_2H_5Cp_2ZrCl$ (1.4 mmole) was treated with $Al(C_2H_5)_3$ (14.7 mmole) at 20 °C and atmospheric pressure. The chloride dissolved rapidly and a yellow-red color developed. After a short time, gas evolution began and the color deepened. Only ethane was evolved, whereas in the corresponding reaction of the titanium compound ethane *and* ethylene were formed. After 19 min, 1 mole of $C_2H_6$ had been liberated per gram-atom of zirconium. The time-yield curve for the evolution of the first mole of $C_2H_6$ indicates a reaction of the second order with respect to zirconium. Two moles of ethane are evolved per gram atom of zirconium within 24 hours.

When gas evolution had ceased the mixture had a susceptibility $\chi_g$ of $-(0.69 \pm 0.02) \times 10^{-6}$, *i.e.* the compound formed by loss of ethane is diamagnetic.

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## Iron(III) Sulfide

By Prof. H. P. Boehm and E. Flaig

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The existence of an iron(III) sulfide, $Fe_2S_3$, has been repeatedly asserted [1] and at least as often disputed [2]. Most of the studies were carried out in connection with the purification of coal gas with iron(III) oxide hydroxides; the products were rarely characterized by X-ray diffraction but only by elemental analysis and by their behavior on dissolution in HCl. $Fe_2S_3$ cannot be prepared from the elements since in the system Fe–S only $Fe_{0.88-1.00}S$ and $FeS_2$ (pyrites) are stable, at least at higher temperatures [3].

On addition of $SH^-$ ions to ammoniacal $Fe^{3+}$ solutions stabilized by complex formation with tartrates, we obtained an ammonia-containing, pyrophoric iron(III) sulfide which lost $NH_3$ and $H_2S$ on drying; after the material had been degassed in a vacuum at 100–130 °C its composition corresponded to $Fe_2S_3 \cdot ca.\ 0.03(NH_4)_2S$. The reflections in the X-ray powder diagram were diffuse. In the presence of alkali, alkali-metal thioferrates(III) were always formed, *e.g.* the well known $KFeS_2$.

The same X-ray diagram, but much less diffuse, was given by iron(III) sulfide that we obtained by passing pure $H_2O$ into a solution of iron(III) methoxide or ethoxide [4] in a mixture (2:1 v/v) of anhydrous alcohol and benzene. After the mixture had been kept for 3 to 4 days in an atmosphere of $H_2S$, the precipitate was centrifuged off and dried in a high vacuum at 100–120 °C. Such preparations always tenaciously retained alcohol and $H_2S$ (0.06–0.28 mole of $CH_3OH$ and 0.16–0.20 mole of $H_2S$ per $Fe_2S_3$ unit). We studied a sulfide of composition Fe 50.7 wt.-%, S. 45.9 %, active H 0.32 %, $OCH_3$ 4.09 %; it was not pyrophoric but was oxidized in air within a few days.

Iron(III) sulfide dissolved in acids such as dilute HCl to give the Fe(II) salt, a corresponding amount of sulfur remaining.

The Mössbauer spectrum also accorded with the presence of $Fe^{3+}$ ions [5]. The 28 reflections[*] in the Debye diffraction pattern (Co–$K_\alpha$ radiation) can be indexed in the tetragonal system with $a_o = 11.30$ Å and $c_o = 13.05$ Å. The extinctions accord with the $D_4^4$ or $D_4^8$ space group. The interferences can be equally well indexed on the basis of a monoclinic unit cell of half the size: $a_o = 7.11$ Å, $b_o = 11.30$ Å, $c_o = 11.30$ Å, $\beta = 113.4°$, possible space group $C_{2h}^6$. On the basis of the density $d = 3.25$ g cm$^{-3}$ found pyknometrically, the unit cell contains 16 or 8 formula units, respectively. A final decision about the crystal system is not possible because of lack of larger crystals. Approximately square, small platelets with sides of maximally *ca.* 0.3 μ can be seen in the electron microscope.

When heated in a vacuum, iron(III) sulfide loses sulfur at *ca.* 150 °C and gives ferromagnetic $Fe_3S_4$, which dissolves only very slowly in dilute HCl. The X-ray diagram of $Fe_3S_4$, which crystallizes in the cubic system, corresponds to that of magnetite; we found the lattice constants to be 9.810 ± 0.006 Å. This iron thiospinel has been mentioned earlier [6] and was recently found as the mineral greigite [7]. On treating an aqueous suspension of amorphous or crystalline (α- or γ-)-iron(III) oxide hydroxides with $H_2S$ we obtained mainly $FeS_2$ and $Fe_3S_4$.

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[5] We thank Dr. *E. Fluck* and *P. Kuhn* for measurement and discussion of the $^{57}Fe$-Mössbauer spectra.

[*] The following reflections were observed:
$d$ = 5.2 Å (intensity 10), 4.12 (2), 3.49 (2), 3.25 (1), 2.98 (8), 2.82 (1), 2.568 (1), 2.458 (7), 2.334 (2), 1.992 (2), 1.885 (3), 1.837 (6), 1.733 (9), 1.622 (1), 1.566 (2), 1.502 (1), 1.452 (1), 1.420 (1), 1.314 (1), 1.287 (1), 1.262 (1), 1.233 (1), 1.129 (1), 1.097 (2), 1.031 (1), 1.001 (3), 0.9603 (2), 0.9383 (1).

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## A Convenient Preparation of Isothiocyanates [1]

By Dr. R. Gottfried

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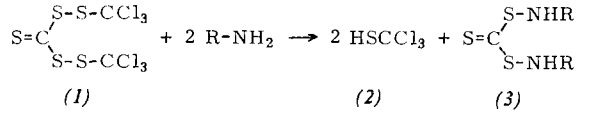
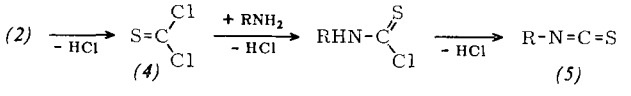
Like other disulfides, trichloromethyl disulfides are cleaved by bases [2, 3] to a sulfenyl compound and a thiol. Trichloromethanethiol *(2)*, which is indicated as intermediate by the kinetics of the aminolysis, gives thiophosgene *(4)* by elimination of HCl [2]. Trichloromethyl disulfides, which are easy to handle, can thus be used for the same reactions as the toxic thiophosgene. For instance, with thiols in alkaline solution they yield trithiocarbonates [4, 5]. With not less than 6 moles of amine per mole of trichloromethyl disulfide in ether or benzene solution one obtains *N,N'*-disubstituted thioureas [2]; with at most 5 moles of amine, isothiocyanates are formed.

Bis(trichloromethyl) pentathiodiperoxycarbonate *(1)*, from which thiophosgene also can be obtained directly (by thermal decomposition) is an inexpensive, reactive compound particularly suited to replace thiophosgene. When pure, the ester *(1)* is a stable, slightly volatile, and only slightly toxic red liquid. It is obtained [2, 6, 7] from trichloromethanesulfenyl chloride and sodium trithiocarbonate.

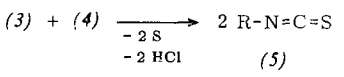
Like thiophosgene, the ester *(1)* also reacts in aqueous suspension with amines, giving isothiocyanates *(5a)–(5d)*; only 3 moles of amine per mole of ester are needed since the *N,N'*-disubstituted trithiodiperoxycarbondiamides *(3)* (which have been identified[2]) also yield isothiocyanates on reaction with thiophosgene *(4)*.



*(1)* *(2)* *(3)*



*(4)* *(5)*



*(5)*

| | R | Yield (%) |
|---|---|---|
| *(5a)* | Benzyl | 80 |
| *(5b)* | Phenyl | 75 |
| *(5c)* | *p*-Tolyl | 80 |
| *(5d)* | *p*-Chlorophenyl | 72 |

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[7] Prepared according to *F. Fischer* and *R. Gottfried*, East Ger. Pat. Appl. (Aug. 9th and Nov. 26th, 1965).

## Reaction of D-Glucosamine with Carbon Disulfide

By Dr. J. C. Jochims

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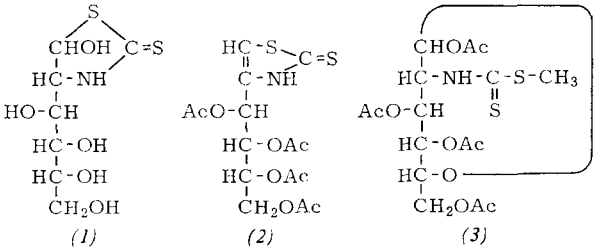
D-Glucosamine and $CS_2$ in methanol give 5-hydroxy-4-(D-*arabino*-1,2,3,4-tetrahydroxybutyl)thiazolidine-2-thione *(1)* in 80% yield.



*(1)* *(2)* *(3)*

5-Hydroxythiazolidines appear not to have been described previously. The product *(1)* is precipitated as a mixture of about 80% of the α-form and 20% of the β-form. The mixture has $[\alpha]_D^{20} = 108°$ ($c = 1$; in dimethylformamide) and decomposes from 146 °C. With the calculated amount of acetic anhydride in pyridine at 0 °C it gives the penta-*O*-acetyl derivative which can be separated into its anomers by fractional crystallization from ethyl acetate:

α-5-Acetoxy-4-(D-*arabino*-1,2,3,4-tetraacetoxybutyl)thiazolidine-2-thione, $[\alpha]_D^{20} = +238°$ ($c = 1$; in dimethylformamide), m.p. 137–138 °C.

β-5-Acetoxy-4-(D-*arabino*-1,2,3,4-tetraacetoxybutyl)thiazolidine-2-thione, $[\alpha]_D^{20} = -218°$ ($c = 1$; in dimethylformamide), m.p. 165–168 °C.

When boiled for 16 hr in anhydrous pyridine, both these compounds afford D-*arabino*-1,2,3,4-tetraacetoxybutyl-$\Delta^4$-thiazoline-2-thione *(2)*, $[\alpha]_D^{20} = -37°$ ($c = 1$; in dimethylformamide), m.p. 169–170 °C[1].

The thiazolidinethione ring in compound *(1)* can be easily opened. Use of methyl iodide + triethylamine in pyridine leads to an α,β-mixture of 2-deoxy-2-[methylthio(thiocarbonyl)amino]-D-glucopyranoses, isolated as the crystalline 1,3,4,6-tetra-*O*-acetyl derivative *(3)*, m.p. 143–145 °C (decomp.), $[\alpha]_D^{20} = +100°$ ($c = 1$; in dimethylformamide). Compound *(1)* can be titrated as an acid with alkali; salts of 2-deoxy-2-[methylthio(thiocarbonyl)amino]-D-glucopyranose are thus obtained, form which *(1)* is regenerated on acidification. The yellow Cu(II) salt of *(1)* is practically insoluble in all solvents. Compound *(1)* is stable in glacial acetic acid, but in boiling 2 N hydrochloric acid it affords glucosamine hydrochloride quantitatively. The structures of all the products are proved by, *inter alia*, elemental analyses, molecular-weight determinations, and IR and NMR spectra.

Formation of 5-hydroxythiazolidine-2-thiones appears to be a general reaction of α-amino carbonyl compounds with $CS_2$.

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## Cyclododecasulfur, $S_{12}$

By Prof. Max Schmidt and Dr. E. Wilhelm

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In sulfur melts innumerable forms of sulfur, $S_x$, with $x = 8$ to about $10^6$, coexist in hitherto unelucidated equilibria. Nevertheless, only two definite structures have so far been isolated, namely cyclooctasulfur, $S_8$ (crystallizing as $S_\alpha$, $S_\beta$, and $S_\gamma$), and cyclohexasulfur, $S_6$ ($S_\rho$)[1]. Recently[2] we developed a process for the planned synthesis of rings or chains of identical atoms and used it to obtain the unstable molecules $S_6$ and $S_{10}$, of which the latter, being extremely, unstable, was insufficiently characterized. We have now prepared a new, surprisingly stable modification of sulfur, *viz.* cyclododecasulfur, $S_{12}$:

$$H_2S_x + Cl_2S_y \rightarrow 2\,HCl + S_{12}$$
$$(x + y = 12)$$

$S_{12}$ is formed, together with polymeric sulfur, from sulfanes and chlorosulfanes ($x + y = 12$) in $CS_2$-ether mixtures by use of the dilution principle. It forms small, pale yellowish rectangular prisms from benzene, which melt at 148 °C (with decomposition), *i.e.* appreciably higher than all previously known forms of sulfur; the resolidified melt consists of $S_8$, m.p. 119 °C, which is formed by way of polymeric sulfur. The solubility of $S_{12}$ in benzene, about 0.4 g/l, is too low for vapor-pressure osmometric or ebullioscopic determination of the molecular weight. On concentration of its solutions in carbon disulfide, $S_{12}$ separates as colorless plates with a circular indentation in the centers of the large faces and containing solvent which they rapidly lose with disintegration, but the solubility in carbon disulfide is also remarkably low (*ca.* 2 g/l), so that vapor-pressure osmometric determination of the molecular weight gives values between 377 and 390 (theory 384).

$S_{12}$ cannot be volatilized without decomposition in a vacuum (above 148 °C it is converted into $S_8$ *via* polymeric forms), but it can be identified mass-spectrometrically by bringing it into an ion source preheated to 90 to 120 °C (the spectrum, with $S_{12}$ as its highest mass, shows all fragments from $S_{10}$ to $S_2$; intensity ratio $S_8:S_{12} = 100:0.3$; the isotope fine structure of the $S_{12}^+$ ion corresponds with expectation) [3].

$S_{12}$ is intermediate between $S_8$ and $S_6$ in its activity as Lewis acid, *e.g.* towards $(C_6H_5)_3P$ [4].

Contrary to *Pauling*'s prediction [5], $S_{12}$ is much more stable than $S_{10}$ or $S_6$. His prediction was based on the assumption that sulfur chains or rings with a bond angle of about 105° would be the more stable the nearer the torsion angle approached the ideal value of *ca.* 100° (deviation from the ideal value for $S_8$ is *ca.* 1°, and for $S_6$ *ca.* 25°). With the atoms arranged in two planes, as postulated for $S_{12}$, deviation of the torsion angle from the ideal value would amount to *ca.* 30°. Structure determination [6] has, however, shown that in twelve-membered rings the sulfur atoms lie not in two planes, but in three, with a resulting torsion angle of *ca.* 107°. This relatively small deviation from the ideal value explains the great stability of the new sulfur modification: it remains unchanged at room temperature in air and is not destroyed even by long exposure to light or X-rays.

*Preparation of $S_{12}$ (Example)*

Solutions of 5 g of $S_4Cl_2$ and 6.5 g of $H_2S_8$, each in 150 ml of $CS_2$, were added simultaneously and at equal rates to a well-stirred mixture of 900 ml of ether (dried over Na–K alloy) and 300 ml of very pure $CS_2$ at room temperature. The addition was made, during 25 hours, from dropping funnels fitted with glass taps controlled by finely threaded screws. Twelve hr after addition was complete the liquid phase was decanted from the precipitate, which was then washed repeatedly with 500 ml portions of pure $CS_2$ preheated to about 40 °C. Cautious concentration of the extract in vacuum gave 1.5 to 2 g (15 to 20 %) of $S_{12}$, which was recrystallized from much anhydrous benzene.

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## Crystal Structure of Cyclododecasulfur, $S_{12}$

By Dr. A. Kutoglu and Prof. E. Hellner

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The $S_{12}$ modification [1] of sulfur crystallizes in the orthorhombic system with lattice constants $a_0 = 4.730$ Å, $b_0 = 9.104$ Å, and $c_0 = 14.574$ Å. The pyknometric density is 2.04, the X-ray density 2.02 g cm$^{-3}$. The extinction rules lead to the space group Pnnm-$D_{2h}^{12}$.

For the structure investigation 634 X-ray intensities were estimated from Weissenberg equiinclination photographs. All the parameters of the sulfur atoms could be obtained from a three-dimensional Patterson synthesis.

The parameters were refined by the method of least squares. After five iterations with the four atoms in the asymmetric unit and individual isotropic temperature factors the *R* value was reduced from 0.27 to 0.11.

The unit cell of cyclododecasulfur contains 24 atoms (Fig. 1). The two zigzag rings of twelve atoms each, one around the origin, the other around the point $\frac{1}{2}\,\frac{1}{2}\,\frac{1}{2}$, are nearly parallel to the plane {100}. The average of the shortest S–S distances in a ring is 2.055 Å; and the average S–S–S angle is 106°30′. The shortest distance between two rings is 3.60 Å. Thus the distances and angles in this modification are the same as those found previously for other S modifications ($S_8$ and $S_6$ rings).

Distances (error ± 0.01 Å) and angles (error ± 0.5°) within a ring:

| | | |
|---|---|---|
| $S_1$–$S_2$ 2.05 Å | $S_2$–$S_3$ 2.06 Å | $S_1$–$S_2$–$S_3$ 107.8° |
| $S_1$–$S_3$ 3.32 Å | $S_2$–$S_4$ 3.28 Å | $S_2$–$S_3$–$S_4$ 105.9° |
| $S_1$–$S_4$ 4.27 Å | $S_3$–$S_4$ 2.05 Å | $S_3$–$S_4$–$S_5$ 107.2° |
| | | $S_{12}$–$S_1$–$S_2$ 105.0° |

Distances between two rings:

| | | |
|---|---|---|
| $S_1$–$S_1'$ 5.17 Å | $S_2$–$S_2'$ 4.55 Å | $S_3$–$S_3'$ 4.79 Å |
| $S_1$–$S_2'$ 4.09 Å | $S_2$–$S_3'$ 3.60 Å | $S_3$–$S_4'$ 6.03 Å |
| $S_1$–$S_3'$ 3.68 Å | $S_2$–$S_4'$ 5.26 Å | $S_4$–$S_4'$ 7.78 Å |
| $S_1$–$S_4'$ 4.34 Å | | |

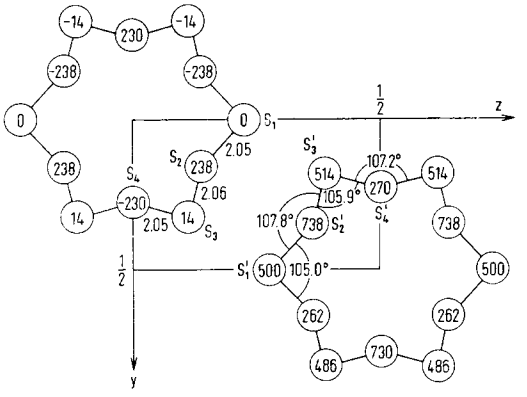


Fig. 1. Projection of the $S_{12}$ modification on the {100} plane. The numbers in the circles show the $x$ values ($10^3x$) of the S atoms. The distance values (in Å) are given in the ring around the origin; the angles are shown in that around $\frac{1}{2}\,\frac{1}{2}\,\frac{1}{2}$.

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[1] *M. Schmidt* and *E. Wilhelm*, Angew. Chem. *78*, 1020 (1966); Angew. Chem. internat. Edit. *5*, 964 (1966).

## Investigation of Cyclododecasulfur, $S_{12}$, by Mass Spectrometry

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In a mass spectrometer the modifications of elemental sulfur previously known do not yield ions heavier than $S_8^+$ (*m/e* 256 and isotope satellites); $S_9^+$ has been recorded (0.4 %, relative to $S_8^+ = 100$ %) in one case only [1].

When cyclododecasulfur, which has been recently synthesized [2], is introduced into the ion source of a mass spectrometer at 90 °C and then heated to 120 °C the mass spectrum of cyclododecasulfur appears alongside a typical mass spectrum of $S_8$ (Fig. 1). The intensity of this $S_{12}$ spectrum is about three orders of magnitude smaller than that of the $S_8$ spectrum.

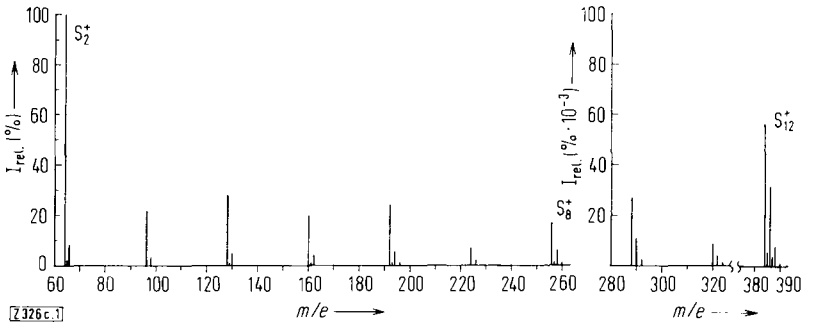


Fig. 1. Mass spectrum of cyclododecasulfur.

During the change of $S_{12}$ to $S_8$ that occurs at the temperature of measurement [3] and gives rise to the intense $S_8$ spectrum, enough $S_{12}$ is vaporized to allow the $S_{12}^+$ ion (*m/e* 384) to be identified and the isotope pattern to be measured (Table 1).

Table 1. Isotope pattern of the $S_{12}^+$ ion.

| *m/e* | Formula | Relative intensity (%) | |
|---|---|---|---|
| | | calc. [4] | found [5] |
| 384 | $^{32}S_{12}$ | 100 | 100 |
| 385 | $^{32}S_{11}{}^{33}S$ | 9.6 | 9.4 ± 0.5 |
| 386 | $^{32}S_{11}{}^{34}S$ | 53.6 | 54.0 ± 0.6 |
| 387 | $^{32}S_{10}{}^{33}S^{34}S$ | 4.7 | 5.2 ± 0.6 |
| 388 | $^{32}S_{10}{}^{34}S_2$ | 13.0 | 13.3 ± 1.1 |
| 390 | $^{32}S_9{}^{34}S_3$ | 1.9 | 2.1 ± 0.2 |

The mass of the $^{32}S_{12}^+$ ion was found[4] by peak matching to be 383.660 ± 0.010 (calc. 383.665).

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German version: Angew. Chem. *78*, 1021 (1966)

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[5] The agreement is satisfactory in view of the high amplification of the ion current. The spectrum and isotope pattern were recorded on an ATLAS mass spectrometer CH 4 (120 °C, trap current 16 μA, ionization energy 70 eV; ion current measured with the aid of an electron multiplier; *m/e* 64–260 in 10 V range, above *m/e* 260 in 30 mV range).

[6] Performed by Dr. *F. von der Haar* using a double-focussing AEI mass spectrometer MS 9; refence mass 375.9807 ($C_8F_{14}N$).

## Synthesis and Reactions of Lithium Chloromethyldimethylsilanolate

By Dr. M. Wieber and Dr. C. D. Frohning

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Alkali trimethylsilanolates can be prepared by the action of alkali metals on trimethylsilanol. This reaction cannot, however, be applied to the organofunctional chloromethyldimethylsilanol *(1)* [1], because the hydrogen evolved removes the halogen atom. This side reaction is prevented if a stoichiometric amount of methyl-lithium (in ether, ice-cooling) is titatively as a precipitate which is sparingly soluble in ether.

$$(CH_3)_2(CH_2Cl)SiOH + M^0 \rightarrow (CH_3)_2(CH_2Cl)SiOM + {}^1/_2\ H_2$$
*(1)*

used instead of lithium; methane is evolved and lithium chloromethyldimethylsilanolate *(2)* is obtained almost quan-

$$(1) + LiCH_3 \rightarrow (CH_3)_2(CH_2Cl)SiOLi + CH_4$$
*(2)*

Compound *(2)* is a colorless powder, m.p. 208–210 °C (decomp.), that can be sublimed at 200 °C/$10^{-3}$ mm (with partial decomposition). Its structure was determined by elemental analysis, determination of the acid equivalent, and IR and $^1$H–NMR spectra (Varian A60, 5 % solution in $CHCl_3$, tetramethylsilane as internal standard). As expected, the $^1$H–NMR spectrum contains two signals, at $\tau$ = 7.22 and $\tau$ = 9.93 ppm, with area ratio 1:3.

Compound *(2)* serves as starting material for syntheses of new organofunctional heterosiloxanes, three examples of which are shown in Table 1.

Table 1. Organofunctional heterosiloxanes obtained from lithium chloromethyldimethylsilanolate.

| Reaction [a] of *(2)* with | Mol. propns. | Product | Yield (%) | B.p. (°C/12 mm) | $^1$H–NMR ($\tau$ in ppm) Si–$CH_3$ / Ge–$CH_3$ | $-CH_2$ / $-CH_2$ |
|---|---|---|---|---|---|---|
| $(CH_3)_3GeCl$ | 1:1 | $(CH_2Cl)(CH_3)_2Si-O-Ge(CH_3)_3$ | 80 | 62 | 9.87<br>9.6 | 7.4<br>– |
| $(CH_2Cl)(CH_3)_2GeCl$ | 1:1 | $(CH_2Cl)(CH_3)_2Si-O-Ge(CH_2Cl)(CH_3)_2$ | 74 | 96 | 9.85<br>9.5 | 7.4<br>7.0 |
| $(CH_2Cl)(CH_3)GeCl_2$ | 1:2 | $(CH_2Cl)(CH_3)_2Si-O-Ge(CH_2Cl)(CH_3)-O-Si(CH_2Cl)(CH_3)_2$ | 68 | 147 | 9.8<br>9.3 | 7.3<br>7.0 |

[a] 24 hr in boiling ether.

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## A Simple Synthesis of 3-Amino-3-deoxy-D-glucose (Kanosamine)

By Dr. W. Meyer zu Reckendorf

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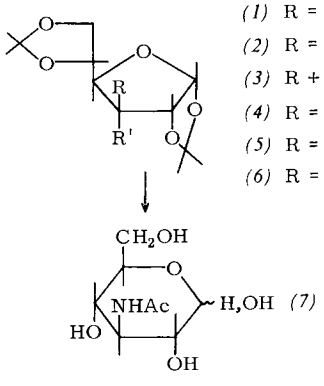
Nucleophilic displacement of the sulfonyl ester group in compounds *(1)*[1] by α-attack is sterically hindered by the 1,2-*O*-isopropylidene group. The methanesulfonate *(5)* with the opposite configuration at C-3 should be more reactive since attack from the β-side is not hindered. This is the case, as is shown by the following experiments.

Compound *(3)* is obtained in 30% yield from the readily accessible substance *(2)* by dehydrogenation[2] with dimethyl sulfoxide/$P_2O_5$. It is stereospecifically reduced by $NaBH_4$ in methanol to the alcohol *(4)*, which on mesylation with methanesulfonyl chloride and pyridine affords the ester *(5)*, m.p. 129–130 °C, $[\alpha]_D^{20} = +80.0°$ ($c$ = 1.0 in $CHCl_3$). It was not necessary to isolate the difficultly crystallizing intermediates *(3)* and *(4)*.



*(1)* R = OMs; OTs; R' = H
*(2)* R = OH; R' = H
*(3)* R + R' = O
*(4)* R = H; R' = OH
*(5)* R = H; R' = OMs
*(6)* R = $N_3$; R' = H



*(7)*

Heating the product *(5)* with sodium azide in dimethylformamide (16 hr, reflux) gave the azide *(6)* as a chromatographically pure oil (yield 90%), which on catalytic hydrogenation (Pd/C), acetylation, and hydrolysis with Lewatit S 100 ion-exchange resin ($H^+$ form) afforded *N*-acetylkanosamine *(7)*[3,4] in 80% yield; m.p. and mixed m.p. with authentic material[4,5] 203–204 °C; $[\alpha]_D^{20} = +20.5° \rightarrow +53.0°$ ($c$ = 1.0 in water; lit.[4] +18.6° → +52.7°).

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German version: Angew. Chem. *78*, 1023 (1966)

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[5] I thank Prof. *H. H. Baer*, Ottawa, for a reference sample.

## 2-Arylisoindoles[1]

By Dr. R. Kreher and J. Seubert

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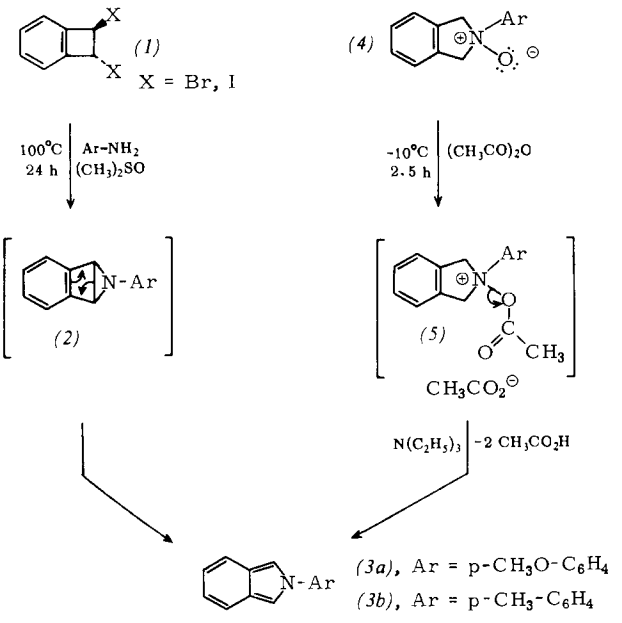
2-(*p*-Methoxyphenyl)isoindole *(3a)*, m.p. 175–176 °C (from 2-propanol), and 2-(*p*-tolyl)isoindole *(3b)*, m.p. 173–174 °C (from 2-propanol) have been prepared by two new methods, as follows:




7,8-Dihalogenobicyclo[4.2.0]octa-1,3,5-trienes *(1)*, which are relatively simply accessible from α,α,α',α'-tetrabromo-*o*-xylene[2], are treated with the appropriate primary aromatic amine in dimethyl sulfoxide, with $N[CH_2CHOHCH_3]_3$ as halide acceptor; products *(3a)* and *(3b)* are thus obtained in yields of up to 40%. Because of the relatively high reaction temperature this process can be used only for the 2-arylisoindoles which are particularly stable to heat. Presumably formation of these products *(3)* depends on whether the *trans*-form of the dihalides *(1)* is rearranged to the *cis*-form in the polar solvent dimethyl sulfoxide[2a], the latter being able to react with the primary amine to give the ethylene imine derivatives *(2)*. The strained ring system *(2)* can, by cyclic electron shift, give structures *(3)* that are favored by resonance stabilization. In a comparable reaction, *cis*-3,4-dichloro-1,2,3,4-tetramethylcyclobutene and primary amines yield pyrrole derivatives[3].

2-Arylisoindoline *N*-oxides *(4)* are converted by acetic anhydride/triethylamine, even at −10 °C, directly into isoindoles *(3)* in yields of up to 70%. The sensitive *N*-oxides *(4)* were obtained from the readily accessible 2-arylisoindolines by means of 30% $H_2O_2$/formic acid and were converted into the products *(3)* without isolation. We have previously used this process for the synthesis of 2-alkylisoindoles[4]. We believe that formation of the *N*-acetoxyammonium salts *(5)* as intermediate is indicated by formation of 2-(2-acetoxy-4-methoxyphenyl)isoindoline (m.p. 112–114 °C; $^1H$–NMR spectrum containing 3H singlets at $\tau$ = 7.6 and $\tau$ = 6.15, a 4H singlet at $\tau$ = 5.25, and a 7H multiplet at $\tau$ = 2.4–3.2), which arises, together with *(3a)*, on acetolysis of *(4a)*, evidently by rearrangement of[5] *(5a)*, Ar = *p*-$CH_3O$–$C_6H_4$.

The isoindole structure is indicated by the $^1H$–NMR spectra: the multiplet from the 5- and 6-ring protons appears between $\tau$ = 2.0 and 3.2; the protons of the methoxy group and of the methyl group give singlets at $\tau$ = 6.13 and $\tau$ = 7.56, respectively.

The UV spectra of products *(3a)* and *(3b)* are very similar to those of the 1-arylisoindoles first prepared by *Lwowski*[6]:

*(3a)* in methanol: $\lambda_{max}$ = 245 mμ (log ε = 4.45); 287.5 (4.02); 298 mμ (log ε = 4.03); 337 (3.66).

*(3b)* in methanol: $\lambda_{max}$ = 242.5 mμ (log ε = 4.50); 288 (3.94); 298 mμ (log ε = 3.94); 337 (3.62).

Structure *(3)* is further supported by conversion of 2-arylisoindoles by *N*-phenylmaleimide at room temperature into Diels-Alder adducts, namely *N*-phenyl-1,4-(arylepimino)-

1,2,3,4-tetrahydronaphthalene-2,3-dicarboximides, *e.g.* Aryl = *p*-tolyl, of which the *endo*-form has m.p. 136–137 °C and in the $^1$H–NMR spectrum has a 3H singlet at $\tau = 7.7$ and 2H quartets at $\tau = 6.0$–$6.1$ and $\tau = 4.3$–$4.4$, while the *exo*-form has m.p. 226–227 °C and in the $^1$H–NMR spectrum a 3H singlet at $\tau = 7.8$ and 2H singlets at $\tau = 6.8$ and $\tau = 4.5$.

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German version: Angew. Chem. *78*, 984 (1966)

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## Bis(2,2′-biphenylylene)phosphorane and the Bis(2,2′-biphenylylene)phosphoranyl Radical

By Dr. D. Hellwinkel

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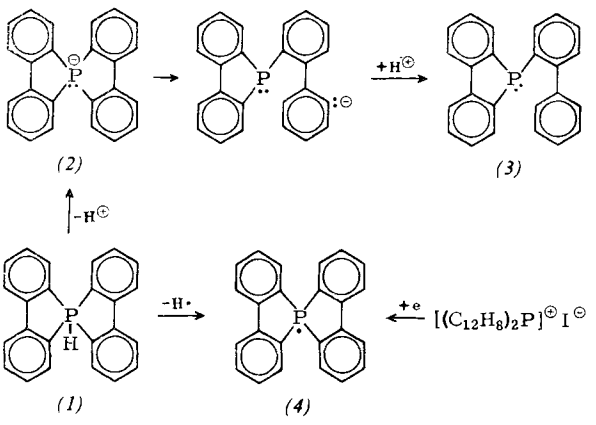
Whereas earlier attempts to prepare hydrido derivatives of quinquevalent phosphorus, arsenic, and antimony were unsuccessful[1–3], we have now succeeded in synthesizing a stable derivative of the hypothetical phosphorane, $PH_5$.

Bis(2,2′-biphenylylene)phosphonium iodide[4] is treated with a small excess of $LiAlH_4$ in ether under nitrogen in a double Schlenk tube with ice cooling. After filtration and cooling to −70 °C bis(2,2′-biphenylylene)phosphorane *(1)* crystallizes. Several recrystallizations from ether afford the pure product in 45% yield; the compound is stable indefinitely under nitrogen in the dark and can be kept for some days in air, but decomposes with discoloration between 95 and 100 °C, depending on the rate of heating.

The product *(1)* was identified by elemental analysis (C, H, P), by its $^1$H–NMR spectrum ($\delta_{H-P} = 9.33$ ppm; $J_{H-P} = 482$ Hz; in benzene, TMS as internal standard), and by its IR spectrum ($\tilde{\nu}_{P-H} = 2097$ cm$^{-1}$). Further evidence of structure is provided by evolution of hydrogen on treatment with ethanolic HCl or ethanolic iodine solution, which regenerate the bis(2,2′-biphenylylene)phosphonium cation in good yield:

$$[(C_{12}H_8)_2P]^{\oplus}I^{\ominus} \underset{LiAlH_4}{\overset{HCl/KI}{\rightleftarrows}} (1) \xrightarrow[-H_2]{I_2} [(C_{12}H_8)_2P]^{\oplus}I_3^{\ominus}$$

The phosphorane *(1)* reacts with methyl- or butyl-lithium in ether with evolution of methane or butane, respectively, giving a dark violet solution which is almost completely decolorized within an hour. An excess of $LiAlH_4$ reacts with *(1)* only after addition of tetrahydrofuran, $H_2$ being evolved and an intensely blue-green solution formed which is also decolorized within an hour. On ethanolysis, 2-biphenylyl-2′,2″-biphenylylenephosphine *(3)* can be isolated from both these reaction mixtures in about 75% yield. With strong bases *(1)* evidently forms the corresponding base, the bis(2,2′-biphenylylene)phosphoranyl anion *(2)*[5], which is violet in ether and blue-green in THF and rearranges with fission of a P–C bond to a colorless carbanion which is finally protonated to the phosphine *(3)*.




Organic phosphorus radicals usually are unstable, and therefore few ESR-spectroscopic studies of them have been reported[6–9]. If a *ca.* 0.5 M solution of the phosphorane *(1)* in benzene is prepared at 20 °C with stringent exclusion of oxygen and moisture, a pale violet coloration is observed which becomes very intense in the course of several hours (even if the solution is exposed only to diffuse daylight). Half an hour after preparation of the solution the ESR spectrum shows a well-formed doublet with a coupling constant of 18 gauss; the intensity of the signal increases during about 7 hr to a constant value while the doublet is gradually transformed into a singlet owing to the increasing radical concentration (in less concentrated solutions the doublet remains). Simultaneously the $^1$H–NMR spectrum is observed to lose the original strong doublet ($J = 482$ Hz) due to the hydrogen bound to phosphorus. These results indicate quantitative conversion of *(1)* into the bis(2,2′-biphenylylene)phosphoranyl radical *(4)*.

The radical *(4)*, characterized by its ESR doublet, also arises when bis(2,2′-biphenylylene)phosphonium iodide[4] is treated with Na/K alloy in benzene, the solution being filtered immediately on appearance of a red-violet color in order to prevent further reaction to the anion.

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German version: Angew. Chem. *78*, 985 (1966)

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## Nucleophilic Ligand Exchange by Phosphoranes [*]

By Dr. M. Schlosser, T. Kadibelban, and Dr. G. Steinhoff

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The organic groups of phosphorus ylides[1], phosphines[2], phosphine oxides[3], or phosphine sulfides[4] undergo nucleophilic exchange with organolithium reagents. We have now observed similar replacements also with pentaorganylphosphorus compounds.

If an ethereal solution ($c \approx 0.01$ M) of pentaphenylphosphorus is treated at room temperature with, for instance,

5 equivalents of *p*-tolyl-lithium, the tetraarylphosphonium salt obtained by subsequent action of acids shows the IR bands of a tolyl group. Phenyl-lithium (7 %) is liberated and can be converted into bromobenzene by 1,2-dibromoethane. Whether this exchange occurs by way of a sexicovalent ate complex *(1)* [5] is being studied by kinetic and NMR methods.

$$Li^{\oplus}\ [(C_6H_5)_5P{-}C_6H_4{-}CH_3{-}p]^{\ominus} \qquad (1)$$

When primary or secondary alkyl-lithium compounds in petroleum ether are allowed to act on pentaphenylphosphorus, phosphorus ylides (and resins) are obtained. n-Butyl-lithium affords triphenylphosphine n-butylide as the LiCl adduct *(2)*, which was characterized as n-butyltriphenylphosphonium bromide (yield 12–24 %), m.p. 233–236 °C, and 1-phenyl-1-pentene (yield 8 %; formed by reaction with benzaldehyde). With an excess of butyl-lithium some of the product *(2)* is metalated further, giving *(3)* (yield up to 14 % calculated on pentaphenylphosphorane) [6]; *(3)* was trapped as ([1,1-$D_2$]-butyl)triphenylphosphonium bromide, m.p. 232–234 °C, with DBr.

$$(C_6H_5)_5P \xrightarrow[(+\ LiCl)]{C_4H_9{-}Li} (C_6H_5)_3\overset{\oplus}{P}{-}\overset{C_3H_7}{\underset{H}{C}}{}^{\ominus}\cdots LiCl \qquad (2)$$

$$(2) \xrightarrow[(+\ LiCl)]{C_4H_9{-}Li} (C_6H_5)_3\overset{\oplus}{P}{-}\overset{C_3H_7}{\underset{Li}{C}}{}^{\ominus}\cdots LiCl \qquad (3)$$

Only the singly bound ligand R of the phosphoranes *(4)* and *(5)* could be removed (in ether or tetrahydrofuran) (cf. the following communication).


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[5] *W. Tochtermann*, Angew. Chem. *78*, 355 (1966); Angew. Chem. internat. Edit. *5*, 351 (1966); cf. also [7].

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## Ligand Exchange with Compounds of Quinquevalent Arsenic [*]


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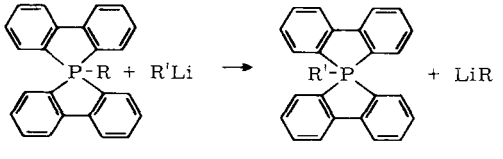
Aryl- and alkyl-bis-2,2'-biphenylylenearsenic *(1)*, which can be prepared from bis-2,2'-biphenylylenearsonium iodide and lithium aryls [1], alkyls [2], or Grignard compounds [3], undergo ligand exchange [4] on reaction with suitable organolithium reagents in ether ($c \approx 0.05$ M) (cf. table).

| R' | R = $CH_3$ | | R = $C_6H_5$ | | R = $C_4H_9$ | | R = *p*-$CH_3$–$C_6H_4$ | | R = *p*-Cl–$C_6H_4$ | | R = *p*-$(CH_3)_2N$–$C_6H_4$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R':R [a] | Exchange (%) | R':R | Exchange (%) | R':R | Exchange (%) | R':R | Exchange (%) | R':R | Exchange (%) | R':R | Exchange (%) |
| $CH_3$ | – | – | 2:1 | 95 | 10:1 | – | 5:1 | 95 | 5:1 | 95 | 10:1 | 70 |
| $C_6H_5$ | 10:1 | – | – | – | 10:1 | – | 10:1 | – | 10:1 | – | 10:1 | – |
| $C_4H_9$ | 1:1 | 96 | 1:1 | 95 | – | – | 2:1 | 96 | 2:1 | 95 | 10:1 | 95 |
| *p*-$CH_3$–$C_6H_4$ | 4:1 | 92 | 3:1 | 96 | 10:1 | – | – | – | 10:1 | 96 | 10:1 | 85 |
| *p*-Cl–$C_6H_4$ | 10:1 | – | 10:1 | 80 | 10:1 | – | 8:1 | 90 | – | – | 10:1 | – |
| *p*-$(CH_3)_2N$–$C_6H_4$ | 10:1 | 97 | 3:1 | 95 | 10:1 | – | 10:1 | 90 | 4:1 | 90 | – | – |

[a] Molar proportions in each case.




*(4)*, R : $CH_3$

*(5)*, R : $C_6H_5$

*(5)*, R : $C_6H_5$, 45%
*(6)*, R : p-$CH_3$-$C_6H_4$, 10%
*(7)*, R : p-$CH_3O$-$C_6H_4$, 38%
*(8)*, R : $C_4H_9$, 73%

*(8)*, R : $C_4H_9$, 98%

The structures of the phosphoranes *(4)*–*(8)* were proved by elemental analysis, NMR and IR spectra, or comparison with authentic material. Compounds *(4)* [7] and *(5)* [8] were known; compounds *(6)*, m.p. 185–186 °C, *(7)*, m.p. 198.5 to 200 °C, and *(8)*, m.p. 177.5–178 °C, were synthesized analogously.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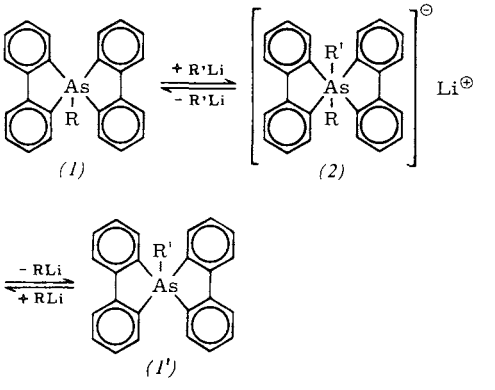
All the mixtures indicated in the table were stirred for 10 hr and then hydrolysed. The exchange products were identified by mixed melting points and by comparison of IR spectra.




The table shows that the strength of bonding of the ligands R decreases in the order:

$$C_4H_9 \gg p\text{-}(CH_3)_2N{-}C_6H_4 \approx CH_3 \approx p\text{-}CH_3{-}C_6H_4 \approx p\text{-}Cl{-}C_6H_4 > C_6H_5.$$

Formulation of these exchange reactions *via* intermediate hexaarylarsenate(v) complexes *(2)* is supported by the fact


[*] We are grateful to Prof. *G. Wittig* for suggestions and discussions, and to the *Deutsche Forschungsgemeinschaft* for generous support.



[1] *G. Wittig* and *G. Geißler*, Liebigs Ann. Chem. *580*, 44 (1953); *G. Wittig* and *M. Schlosser*, Chem. Ber. *94*, 1377 (1961); *M. Schlosser*, Angew. Chem. *74*, 291 (1962); Angew. Chem. internat. Edit. *1*, 266 (1962).

that stable organic ate complexes with six-coordinate arsenic have recently been prepared [3].

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[1] *G. Wittig* and *D. Hellwinkel*, Chem. Ber. *97*, 769 (1965).

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[4] For ligand exchange with triarylarsines see *A. Maercker*, Diploma Thesis, Universität Heidelberg, 1960.

## Formation of 1,3,4-Thiadiazoles and 1,4,2-Oxathiazoles from Thioketenes

By Dr. K. Dickoré and Dr. R. Wegler

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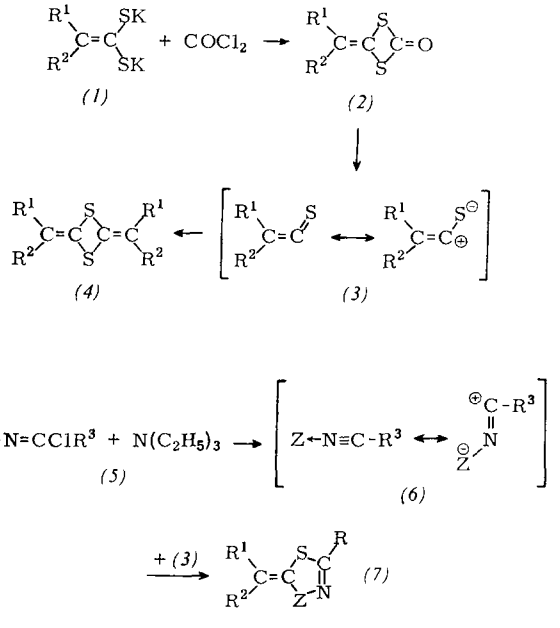
Little is known about monomeric thioketenes because of their great tendency to polymerize. They can be obtained by pyrolysis of ethynyl sulfides, but polymerization begins already at −80 °C [1].

We have found that reaction of phosgene with alkali salts *(1)* of 2,2-disubstituted ethylene-1,1-dithiols [2,3] in suspension in methylene chloride gives 1,3-dithietanes *(2)*. These yellow to brown substances give a characteristic strong IR band at 1790–1810 $cm^{-1}$ (stretching vibration for carbonyl in a four-membered ring); they decompose to thioketenes *(3)* and COS under catalysis by Lewis bases, surface-active compounds, or polar solvents or even when heated. In the absence of a suitable reactant these thioketenes dimerize generally to 2,4-dialkylidene-1,3-dithietanes *(4)* [*] [2,4,5]. In the presence of nitrile oxides or nitrile imines *(6)*, obtained *in situ* from oximes or hydrazones *(5)*, Z = O or $NC_6H_5$, with triethylamine, the thioketenes *(3)* undergo 1,3-dipolar cycloaddition [6] to give heterocyclic products *(7)* [*].



Other strongly polar addends such as chloral [7] and compounds of the type $RN{=}C(SR')_2$ [8], which have proved useful for trapping ketenes generated *in situ*, do not add to thioketenes, even when used in great excess.

| *(2)* | $R^1$ | $R^2$ | Yield (%) | M.p. (°C) |
|---|---|---|---|---|
| *(a)* | CN | CN | 78 | 103–106 (decomp.) |
| *(b)* | CN | $COOCH_3$ | 93 | 105–107 (decomp.) |
| *(c)* | CN | $COOC_2H_5$ | 89 | 84–87 (decomp.) |

| *(7)* | $R^1$ | $R^2$ | Z | $R^3$ | Yield (%) | M.p. (°C) |
|---|---|---|---|---|---|---|
| *(a)* | CN | CN | $NC_6H_5$ | $C_6H_5$ | 55 | 224–225 |
| *(b)* | CN | CN | O | *p*-$C_6H_4Cl$ | 76 | 210 (decomp.) |
| *(c)* | CN | $COOCH_3$ | O | $C_6H_5$ | 87 [a] | 165–167 [b] |
| *(d)* | CN | $COOCH_3$ | O | *p*-$C_6H_4Cl$ | 56 [a] | 212 (decomp.) [b] |
| *(e)* | CN | $COOCH_3$ | $NC_6H_5$ | $C_6H_5$ | 61 [a] | 216–217 [b] |

[a] Yield of mixture of geometrical isomers.
[b] M.p. of less soluble isomer (from acetone).

*Experimental*: 92 g of phosgene is introduced into a suspension of 194 g of compound *(1)*, $R^1 = R^2 = CN$, in 1.2 l of $CH_2Cl_2$ at 10 to 15 °C. The mixture is stirred for 1/2 hr at 20 °C, precipitated salts are removed by filtration, and the solvent is removed in vacuum at not more than 30 °C. This procedure yields 117 g of compound *(2a)*. A sample recrystallized from cyclohexane forms pale yellow leaflets melting at 103–105 °C (decomp.).

A solution of 33.6 g of compound *(2a)* and 40.2 g of *p*-chlorobenzohydroxamoyl chloride in 550 ml of $CH_2Cl_2$ is treated dropwise with 21.2 g of triethylamine at 0 to 10 °C. The mixture is stirred for 2 hr at 20 °C and the solid product is filtered off and washed with a little methylene chloride, acetone, and much water, yielding 39.8 g of compound *(7b)*, which forms pale yellow leaflets, m.p. 210 °C (decomp.), from acetone.

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[*] The relative geometric positions of $R^1$ and $R^2$ were not determined.

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## Arylammonium Polyphosphates from *O,O,S*-Trialkyl Thiophosphates and Arylamines

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Trialkyl phosphates alkylate primary aliphatic amines, giving up one alkyl group, but they alkylate the more weakly basic primary aromatic amines with all three alkyl groups [1]. Dialkyl phosphorochloridates, phosphoramidates, and phosphorazidates also can transfer both alkyl groups to arylamines; this reaction has been suggested for the preparation of *N*-arylphosphoramidic acids *(1)*, which are reported to be thus formed [2].

In analogous reactions of *O,O,S*-trialkyl thiophosphates with arylamines (molar ratio 1:3 to 1:4.5, temperature 130 to 160 °C) we have obtained, alongside *N*-alkylarylamines and

alkanethiols, high yields of products that are identical with the supposed *N*-arylphosphoramidic acids *(1)* previously described.

$$(RO)_2PO(SR') + 3\ ArNH_2 \rightarrow 2\ ArNHR + R'SH + [ArNHPO(OH)_2]$$
*(1)*

R = $CH_3$, $C_2H_5$, or n-$C_4H_9$;

R' = $CH_3$ or $C_2H_5$;

Ar = $C_6H_5$, *p*-Cl–$C_6H_4$, *m*-$CH_3$–$C_6H_4$, *o*-$CH_3$–$C_6H_4$, *p*-$CH_3$–$C_6H_4$, *p*-$CH_3O$–$C_6H_4$, or 2-naphthyl

These products have precisely the composition of the appropriate *N*-arylphosphoramidic acids. Yet they have remarkably high and unsharp melting points (in the range 230 to 300 °C), are almost insoluble in the usual solvents, and cannot be converted into the known derivatives of *N*-arylphosphoramidic acids (salts, esters, dichlorides). The IR spectra give no indication of a P–N bond, but very definite P–O–P bands at 890 to 940 $cm^{-1}$. Like Kurrol's potassium salt $(KPO_3)_n$, which also is insoluble[3], most of these products dissolve readily in saturated NaCl solution; on paper chromatography of such solutions the substances remain behind those oligophosphates that are separable (up to $n = 9$).

Thus we are not dealing with *N*-arylphosphoramidic acids *(1)*, but with the isomeric arylammonium polyphosphates *(2)*. The same is true for preparations obtained by other methods[4]. The conversion of compounds *(1)* into *(2)* corresponds to the behavior of the parent substance $H_2NPO_3H_2$ when heated to 100 °C[5]. On addition of a suitable alcohol the metaphosphate intermediate can be trapped, *e.g.* as the ester *(3)*.

$$ArNHPO(OH)_2 \rightleftharpoons Ar\overset{\oplus}{N}H_2PO(OH)O^{\ominus}$$
*(1)*

$$\rightarrow [HPO_3] + ArNH_2$$

$$\xrightarrow{c\text{-}C_6H_{11}OH} c\text{-}C_6H_{11}OPO(OH)_2 \quad {}^1/_n\ [Ar\overset{\oplus}{N}H_3\ PO_3^{\ominus}]_n$$
*(3)* *(2)*

*O,O*-Dibutyl *S*-ethyl thiophosphate and aniline (molar ratio 1:4.4; 3.5 hr; 160 °C) afford 81 % of the pure salt *(2)* (Ar = $C_6H_5$), but *O*-butyl *S*-ethyl hydrogen thiophosphate gives only 18 % of impure product under the same conditions; however, reactions of dialkyl *N*-phenylphosphoramidates with aniline yield the salts *(2)* smoothly; *O,S*-dimethyl *O*-phenyl thiophosphate and aniline give phenyl hydrogen *N*-phenylphosphoramidate. It thus follows that the first step in the reaction is phosphorylation of the amine to a diester of the *N*-arylphosphoramidic acid, which is then dealkylated to give the (unstable) acid *(1)*.

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German version: Angew. Chem. *78*, 1019 (1966)

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## A New Synthesis of Tetrakis(dimethylamino)ethylene

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Tris(dimethylamino)methane *(1)* has been prepared previously by treatment of tetramethylformamidinium salts with alkali dimethylamides[1]. We have now found that compound *(1)* readily loses dimethylamine on being heated under nitrogen, leading to tetrakis(dimethylamino)ethylene *(2)*, which is purified by distillation; yield 80 % after 2 hr under reflux.

$$H\text{-}C[N(CH_3)_2]_3 \xrightarrow{\Delta} (CH_3)_2N\text{-}C(N(CH_3)_2)=C(N(CH_3)_2)\text{-}N(CH_3)_2 + 2\ HN(CH_3)_2$$
*(1)* *(2)*

The compound *(2)* was first synthesized[2] from chlorotrifluoroethylene and dimethylamine in 54 % yield. It is also obtained on thermal decomposition of aminal esters[3], but only in low yields.

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[1] *H. Bredereck, F. Effenberger*, and *Th. Brendle*, Angew. Chem. *78*, 147 (1966); Angew. Chem. internat. Edit. *5*, 132 (1966).

[2] *R. L. Pruett et al.*, J. Amer. chem. Soc. *72*, 3646 (1950).

[3] *H. E. Winberg et al.*, J. Amer. chem. Soc. *87*, 2055 (1965); U.S.-Pat. 3239534 (March 8th, 1966).

## (Dimethylsulfonio)(phenylsulfonyl)-(vinylsulfonyl)methanide

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In attempts to substitute the protons of the $-SO_2-CH_2-SO_2-$ group of *S*-vinylmethylene disulfones[1] while retaining the vinyl group, we have prepared the first unsaturated, polymerizable sulfur ylide, namely (dimethylsulfonio)(phenylsulfonyl)(vinylsulfonyl)methanide *(2)*. The method of preparation was equivalent to that used for condensation of sulfoxides with sulfonamides[2] or active methylene compounds[3].

$$CH_2{=}CH\text{-}SO_2\text{-}CH_2\text{-}SO_2\text{-}C_6H_5 + S(=O)(CH_3)_2 \xrightarrow{Ac_2O} CH_2{=}CH\text{-}SO_2\text{-}\overset{\ominus}{C}(\overset{\oplus}{S}(CH_3)_2)\text{-}SO_2\text{-}C_6H_5$$
*(1)* *(2)*

An exothermic reaction occurs at 120 °C when 5 g of methylene *S*-phenyl *S'*-vinyl disulfone *(1)* and 15 g of dimethyl sulfoxide are heated together in 20 g of acetic anhydride. After the mixture had cooled, the volatile components were removed in a vacuum (60 °C/2 mm). The ylide solidified after a few days and was recrystallized from water. Yield, 1.5 g (24.2 %); m.p. 133.5–134.5 °C.

Elemental analysis, and the fragments as well as the highest peak (306) in the mass spectrum[4], prove the composition and molecular weight of the product *(2)*. Preponderance of the ylide structure shown over a possible ylene structure (>C=S<) is confirmed by the UV spectrum (in 95 % ethanol). The fine structure ($\lambda_{max}$ = 261 mμ, log $\varepsilon_{max}$ = 2.93; $\lambda_{max}$ = 267 mμ, log $\varepsilon_{max}$ = 3.09; $\lambda_{max}$ = 274 mμ, log $\varepsilon_{max}$ = 3.02) due to the aromatic system in the starting material *(1)* is absent from the spectrum of the product *(2)*,

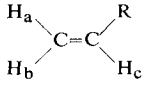
which gives a broad and more intense band at $\lambda_{max} = 248$ mμ (log $\varepsilon_{max} = 3.93$) comparable with that due to the methylene *S,S'*-diphenyl disulfone anion, $C_6H_5-SO_2-{}^{\ominus}CH-SO_2-C_6H_5$ ($\lambda_{max} = 267$ mμ, log $\varepsilon_{max} = 3.85$) [5].

Characteristic differences in the IR and NMR spectrum of compounds *(1)* and *(2)* are collected in Tables 1 and 2.

Table 1. Positions of the IR bands ($cm^{-1}$) due to the $SO_2$ stretching vibrations of compounds *(1)* and *(2)*.

| | *(1)* | *(2)* |
|---|---|---|
| ν ($SO_2$) | 1317/1305 | 1300/1285 |
| ν ($SO_2$) | 1160/1150 | 1135/1120 |

Table 2. Chemical shifts (τ) and coupling constants (*J*) of compounds *(1)* and *(2)* [measured in $(D_3C)_2SO$, TMS as internal standard, at 20 °C and 60 MHz].



| | $\tau_a$ | $\tau_b$ | $\tau_c$ | $J_{ac}$ | $J_{bc}$ | $\tau C_6H_5$ | $\tau CH_3$ | α [a] |
|---|---|---|---|---|---|---|---|---|
| *(1)* | 3.64 | 3.68 | 2.91 | 9.5 | 17.0 | 2.1 | – | 0.37 |
| *(2)* | 4.23 | 4.03 | 3.07 | 9.8 | 16.3 | 2.3 | 7.07 | 0.28 |

[a] $\alpha = J_{bc}/(\nu_b - \nu_c)$; cf. [6].

The higher electron density of the vinyl group in the ylide *(2)* than in *(1)* is reflected in the chemical shifts of the vinyl protons and in the α values [6].

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## Reduction of Phthalocyanine to Tri- and Tetra-lithium Phthalocyanine

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We have found earlier [1] that transition-metal derivatives of phthalocyanine (MPc) can be reduced in tetrahydrofuran, in a series of steps, by lithium, sodium, or radical anions of aromatic compounds:

$$[MPc] \xrightarrow{+n\ominus} [MPc]^{n-}$$

The anionic phthalocyanine complexes formed can be isolated as well-crystalline lithium salts that contain tetrahydrofuran [2]. In order to elucidate the structure of these new electron-rich complexes it was necessary to find whether the ligand $Pc^{2-}$ is itself reducible [3].

If dilithium phthalocyanine ($Li_2Pc$) [4], in which only reduction of the phthalocyanine system is theoretically possible [5], is treated in tetrahydrofuran with dilithiobenzophenone ($Li_2Bzph$), then trilithium phthalocyanine *(1)* is obtained.

$$Li_2Pc + {}^1/_2\ Li_2Bzph \xrightarrow{THF} {}^1/_2\ Bzph + Li_3Pc{\cdot}6THF \quad (1)$$

This product forms shiny, violet-brown needles, dissolves in THF or acetonitrile to intensely blue solutions, can be recrystallized from THF, and in THF consumes one atom of iodine. At 293 °K, $\chi_g = +(1.15 \pm 0.01)\times10^{-6}$ cm³/g, whence it follows that $\mu_{eff} = 2.09 \pm 0.01$ B.M.

Use of an excess of $Li_2Bzph$ leads to tetralithium phthalocyanine *(2)*. This compound forms olive-green crystals with a yellow surface sheen, is only sparingly soluble in THF or

$$Li_3Pc{\cdot}6THF + Li_2Bzph \xrightarrow{THF} LiBzph + Li_4Pc{\cdot}8\ THF \quad (2)$$

acetonitrile, giving intensely violet solutions, consumes two iodine atoms in THF, and at 293 °K has $\chi_g = -(0.05 \pm 0.02)\times10^{-6}$ cm³/g, corresponding to $\mu_{eff} = 1.36 \pm 0.02$ B.M.

Compounds *(1)* and *(2)* are both sensitive to oxygen and moisture, lose the THF quantitatively in vacuum at 150 °C, and, like $Li_2Pc$, are electrolytes, as was shown by transport experiments in acetonitrile. Their structures are represented by the formulae $Li_2[LiPc]{\cdot}6THF$ and $Li_3[LiPc]{\cdot}8THF$, respectively.

Simple LCAO–MO theory requires that the electrons taken up go into the lowest unoccupied orbital in the complex. For $D_{4h}$ symmetry this is the two-fold degenerate, weakly antibonding π-orbital $6e_g$ of phthalocyanine [5]. Accordingly compound *(2)* must have $(6e_g)^2$ occupied and therefore, by Hund's rule, a triplet ground state. The observed magnetic moment, however, indicates a singlet state. For a multielectron scheme this should result from consideration of configuration interaction [6], but it could also be caused by lowering of symmetry by geometrical instability of the complex [7] which would remove the degeneracy of the $6e_g$ orbital.

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German version: Angew. Chem. *78*, 1022 (1966)

[1] M = Mn, Fe, Co, Ni, Cu, or Zn; Pc = $C_{32}H_{16}N_8$; $n = 1$–4 or 5.

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[3] The electron affinity of the phthalocyanine anion $Pc^{2-}$ is also of importance for the electric and catalytic properties of the phthalocyanines.

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## Rearrangement of Unsaturated Compounds to Cyclopropane and Cyclobutane Derivatives

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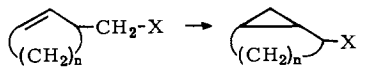
In carbonium-ion reactions homoallylic compounds readily rearrange to cyclopropylmethyl and cyclobutyl derivatives. This reaction has been studied for cyclic compounds of various structures in relation to ring size.

Compounds of formula *(1)*, X = OTs or $NH_2$, rearrange to bicyclic derivatives *(2)*, X = OH, if n > 2.



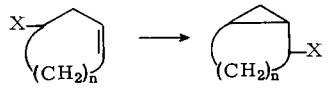
*(1)* *(2)*

However, 2-cyclobutenylmethyl derivatives *(1)*, n = 1, X = OTs, do not cyclize during solvolysis. Moreover, no participation of the double bond in carbonium-ion reactions could be detected by kinetic measurements.

Cyclopropylmethyl derivatives *(4)*, X = OH, are formed also from systems of structure *(3)*, X = OTs or $NH_2$, if n > 2.

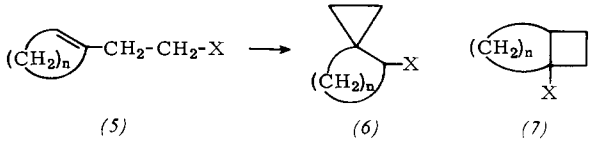
3-Cyclopentenyl derivatives *(3)*, n = 1, X = Br or OTs, however, do not react to give bicyclic compounds.

Compounds of structure *(5)*, n = > 3, rearrange to give spiro compounds *(6)*, X = OH, and condensed cyclobutane derivatives *(7)*, X = OH, which thus become easily accessible.



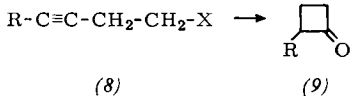
*(3)* *(4)*

Acetylenes of structure *(8)*, R = alkyl, X = *m*-$NO_2$-$C_6H_4$-$SO_3$, can be cyclized to cyclobutanones *(9)*, R = alkyl. When trifluoroacetic acid is used as the ionizing solvent, the cyclobutanones *(9)* are obtained almost quantitatively and thus become readily available for the first time.



*(5)* *(6)* *(7)*

Reaction of 4-phenyl-3-butynyl derivatives gives preponderatingly phenyl cyclopropyl ketones; solvolysis of the ethoxy derivative *(8)*, R = $OC_2H_5$, X = *m*-$NO_2$–$C_6H_4$–$SO_3$, affords ethyl cyclopropanecarboxylate.



*(8)* *(9)*

[Lecture at Tübingen (Germany) on May 13th, 1966]

[VB 997 IE]

German version: Angew. Chem. *78*, 987 (1966)

## Reactions of Nucleophiles with Pyridinium Ions

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The extreme electrophilicity of the pyridinium ion makes it a convenient substrate for the study of reactions of aromatic systems with nucleophiles. A pyridinium ion having an electron-withdrawing substituent in the 3-position may form a 1,2-, 1,4-, or 1,6-dihydropyridine. The factors which determine the site of reaction with the nucleophile, and thus the structure(s) of the product(s), are not well defined. The results of a study of the reactions of cyanide ion with 5-bromo-3-ethoxycarbonyl-1-methylpyridinium iodide, 1-benzyl-3-cyanopyridinium bromide, and 3-benzoyl-1-methylpyridinium iodide showed that the product of "kinetic control" was a 6-cyano-1,6-dihydropyridine, but in solution in ethanol or chloroform this derivative was converted into the 4-cyano-1,4-dihydropyridine. Evidence was presented that these reactions are reversible, showing that the 1,4-dihydropyridine is formed by "thermodynamic control".

The importance of steric interference to approach of the nucleophile to the position adjacent to the quaternary nitrogen in a "kinetically controlled" process was illustrated with results from sodium borohydride reductions.

The generalization of these results suggests that irreversible reactions of pyridinium ions with nucleophiles (kinetic control) occur at the positions adjacent to the quaternary nitrogen if steric interference of the nucleophile with the nitrogen substituent is not too large.

Reactions with nucleophiles which produce dihydropyridines capable of dissociation under the reaction conditions lead to 1,4-dihydropyridines, the isomers of apparently greater stability under equilibrium conditions.

The reversibility or irreversibility of the reaction of a nucleophile with a pyridinium ion provides a basis for correlating many of the known reactions of pyridinium ions.

[Lecture at Freiburg (Germany) on May 13th, 1966]

[VB 19 IE]

German version: Angew. Chem. *78*, 1025 (1966)

## Preparation of High-Melting Substances by Pyrolysis

*E. Fitzer*, Karlsruhe (Germany)

High-melting substances can be prepared by thermal decomposition of compounds containing their components. If the pyrolysis is carried out on the boundary between a fluid and a heated solid surface the pyrolysis products are obtained as growth layers. In such growth reactions the kinetics of pyrolysis, transport processes, nucleation, or crystallization may have a decisive effect on the chemical composition and habit of the deposited material.

These interdependent processes can be demonstrated for the growth reaction of SiC produced by decomposition of chloro(methyl)silanes. Monochloro(trimethyl)silane can be pyrolysed to yield SiC from 1100 °C. Between 1150 and 1350 °C polycrystalline SiC of vitreous appearance can be produced with a rate of growth of the layer of 0.2 to 0.5 mm/hr. In spite of the superstoichiometric presence of carbon the formation of SiC always precedes the separation of free carbon. Depending on the conditions, heterogeneous SiC/C laminates can be obtained, which have layers parallel to the surface of the substrate and are of industrial interest. This type of deposition is indicated by an oscillating surface reaction.

The course of reactions in a fluidized-bed reactor and of growth reactions leading to $B_4C$ and TiC were compared. In formation of $B_4C$, separation of carbon precedes carbide formation. During the pyrolysis of methane at 1 atm and 1200–1500 °C under stationary reaction conditions to pyrocarbon we observed spiral and whisker growth.

Pyrolysis of cross-linked polymers, *e.g.* furan resins, leads to impermeable carbons with He densities of 1.55 g/cm³. Small-angle scattering showed the presence of uniform pores of 20–30 Å diameter.

Cellulose can be thermally degraded to flexible graphite fibers and it was shown by wide- and small-angle X-ray diffraction that the fibrillar structure of the cellulose is retained in the carbon residue. If flexible products are to be obtained it is necessary to avoid formation of tarry by-products by instant removal of pyrolysis gases.

[Lecture Freiburg (Germany) on June 10th, 1966] [VB 6 IE]

German version: Angew. Chem. *78*, 988 (1966)

## Aliphatic Semidiones; Application of Electron Spin Resonance to Problems of Conformation

*G. A. Russell*, Iowa State University (U.S.A.)

Aliphatic semidiones, $RC(O\cdot)=C(O^-)R$, can be readily prepared by the base-catalysed oxidation of cyclic [1], acyclic [2], and bicyclic ketones [3,4]. There is an appreciable conformational preference for the simple alkyl groups (other than methyl) in the symmetrical acyclic semidiones. The acyclic semidiones with R = methyl or ethyl exists as *cis* and *trans* structures. For R = methyl the *cis/trans* ratio (quaternary ammonium cation) is 5/95 at 25 ° and 12/88 at 90 ° in dimethyl sulfoxide solution [5]. Use of lithium as the cation gives only the *cis* structure which shows hyperfine splitting by a single lithium ion. With potassium as cation the *trans* structure is greatly preferred in dimethyl sulfoxide solution but the *cis* structure is the only detectable species in dimethoxyethane solution.

The formation of semidiones from substituted cyclohexanones and decalones can yield information in regard to the conformation of the resulting cyclic semidiones (a cyclohexene or octalin derivative). In addition, by comparison of the percent attack at C-2 and C-4 for 3-keto steroids and decalones it is possible to empirically assign the conformational preference of the starting ketone. We find that both *cis*-9-methyl-2-decalinone and *cis*-10-methyl-2-decalinone prefer the "non-steroidal" conformation, that is, the methyl group occupies an axial position of the ring containing the carbonyl group.

Oxidation of 4-substituted cyclohexanones yields the 4-substituted cyclohexane-1,2-semidiones as a pair of unequally populated but rapidly time averaged half-chair conformers at 25 ° [6]. The equilibrium constant for the 4-methylcyclohexane-1,2-semidione has a value of about 5 (in favor of the equatorial substituent) at 25 °.

The rate of conformational interconversion of 3,3,5,5-tetramethylcyclohexane-1,2-semidione has been investigated by line broadening analysis from −50 to +80 °. The data yield $E_a = 3.3 \pm 0.5$ kcal/mole, $\Delta S^{\neq} = 5.9 \pm 3$ e.u.

[Lecture at Marburg (Germany), June 10th, 1966] [VB 18 IE]

German version: Angew. Chem. *78*, 989 (1966)

[1] *G. A. Russell*, J. Amer. chem. Soc. *86*, 744 (1964).

[2] *E. T. Strom, G. A. Russell*, and *R. D. Stephens*, J. physic. Chem. *69*, 2131 (1965).

[3] *G. A. Russell* and *E. R. Talaty*, Science *148*, 1217 (1965); *G. A. Russell* and *K.-Y. Chang*, J. Amer. chem. Soc. *87*, 438 (1965).

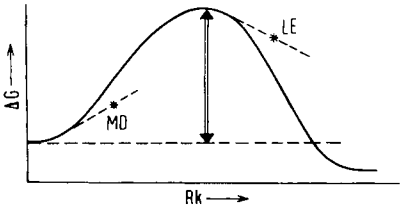
[4] *G. A. Russell* and *R. D. Stephens*, J. physic. Chem. *70*, 1320 (1966).

[5] *E. R. Talaty* and *G. A. Russell*, J. Amer. chem. Soc. *87*, 4867 (1965).

## Quantum-Theoretical Estimates of Chemical Reactivities

*O. E. Polansky*, Vienna (Austria)

Chemical reactivities can be discussed by the simple HMO theory on the basis of molecular diagrams (MD), or of localization energies (LE). In the first case the model for the transition state is a state between the initial system and the activated complex, in the second a state between the activated complex and the reaction product (see Figure). Since both these states are fictitious and not equivalent to the transition state, both methods give some unrealistic results [1].




Provided that the activated complex involved in individual reactions of a given type is always in the same, not too broad region of reaction coordinates (Rk), and further that the substituents at the reaction centers exert no steric effect, relative free activation energies can be estimated by simple HMO calculations. To this end the π-electron contribution $(\Delta H_i^{\neq})_\pi$ to the activation enthalpy $\Delta H_i^{\neq}$ is separated as follows:

$$\Delta H_i^{\neq} = (\Delta H_i^{\neq})_\pi + (\Delta H_i^{\neq})_{\text{residual}}$$

Defining the residual amount of the free energy of activation as

$$(\Delta G_i^{\neq})_{\text{residual}} = (\Delta H_i^{\neq})_{\text{residual}} - T\Delta S_i^{\neq},$$

which is approximately constant under the above conditions for constant temperature and solvation, then expression (1) is obtained for the free energy of activation of a reaction i.

$$\Delta G_i^{\neq} = (\Delta H_i^{\neq})_\pi + (G_i^{\neq})_{\text{residual}} \quad (1)$$

Expression (2) then follows for the relative free activation energy of two reactions i and j.

$$[\Delta G_i^{\neq} - \Delta G_j^{\neq}] = [(\Delta H_i^{\neq}) - (\Delta H_j^{\neq})_\pi] + G_{i,j}^{\neq} \quad (2)$$

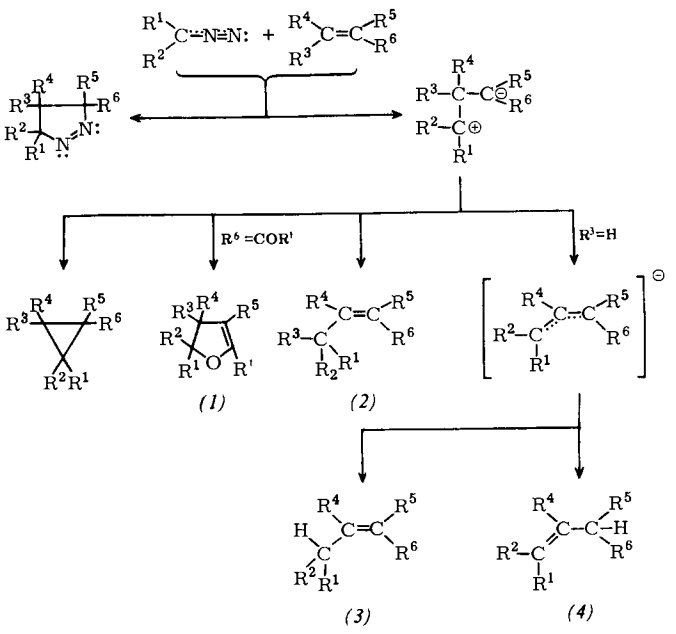
Whereas $(\Delta H^{\neq})_\pi$ is estimated by HMO calculations, $G_{i,j}^{\neq} = [(\Delta G_i^{\neq})_{\text{residual}} - (\Delta G_i^{\neq})_{\text{residual}}]$ is a constant determined empirically.

Further, since $[\Delta G_i^{\neq} - \Delta G_j^{\neq}] = -RT \ln (k_i/k_j)$, this method can be used to calculate relative yields in competitive reactions following the same rate law. The combination with eq. (2) leads to

$$-RT \ln (k_i/k_j) = [(\Delta H_i^{\neq})_\pi - (\Delta H_j^{\neq})_\pi] + G_{i,j}^{\neq}$$

which allows empirical determination of $G_{i,j}^{\neq}$ if the competitive reactions of the same rate law lead to equal amounts of products formed; in that case $\ln(k_i/k_j) = 0$ and therefore $G_{i,j}^{\neq} = -[(\Delta H_i^{\neq})_\pi - (\Delta H_j^{\neq})_\pi]$. If unequal yields are obtained, the comparison of calculations and experimental results of several reactions of the type discussed leads to a rather sharp restriction of $G_{i,j}^{\neq}$.

Application of this method to the reactions of diazoalkanes with olefins according to a mechanism involving seven types



of products[2] shows surprisingly good agreement between calculated and experimental results[3].

[Lecture at Berlin (Germany), June 24th, 1966] [VB 20 IE]

German version: Angew. Chem. 78, 1024 (1966)

[1] *R. D. Brown*, Quart. Rev. (Chem. Soc., London) *6*, 63 (1952).

[2] Compounds *(1)–(4)* may react with a further molecule of the diazoalkane.

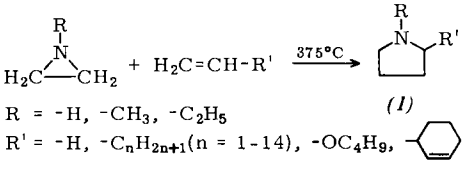
[3] Messrs. *P. Schuster* and *A. Eitel* (Farbenfabriken Bayer, Leverkusen) collaborated in setting up the mathematical model and the mechanism. See also: *A. Eitel*, Dissertation (University of Vienna, 1964) and *P. Schuster*, Dissertation (University of Vienna 1966).

## Cycloaddition on Thermal Cleavage of Aziridines in the Presence of Olefins[1]

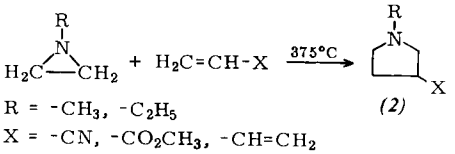
*M. Fremery*, Hamburg (Germany)

Aziridines add to olefins above 300 °C with formation of pyrrolidines *(1)*. This one-stage reaction can be carried out either in the liquid phase under autogenous pressure in autoclaves or in the gas phase in a flow reactor. Depending on the nature of the olefin the additions occur with 35 to 98 % yield. The olefin must be present in 10- to 20-fold excess.

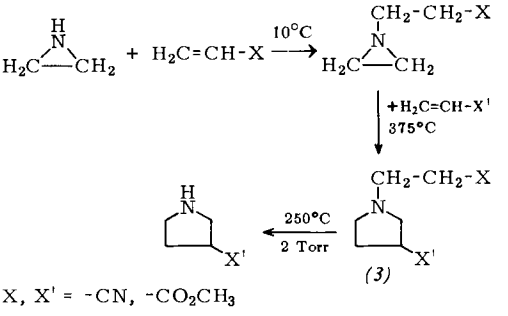
Alkenes with terminal double bonds are appreciably better acceptors than are cycloalkenes or olefins with non-terminal double bonds. NMR studies have shown that the alkyl group of olefins with terminal double bonds are found exclusively at position 2 of the pyrrolidines.



Olefins activated by electronegative substituents react with aziridines to give pyrrolidines *(2)* with the substituents on C-3.



However, only *N*-substituted aziridines can be used for this reaction, since those without such substituents undergo side reactions. Nevertheless, pyrrolidines with functional groups on C-3 but no substituent on the nitrogen are obtained if the ethylene imine used as starting material has on the nitrogen a group which can be exchanged for hydrogen after addition. Favorable for this purpose was the reaction of ethylene imine with olefins activated by electronegative groups [principle of the Michael reaction].



The *N*-substituent of the resulting pyrrolidines *(3)* could then be removed by a thermal retro-Michael reaction.

Above 300° C acetylene also react with aziridines, yielding pyrrolines and pyrroles by 1,3-cycloaddition.

In the above reactions the aziridine is cleaved at a C–N bond. It is not yet known whether the cycloaddition involves a radical or an ionic reaction. Either mechanism suffices to explain the stereoselectivity of the reactions leading to compounds *(1)* and *(2)*.

[Lecture at Mülheim (Germany), July 14th, 1966] [VB 22 IE]

German version: Angew. Chem. 78, 1024 (1966)

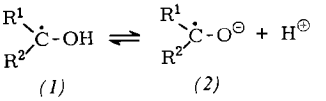
[1] This work was carried out at the Shell Development Co., Emeryville, Cal. (U.S.A.).

## Study of Fast Chemical Reactions of Electrons and Radicals by Pulse Radiolysis

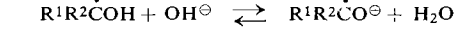
*A. Henglein*, Berlin (Germany)

When an aqueous solution is irradiated with a short pulse (1–10 μsec) of energetic electrons, OH radicals and hydrated electrons are formed. The reactions of these intermediate products of radiolysis can be followed by recording the decay of their optical absorption after the radiation pulse, or the rise in absorption of the resulting products, as a function of time.

The OH radical reacts with primary or secondary alcohols $R^1R^2CHOH$ by abstraction of H and formation of an α-alcohol-radical. In alkaline solution the OH radical and the alcohol yield a species *(2)* which absorbs strongly in the ultraviolet and is in equilibrium with the α-alcohol-radical.



These forms *(1)* and *(2)* also arise when the hydrated electron adds to a dissolved aldehyde or ketone. The pK value of an alcohol-radical is greater the greater is the Taft σ* value for the inductive effect of the organic groups attached to the α–C atom. Equilibrium is established with participation of the $OH^-$ ion:



The anionic form of the alcohol-radical transfers an electron to nitrobenzene with $k = 3\times10^9$ mole$^{-1}$ l sec$^{-1}$, independently of the structure of the alcohol. The acidic form *(1)* can also transfer an electron, but the reaction is then about 10 times slower and depends on the structure: the electron is in this case transferred more easily the greater is the Taft $\sigma^*$ value.

A hydrated electron adds to nitrobenzene, giving the anion $C_6H_5NO_2^-$ ($\varepsilon_{max}$ at 2850 Å; $k = 1.4\times10^4$ mole$^{-1}$ l cm$^{-1}$). In acidic solution mainly $C_6H_5NO_2H$ is present. The pK of the equilibrium

$$C_6H_5NO_2H \rightleftarrows C_6H_5NO_2^{\ominus} + H^{\oplus}$$

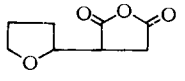
is 3.2. The ion $C_6H_5NO_2^{\ominus}$ is very stable. Two $C_6H_5NO_2H$ particles disproportionate to $C_6H_4N(OH)_2$ and $C_6H_5NO_2$ with $k = 6\times10^8$ mole$^{-1}$ l sec$^{-1}$. $C_6H_5N(OH)_2$ then decomposes with loss of water to nitrosobenzene. The rate constant of this unimolecular decomposition depends on the $H^{\oplus}$ concentration. $C_6H_5NO_2^{\ominus}$ can transfer an electron to nitrosobenzene with $k = 4.1\times10^7$ mole$^{-1}$ l sec$^{-1}$. The free H atom does not attack the $NO_2$ group of nitrobenzene, but adds to the aromatic nucleus, giving the nitrocyclohexadienyl radical. An OH radical reacts similarly, giving a hydroxynitrocyclohexadienyl radical.

[Lecture at Mainz (Germany), July 21st, 1966] [VB 17 IE]

German version: Angew. Chem. *78*, 988 (1966)

# SELECTED ABSTRACTS

**An adduct of maleic anhydride and tetrahydrofuran** is produced on irradiation with ultraviolet light, according to *L. Ledwith* and *M. Sambhi*. Primarily a donoracceptor complex absorbing at 270 mμ is formed, which yields the 2-tetrahydrofurylsuccinic



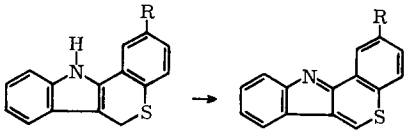
*(1)*

anhydride *(1)*. This highly hygroscopic compound can be easily hydrolysed to the corresponding substituted succinic acid, m.p. 136 to 137 °. / J. chem. Soc. (London) B *1966*, 670 / –Bu. [Rd 547 IE]

**A simple method for the determination of $D_2O$ in water** is based on the different solubility of anhydrous $CuSO_4$ in $D_2O$ and $H_2O$. Differential photometry is used by *J. Cabican* and *F. Einhorn* to compare the extinctions of saturated $CuSO_4$ solutions in $H_2O$ and in the water sample containing an unknown amount of $D_2O$. At 650 mμ the difference in extinction between the saturated $H_2O$ and $D_2O$ solutions reaches a maximum of $\Delta E = 0.7$. Since there is an almost linear relationship between $\Delta E$ and the $D_2O$ content, the determination can be carried out with an accuracy of better than 0.5% in the whole concentration range. / Z. Naturforsch. *21a*, 504 (1966) / –Bu. [Rd 541 IE]

**An enzyme that catalyses thiol-disulfide interactions in proteins** has been concentrated by a factor of 960 from ox-liver microsomes by *F. de Lorenzo et al.* The enzyme catalyses either the renaturation of a protein the disulfide bridges of which have been reductively broken, or the re-establishment of the original arrangement of the disulfide bridges in a randomly bridged protein. Ribonuclease and the trypsin inhibitor from soybeans were used as test substrates. Electrophoresis in starch and polyacrylamide gels gave two enzymatically active bands, which unite on reduction and alkylation. The molecular weight was found to be 42000; the molecule contains three cysteine residues. / J. biol. Chemistry *241*, 1562 (1966) / –Hö. [Rd 553 IE]

**[1]Benzothiopyrano[4,3-*b*]indoles, a new group of pseudoazulenes** (heterocyclic iso-π-electronic analogues of azulenes), have been synthesized by *N. P. Buu-Hoï, A. Croisy, A. Ricci, P. Jacquignon*, and *F. Perin*. Dehydrogenation of compounds of type *(2)* by picric acid in boiling alcohol affords readily the [1]benzothiopyrano[4,3-*b*]indoles *(1)*. The parent *(1a)* is an iso-π-electron analogue of dibenz[*b,f*]azulene. The constitutions of the new products are proved by NMR spectra.

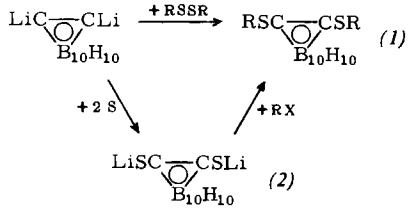


*(2a)*, R = H
*(2b)*, R = $CH_3$
*(2c)*, R = Cl

*(1a)*, R = H
*(1b)*, R = $CH_3$
*(1c)*, R = Cl

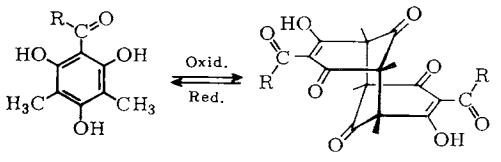
Also, compounds *(1)* are structural analogues of the carcinogenic benz[*c*]acridines. / Chem. Commun. *1966*, 269 / –Ma. [Rd 526 IE]

**Carborane bis(thioethers) *(1)*, the first compounds containing carborane-sulfur bonds,** have been synthesized by *H. D. Smith Jr., C. O. Obenland*, and *S. Papetti* from dilithio-*o*- or -*m*-carborane and organic disulfides, or from the same carborane derivative and sulfur *via* the intermediate *(2)*, which with halogenoalkanes gives the thioethers *(1)*.

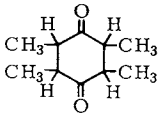



Hydrolysis of *(2)* leads to the dithiol. Boron-substituted mono-, di-, and tribromocarboranes may also be used. Examples: *o*-carborane 1,2-bis(methyl thioether), m.p. 101–102 °C; 1,2-bis(mercapto)-*o*-carborane, m.p. 265–267 °C; *m*-carborane 1,7-bis(ethyl thioether), b.p. 114 °C/0.1 mm Hg. In contrast to the ready metalation of dialkyl or aryl alkyl sulfides, the reaction of *o*-carborane 1,2-bis(methyl thioether) with butyl-lithium leads to cleavage of the carborane-S bond to give dilithiocarborane and butyl methyl sulfide. The thioethers do not form adducts with chlorine or bromine. / Inorg. Chem. *5*, 1013 (1966) / –Kr. [Rd 539 IE]

**A new type of phenol dehydrogenation** has been observed by *H. Davies, H. Erdtman*, and *M. Nilsson*. 2,4,6-Trihydroxy-3,5-dimethylacetophenone *(1a)* is oxidized by $FeCl_3$ in alcohol to a dimeric product *(2a)*, m.p. 270–273 °C, in 85% yield. This product regenerates the starting material on catalytic hydrogenation or on reduction with Zn/acetic acid; on oxidation with $H_2O_2$ it affords 2,3,5,6-tetramethyl-1,4-cyclohexanedione *(3)* in 18% yield. Oxidation of 2,4,6-trihydroxy-3,5-dimethylbenzaldehyde with $FeCl_3$ leads to the dimeric product *(2b)*, m.p. 278–282 °C, which regenerates the aldehyde *(1b)* on treatment with Zn/acetic acid.



*(1a)*, R : $CH_3$ *(2a)*, R : $CH_3$
*(1b)*, R : H *(2b)*, R : H



*(3)*

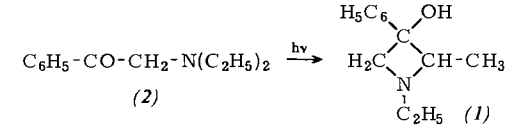
The spectra of compounds *(2a)* and *(2b)* indicate that they are dimers of enolized β-tricarbonyl compounds. / Tetrahedron Letters *1966*, 2491 / –Ma. [Rd 525 IE]

**Resolution of ethyl *p*-tolyl sulfoxide into optical antipodes** has been reported by *A. C. Cope* and *E. A. Caress*. Reaction of (+)- or (–)-*trans*-ethylene(α-methylbenzylamine)platinum(II) dichloride with ethyl *p*-tolyl sulfoxide in $CH_2Cl_2$ gives two diastereoisomeric *trans*-(ethyl *p*-tolyl sulfoxide) (α-methylbenzylamine)platinum(II) dichlorides in each case. The complexes are fractionally precipitated. Then decomposition

$$PtCl_2(C_2H_4)\ (^*RNH_2) + R^1SOR^2 \rightarrow PtCl_2(R^1SOR^2)\ (^*RNH_2) + H_2C{=}CH_2$$

with aqueous NaCN affords (–)-ethyl *p*-tolyl sulfoxide, $[\alpha]_D^{25} = 203.6°$, and the (+)-enantiomer, $[\alpha]_D^{25} = +203.2°$. / J. Amer. chem. Soc. *88*, 1711 (1966) / –Ma. [Rd 521 IE]

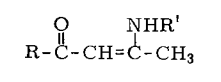
**The synthesis of 3-azetidinols** has been described by *R. A. Clasen* and *S. Searles jr.* 3-Azetidinols *(1)* are readily obtained by UV-irradiation of β-dialkylamino ketones. Thus photocyclization of *N,N*-diethylphenacylamine *(2)* affords 1-ethyl-2-methyl-3-phenyl-3-azetidinol, b.p. 72–73 °C/0.05 mm. Analogously, *N,N*-dimethyl- and *N,N*-diisopropylphenacylamine give 1-methyl-3-phenyl-3-azetidinol and 1-isopropyl-2,2-dimethyl-3-phenyl-3-azetidinol, respectively



*(2)* *(1)*

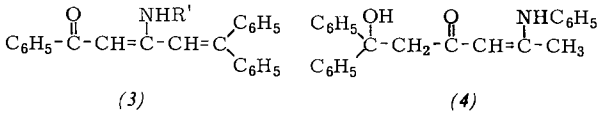
(yields in the three cases are 2 %, 9 %, and 22 %, respectively). In all cases acetophenone and the trimeric imine expected are formed as by-products. The reaction is the first synthesis of an azetidine by C–C ring closure. / Chem. Commun. *1966*, 289 / –Ma. [Rd 522 IE]

**Condensations with β-oxo enamines** can be achieved in compounds *(1)* and *(2)* with aromatic substituents R′ on the nitrogen, according to *S. Boatman* and *C. R. Hauser*, by



*(1)*: R = $C_6H_5$
*(2)*: R = $CH_3$

preparation of the dialkali salts with alkali amide in liquid ammonia. Condensation of *(1)* with benzophenone followed by dehydration with $H_2SO_4$ or polyphosphoric acid leads to the unsaturated β-oxoenamine *(3)* in a yield of about 80%; *(2)* forms only the dianion on the γ-C atom, which reacts with benzophenone to give *(4)*, m.p. 144–145 °C, in 45% yield.



*(3)* *(4)*

The dialkali salts also can be condensed with esters or alkylated. For example, the dialkali salt of *(1)* (with R = R′ = $C_6H_5$) reacts with methyl benzoate to give 3-anilino-1,5-diphenyl-2-pentene-1,5-dione, m.p. 120–122 °C in 50% yield; with benzoyl chloride it gives 3-anilino-1,5-diphenyl-2-penten-1-one, m.p. 64–65 °C, in 62% yield. / J. org. Chemistry, *31*, 1785 (1966) / –Bu. [Rd 549 IE]

**3-Alkyl- and 3,3-dialkyl-1-bromoallenes,** which are useful in the preparation of allene derivatives, can be prepared in good yields at room temperature from secondary and tertiary alkynols and hydrogen bromide, according to *S. R. Landor, A. N. Patel, P. F. Whiter*, and *P. M. Greaves*. The reaction is considerably accelerated by equimolar amounts of CuBr and $NH_4Br$. The IR spectra of 1-bromoallenes contain unusually intense allene bonds at 1950 $cm^{-1}$; strong bands at 1165 and 725 $cm^{-1}$ are due to the hydrogen on C-1, as could be shown by labeling with deuterium. Examples: 3-isopropyl-4-methyl-1-pentyne-3-ol → 82% of 1-bromo-3-isopropyl-4-methylpenta-1,2-diene, b.p. 49–50 °C/6 mm; 3-methyl-1-pentyne-3-ol → 73 % of 1-bromo-3-methylpenta-1,2-diene, b.p. 51–52 °C/24 mm Hg. / J. chem. Soc. (London) C *1966*, 1223 / –Bu. [Rd 550 IE]

**Iodotetrakis(trifluorophosphine)cobalt(I)** *(1)* has been described by *Th. Kruck* and *W. Lang*. Under quite low $PF_3$ pressures a mixture of anhydrous cobalt(II) iodide and copper powder gives the crystalline, brown iodotetrakis-(trifluorophosphine)cobalt(I), which can also be obtained from hydridotetrakis(trifluorophosphine)cobalt(I) and iodoform.

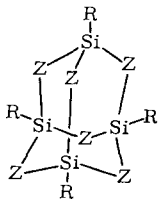
$$CoI_2/Cu \xrightarrow{PF_3\,(50\ atm)} ICo(PF_3)_4 \xleftarrow{I_3CH} HCo(PF_3)_4$$

*(1)*

Compound *(1)* is very volatile and is sensitive to air; it is a non-electrolyte which dissolves without decomposition only in non-polar solvents; from 70 °C it decomposes with total loss of $PF_3$ into an unstable, pale brown substance, amorphous according to its X-ray diagram, and apparently being the hitherto unknown cobalt(I) iodide.

Compound *(1)* is important as starting material for preparation of other trifluorophosphine complexes of cobalt. With triphenylphosphine it gives the disubstitution product $ICo(PF_3)_2[P(C_6H_5)_3]_2$, which is very much more stable thermally and chemically and dissolves without decomposition in aromatic hydrocarbons and in ether; its reduction with potassium amalgam leads to the salt $KCo(PF_3)_4$, which is stable in air, and from which the volatile hydride $HCo(PF_3)_4$ is liberated by acids. This hydride is stable in air and dissolves in polar and non-polar solvents; it has m.p. 174–175 °C; from 193 °C discoloration and decomposition set in; substitution by triphenylphosphine becomes possible only at 135 °C. / Z. anorg. allg. Chem. *343*, 181 (1966) / –Sch. [Rd 535 IE]

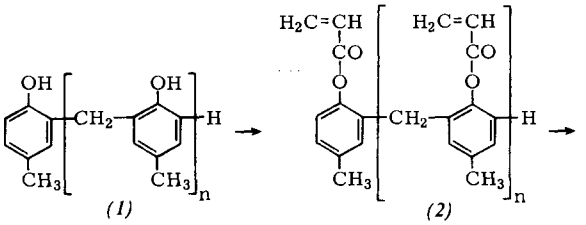
**Tetraalkyltetrasilicon hexachalcogenides with the adamantane structure** *(1)*, which form a new class of compounds, have been prepared by *J. A. Forstner* and *E. L. Muetterties*. Methylsilane with $H_2S$ at 200 °C or $H_2Se$ at 400 °C gives $(CH_3Si)_4S_6$ or $(CH_3Si)_4Se_6$, respectively. $(CH_3Si)_4S_6$ is readily soluble in pentane, chloroform, or benzene, moderately soluble in acetonitrile or alcohol, melts at 272 °C, and gives only one signal in the proton resonance spectrum ($CDCl_3$). $(CH_3Si)_4Se_6$ can be purified by sublimation; it melts at 283 °C and also gives only one signal in the $^1H$–NMR spectrum.



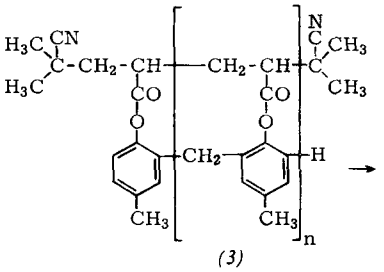
*(1)*, Z = S, Se

The corresponding ethyl derivatives cannot be prepared from ethylsilane, but only from trichloro(ethyl)silane, which reacts with thiols and selenols in the presence of metallic aluminum. All the products are very sensitive to moisture. / Inorg. Chem. *5*, 552 (1966) / –Sch. [Rd 536 IE]

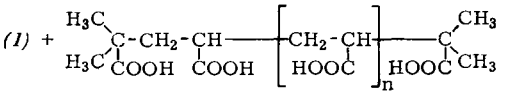
**A new preparation of oligomers** from acrylic and vinyl compounds, as a model of a template reaction, was described by *H. Kämmerer* and *S. Ozaki*. Well-defined oligomeric phenol-formaldehyde resins of the type *(1)* ($n$ = 1 or 2) are converted into polymerizable esters with acrylic acid, and these esters



*(1)* *(2)*



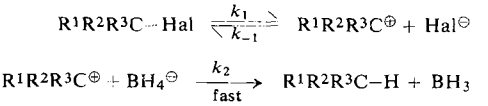
*(3)*



*(4)*

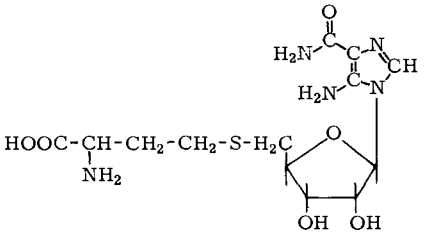
are then polymerized further at high dilution in the presence of azoisobutyronitrile. The polymers *(3)* can be hydrolysed to the original phenols *(1)* and the oligomeric polyacrylic acids *(4)*. The polyphenolic resin template *(1)* can then be used again. / Makromolekulare Chem. *91*, 1 (1966) / –Hl. [Rd 556 IE]

**Reduction of secondary and tertiary halogen compounds under $S_N1$ conditions** can be achieved with $NaBH_4$ in ionizing media, according to *H. M. Bell* and *H. C. Brown*. While the reduction of halogen compounds with $LiAlH_4$ in ether proceeds by an $S_N2$ mechanism (second-order reaction, inversion), and secondary and tertiary halides consequently often react slowly and in poor yields (extensive elimination to form the olefin), excellent yields of hydrocarbons are sometimes obtained under $S_N1$ conditions. A suitable ionizing medium is diethylene glycol dimethyl ether (diglyme)/water; the only reducing agent that can be considered is $NaBH_4$, which is fairly stable in water. The first-order rate constant ($2.1 \times 10^{-4}$ $sec^{-1}$ at 45 °C, 80% diglyme) for the reduction of diphenylchloromethane is of the same order of magnitude as that for the solvolysis of the substrate under the same conditions, but without $NaBH_4$. This shows that a carbonium-ion intermediate is formed in accordance with the general scheme



The 50% increase in the rate of reduction as compared with solvolysis may be interpreted as a salt effect due to the $NaBH_4$. The high yields of hydrocarbon obtained in 65% diglyme/4.0 M $NaBH_4$/1.0 M NaOH (reduction of diphenylchloromethane, 99%; triphenylchloromethane, 96%; 2-chloro-2-phenylpropane, 81%; 1-phenyl-1-chloroethane, 75%) show that the $BH_4$ ion can compete successfully with water (formation of an alcohol) for the carbonium ion. Apart from alcohols, olefins also are formed as by-products. / J. Amer. chem. Soc. *88*, 1473 (1966) / –Eb. [Rd 557 IE]

**(5-Amino-4-carbamoylimidazolyl)-5-S-homocysteinylriboside *(1)*, a new S-amino acid derivative,** is present in the urine of persons suffering from homocystinuria, a hereditory disturbance of the methionine metabolism. *Th. L. Perry*, *S. Hansen*, *H.-P. Bar*, and *L. MacDougall* found the new amino acid in the two-dimensional thin-layer chromatogram, and isolated it by ion-exchange and paper chromatography. The structure was confirmed by degradation and comparison with known cleavage products.

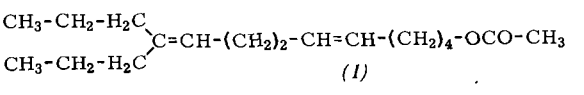


*(1)*

The daily elimination of *(1)* in children with homocystinuria is 0.3 mmole *(1)* per gram of creatinine. Nothing is known as yet about the metabolism of *(1)*. / Science (Washington) *152*, 776 (1966) / –De. [Rd 558 IE]

***N*-Acetyl-L-histidine, the first acetylated basic amino acid, found in nature,** was isolated from frogs' hearts by *Y. Kuroda* and *T. Ikoma*. These authors purified the compound by chromatography on Dowex-50-X8 with pyridine/acetate buffer (pH 3.1) and preparative paper chromatography. 30 mg of a crystalline substance was obtained from 300 bullfrog (*Rana catesbeiana*) hearts and identified by chromatography and spectrography, and by comparison with authentic material, as *N*-acetyl-L-histidine. This is the third known naturally occurring *N*-acetylated amino acid. / Science (Washington) *152*, 1241 (1966) / –De. [Rd 559 IE]

**10-Propyl-*trans*-5,9-tridecadienyl acetate, the sexual attractant** of *Pectinophora gossypiella* (Saunders) has been isolated in the pure form by *W. A. Jones*, *M. Jacobson*, and *D. F. Martin*, who also elucidated its structure. A sample of 1.6mg was obtained from 850000 female animals, and the structure *(1)* was assigned on the basis of mass, NMR, IR, and UV spectra. The authors obtained *(1)* in an overall yield of 0.2% by an 11-step synthesis starting with 4-heptanone.



*(1)*

The attractant of *Pectinophora gossypiella*, which is one of the most dangerous cotton pests, is the first known natural product containing a di-n-propylalkyl group. / Science (Washington) *152*, 1516 (1966) / –De. [Rd 560 IE]

**Organosilicon Compounds.** By *V. Bažant, V. Chvalovský,* and *J. Rathouský*; translated from Czech into English by *Arnošt Kotyk* and *Jiří Saláč*. Publishing House of the Czechoslovak Academy of Sciences, Prague. Academic Press. New York-London 1965. 1st edit., Vol. 1: Chemistry of Organosilicon Compounds. 616 pp., bound $25.–; Vol. 2: Register of Organosilicon Compounds. Part 1: 699 pp., bound $25.–; Part 2: 544 pp., bound, $25.–.

In view of the very rapid development of the chemistry of organosilicon compounds, particularly in the last decade, the appearance of such a work as this is to be warmly welcomed. Volume 1 begins with an explanation of how the characteristics of organosilicon chemistry are related to the lower electronegativity of silicon than of carbon and to the ability of silicon to use 3d orbitals for bond formation. After an account of the physical properties of organosilicon compounds (chapter 2) the character and formation of silicon-halogen and -pseudohalogen bonds are explained. Chapters 4 and 5 treat the preparation and properties of compounds of silicon with elements of the 6th and 5th group of the Periodic System, in particular the Si–N bond. Chapter 6 is devoted to compounds in which silicon is bound to an element of groups 1 to 4 (except Si and C). Chapters 7, 8, and 9 are concerned with the S–H, Si–Si, and particularly the Si–C linkage. "Carbon-functional" organosilicon compounds take up a large amount of space (122 pages).

The individual chapters treat their material very carefully and are clearly subdivided. Clarity is aided by numerous tables. There are exhaustive subject, patent, and author indexes, and a list of references, equally well prepared, which contrary to the usual custom are arranged according to journals. The "register" volumes 2/1 and 2/2 contain the compounds listed in order of molecular formula. For each compound there follow the name, structural formula, physical data, method of preparation, reactions, calculated values of the elemental analysis, and molecular weight. When necessary, derivatives and salts are also listed. The data on preparation give not only the reference but also the yields and, notably, the synthetic process used. For rapidity in use each reaction procedure is given a number. Thus an entry "Prep. 7. 23 %" denotes that the compound was obtained by a reaction of type 7 in 23 % yield.

Register volume 2/1 contains silicon compounds up to $Si_1C_{19}H_{42}O_4$, and volume 2/2 $Si_1C_{20}H_3F_{15}$ to $Si_{26}C_{68}H_{170}O_{31}$. These volumes are a kind of "Beilstein" of organosilicon-compounds.

The books are a mine of information for those active in this field. Unfortunately they contain the literature only up to 1961, or in isolated cases up to 1962 so that publication of a new edition, or at least a supplement to the register volumes, is very desirable. The production of the books and particularly the formulae are very good.

These books can be read with great profit and are warmly recommended to all who are concerned with the chemistry of organosilicon compounds or who wish to enter the field.

*L. Birkofer* [NB 495 IE]

**The Amino Sugars. The Chemistry and Biology of Compounds Containing Amino Sugars.** Vol. IIA: Distribution and Biological Role. Edited by *E. A. Balazs* and *R. W. Jeanloz*. Academic Press. New York-London 1965. 1st edit., 591 pp., numerous tables, bound $22.–.

The present volume contains 20 chapters on the occurrence and biological importance of amino sugars and polymers containing amino sugars in the animal and the vegetable kingdom. Individual chapters deal with amino sugars in plants, microorganisms, and invertebrates (*N.Sharon*), amino sugars and amino sugar-containing polymers in liver and kidney (*R. G. Spiro*), in urine (*N. F. Boas*), in mucus and mucous membranes (*Z. Dische*), in saliva, salivary glands, and sputum (*I. Werner* and *L. Odin*), in skin (*R. H. Pearce*), in tumors (*B. Sylvén*), in pathological effusions (*I. Werner* and *L. Odin*), in mast cells and mast cell tumors (*N. R. Ringertz*), in the umbilical cord (*J. A. Szirmai*), in synovial fluid (*L. Sundblat*), in the connecting tissue of electrical organs (*J. A. Szirmai*), in cartilage, tendons, and spinal discs (*M. Schubert* and *D. Hamerman*), in bones and teeth (*E. A. Balazs* and *H. J. Rogers*), in cell walls (*H. Muir*), in plasma and other body fluids (*R. J. Winzler*), in blood cells and hemopoetic organs (*S. Hakomori*), in the nervous system (*L. Svennerholm*), and in the eye and ear (*E. A. Balazs*).

The literature is considered up to 1963, but most of the chapters contain an appendix giving important papers of 1964. The book provides an excellent survey of the state of our knowledge in this heterogeneous field, in both the chemical and the biological aspects. Each chapter treats in detail the problems of isolating, purifying, and characterizing the polymers containing amino sugars; the practising chemist will be particularly interested in the meticulous description and critical discussion of the analytical methods and their advantages and disadvantages and possible disturbing factors (*e.g.* in *Sundblad*'s article the method of determination of hyaluronic acid in synovial fluid).

Much space is occupied by a biological-medical discussion of the content and nature of amino sugar-containing polymers in the individual tissues. The articles by *Balazs* and *Rogers* on the development of teeth and of *Balazs* on changes in the glycoproteins and glycosaminoglucans during development of the eye are of great importance for biochemical consideration of morphogenetic processes. Almost all the authors report changes in the amount and metabolism of glycosaminoglucans in pathological processes (arthritis, Tay-Sachs disease, detachment of the retina, *etc.*). Discussions of causal relations in such fields are, however, often speculative.

In review compilations where several authors collaborate there is a danger of overlap between individual chapters. In the present book, for instance, the ascites fluid is discussed twice. The article, only two pages long, on pathological effusions would have been better incorporated into the larger article on plasma and other body fluids. The chapter on microorganisms should have contained at least one table listing the bacterial enzymes active in amino sugar-metabolism, which it would have been of interest to compare with *Spiro*'s tables for liver and kidney, inasmuch as there is no detailed discussion of enzyme processes.

A consistent nomenclature for amino sugar-containing substances is given at the beginning of the book, and the editors' initiative is to be warmly welcomed; it avoids the confusion of terms such as mucopeptides, mucolipids, *etc.*

*H.-J. Risse* [NB 503 IE]

**Fluorine Chemistry.** Vol. IV. By *J. H. Simons*. Academic Press, New York - London 1965. 1st ed., xvii, 786 pp. $28.00.

Interest in inorganic and organic compounds of fluorine has increased steadily over the past two decades. The unusual properties of plastics and pharmaceuticals containing fluorine have led to an intensification of industrial studies in fluorine chemistry. Consequently, damage by fluorine to plants and animals in the neighborhood of fluorine-processing factories has steadily gained in importance. The use of inorganic fluorine compounds for the prevention of tooth decay has also become more widespread.

In the fourth volume of the series "Fluorine Chemistry" [*], *H. C. Hodge* and *F. A. Smith* deal exclusively with the biological properties of inorganic fluorides (Chapter 1, 363 pp.) and effects of fluorides on bones and teeth (Chapter 2, 306 pp.).

The acute and chronic toxic properties of fluorine towards man and animals, the biological properties (reactions with enzymes), and the metabolism of inorganic fluoride are described in the first chapter. Doses and effects of fluorides are summarized in 58 tables.

The second chapter describes the role of fluorine in the human and animal organism, and places special emphasis on the problem of the prevention of tooth decay.

Twenty tables deal with the fluoride content of bones and teeth, the elimination of fluoride, histological changes in bones and teeth, and clinical investigations with inorganic fluorides.

The book is richly illustrated with diagrams, and contains 84 pages with 3780 references. The fourth volume of "Fluorine Chemistry" should be particularly important as a reference work. *H. Machleidt* [NB 509 IE]

**Computer Programming for Chemists.** By *K. B. Wiberg*. Frontiers in Chemistry. W. A. Benjamin, Inc., New York-Amsterdam 1965. 1st ed., viii, 269 pp., 13 tables, bound $12.50.

The development of the program languages FORTRAN (FORmula TRANslation) and ALGOL (ALGOrithmic Language) has greatly simplified the programming of electronic computers. These program languages permit the formulation of a problem without reference to the type of computer to be used. This presupposes, naturally, that the computer in question is equipped with a FORTRAN or ALGOL translation program.

This book is an introduction to programming in FORTRAN. One chapter also deals with the symbolic internal program language FAP (Fortran Assembly Program). An introduction to the input and output of data is followed by an explanation of arithmetical expressions, functions, and subprograms. The various "statements" are mostly illustrated by examples, so that their general significance at first remains rather in the background; however the most important statements are again summarized in a special chapter and their operation explained. Nearly every chapter contains exercises for practice, the solutions of which are given in the appendix. Many programs, some of them very comprehensive, from the fields of kinetics, NMR spectroscopy, and quantum chemistry are given in a special chapter These add greatly to the value of the book, since, as photoreproductions of tested programs they are free from errors and offer the reader the opportunity to analyse and understand the programs of others. The author sees this as "the best method of becoming familiar with computer programming", and the reviewer must agree with this view. In order to understand definitions of FORTRAN statements and FAP instructions that lie beyond the scope of the book, many readers will still refer to the existing literature, but *K. B. Wiberg*'s book will prove a great help to both the beginner and the initiate in the construction of serviceable programs.

*G. Ege* [NB 527 IE]

**Melting and Crystal Structure.** By *A. R. Ubbelohde* Clarendon Press. Oxford 1965. 1st ed., xi, 320 pp., several illustrations and tables, paper £3.3.0.

Despite many experimental and theoretical studies on the liquid and crystalline states of matter, the process of melting still presents a host of problems in connection with both the equilibrium and the kinetics of the process. For this reason even the specialist will welcome the publication of *Ubbelohde*'s book, which contains an excellent discussion of melting from the viewpoints of thermodynamics and of atomic structure.

Starting with the phenomenological observations on melting, with special reference to modern findings on behavior under high pressures, a short description of the more traditional ideas of *Lindemann* and others is followed by a systematic discussion of the influence of special structural properties and of cooperative phenomena up to the *Lennard-Jones* and *Devonshire* theory of melting for simple crystals, and its modification for the superposition of several melting mechanisms in more complicated cases. Individual chapters deal with pure crystal lattice transitions (which are related to melting) and the melting of glasses, liquid crystals, and polymeric materials; premelting and precrystallization in the liquid phase and the rates of melting and of nucleation are discussed in detail. These discussions are based on extensive experimental material, which is presented to the reader in the form of numerous tables showing the influence of the various parameters.

A book on a subject that is very much a center of interest is naturally stamped with the author's personal views, so that one or other idea or special theory receives little or no attention (this is true *e.g.* of the *Kirkwood-Monroe* theory); in every case, however, the reader finds a detailed discussion of fundamentally similar ideas, the author probably having given preference to points that demand less theoretical knowledge on the part of the reader, and this should gain the book a wide circle of users. *K. Schäfer* [NB 529 IE]

**Nonexistent Compounds – Compounds of Low Stability.** By *W. E. Dasent*. Marcel Dekker, Inc., New York 1965. 1st ed., ix, 192 pp., several illustrations, bound, $ 8.50.

At a time when new types of compounds whose existence formerly was deemed impossible are being discovered with ever-increasing frequency, the title "Nonexistent Compounds" is as attractive as it is daring. For good reason the author himself adds the neutralizing subtitle "Compounds of Low Stability".

There is scarcely a preparative chemist who has not had the experience of finding that one or other of the compounds he wishes to prepare is unobtainable in spite of all his efforts. Moreover, lecturers at universities are only too familiar with the penetrating questions of students regarding the "gaps" in the otherwise rigid taxonomy of chemistry. For these reasons *Dasent*'s book, which was preceded a few years earlier by an article by the same author [Journal of Chemical Education *40*, 130 (1963)], can expect a good reception.

However, this small volume can, of necessity, only partly satisfy our expectations, although the author discusses a number of interesting examples in such a way that similar problems can also be worked out on this basis. A list of 407 references is particularly valuable in this respect. In view of the examples chosen, this book may be recommended in particular to the inorganic chemist.

*H. Schmidbaur* [NB 516 IE]

**Treatise on Analytical Chemistry.** Edited by *I. M. Kolthoff* and *Ph. J. Elving*. John Wiley & Sons Ltd., London 1965.
Part I, Vol. 6: **Theory and Practice.** xxiii, 899 pp., several illustrations, bound £8.15.0.
Part II. **Analytical Chemistry of Inorganic and Organic Compounds.** Vol. 11: 573 pp., several illustrations, bound £7.10.0. Vol. 12: xvi, 383 pp., several illustrations, bound £5.13.0.

The importance of the entire work to any analytical laboratory has already been stressed [1], though certain reservations should be mentioned concerning the over-emphasis of the

[*] Cf. Angew. Chem. *77*, 599 (1965); Angew. Chem. internat. Edit. *4*, 613 (1965).

theoretical principles and the rather minor place given to the combination of several methods in tackling analytical problems. The various sections in Part I are arranged according to methods and Part II according to elements, and all sections were written by specialists.

The sixth volume of Part I continues the discussion of optical methods in analysis; it contains a section on emission spectrography by *B. F. Scribner* and *M. Margoshes* and a section on flame photometry by *B. L. Vallee* and *R. E. Thiers*. Both sections present good surveys; the section on emission spectrography does not stress sufficiently the importance of this method for the automated analysis of metals. In the chapter on flame photometry, the reader searches in vain for the more recent developments, particularly atomic absorption and the possibilities of the flame fluorescence technique. Indications towards the end of the section, as well as the list of references, suggest that this section, like several others, does not correspond to the latest stage of development.

*A. L. Smith* contributes more than 200 pages on infrared spectroscopy. A closer reference to practice would have been preferable in many places, and in particular a list of the characteristic bands of inorganic and organic compounds might have been included. The next section, in which *E. J. Rosenbaum* deals with Raman spectroscopy, can only be described as poor. Though the importance of Raman spectroscopy as a molecular-spectroscopic method is smaller than that of infrared spectroscopy, advances in both apparatus and methods have been made in recent years which might have been mentioned in this section. Considerably more detailed, the next two sections by *J. H. Reisner* and *G. W. Leddicotte* deal with electron diffraction and scattering and with neutron absorption and scattering. The section on neutron scattering scarcely mentions the possibilities of this method in the structural analysis of organic compounds. *S. Z. Lewin* and *W. S. Struck* then discuss the measurement of refraction, and *E. C. Olson* describes the measurement of optical rotation. Both of these are good surveys. The use of circular dichroism for the structural analysis of organic compounds receives too little attention. The literature (and hence also recent findings) is evidently covered up to 1959 at latest. The last two sections of the book are both good reviews, dealing with optical (*W. C. McCrone* and *L. B. McCrone*) and electron microscopy (*G. G. Cocks*).

The first ten volumes of Part II of Kolthoff-Elving are systematically arranged according to chemical elements, and deal mainly with the analysis of inorganic compounds. Volume 11 begins Section B of the second part, which deals with organic analysis. The present two volumes give a well-rounded impression, and in addition to an introduction on nomenclature (*L. T. Capell* and *K. L. Leoning*), the stability of organic compounds (*H. Eyring* and *F. W. Cagle*), and reaction kinetics (*G. S. Hammond*), they deal with the elementary analysis of organic compounds. The description of the methods for the determination of carbon and hydrogen (*G. Ingram* and *M. Lonsdale*) and of nitrogen and phosphorus (*G. M. Gustin*, *C. L. Ogg*, and *E. Q. Laws*) in Vol. 11 is preceded by general considerations on this field by *E. W. D. Huffman* and a review of ultramicro methods by *M. Williams*. Vol. 12 deals with the determination of oxygen (*A. Steyermark*), sulfur (*J. F. Alicino*, *A. I. Cohen*, and *M. E. Everhard*), fluorine (*T. S. Ma*), boron (*R. D. Strahm*), and silicon (*H. J. Horner*). *T. T. Gorsuch* concludes this volume with a review of the methods for the determination of metallic elements in organic compounds. A special section in Vol. 11 finally deals with biological and biochemical methods of analysis.

Apart from the reservations mentioned above, the three volumes are worthy successors, both in content and in presentation, to those published earlier.

*H. Kienitz* [NB 536 IE]

[1] Angew. Chem. *77*, 927 (1965); Angew. Chem. internat. Edit. *4*, 381 (1965).

**Chemistry of the Rare-Earth Elements.** By *N. E. Topp*. Monograph Series: Topics in Inorganic and General Chemistry. Edited by *P. L. Robinson*. Elsevier Publishing Company, Amsterdam-London-New York 1965. 1st edit., xi + 164 pp., bound. Dutch fl. 27.50 ($7.50).

The author reports the chemistry of the rare earths in an easily intelligible manner. Twelve chapters introduce the occurrence, treatment, and use of the rare earths. Various chapters describe in detail the history of their discovery, their most important minerals, and methods of processing. Methods of separation, *e.g.* by ion exchange and countercurrent extraction, are also treated. Analysis, preparation of rare-earth metals, and the most important technical uses are reported. The book includes the preparation of pyrophoric alloys ("flints"), manufacture of east iron by means of nodular iron, purification of high-melting metals, use of compounds of the rare-earth metals as polishing materials, inclusion of rare earths in ultraviolet- absorbing glass, coloration of glass. and preparation of glass with a high refractive index. In addition, the use of cerium fluoride to increase the light yield from carbon arcs and of sulfides for preparation of materials stable at high temperatures is reported briefly. The isotopes of the rare earths, with their physical properties, are tabulated in an appendix.

*E. Ruf* [NB 501 IE]

**Diels-Alder Reactions. Organic Background, Physico-chemical Aspects.** By *A. Wassermann*. Elsevier Publishing Company, Amsterdam-London-New York 1965. 1st ed., viii, 114 pp., numerous illustrations and tables, paper, Dutch fl. 15.00.

The author, himself a pioneer in this field, presents a concise monograph on Diels-Alder reactions, which is intended mainly for the chemist interested in the relationships between structure and mechanism.

A twenty-page section on preparative aspects of the reaction is followed by 15 pages on its stereochemistry, 9 pages on equilibrium phenomena, 26 pages on kinetic results, and a 25-page discussion of the mechanism. In view of the importance of Diels-Alder additions and the current interest in their mechanism, a much more comprehensive treatment of this subject would have been desirable.

The important aspects of cycloadditions with formation of six-membered rings are presented systematically, but often briefly and without detailed discussion; many readers will probably find it necessary to refer to the original literature. Useful data are presented in tabulated form in chapters 2 to 5.

The references are mainly confined to the years up to 1962, and only a few references bring us up to 1963/1964; consequently, a number of results are out of date or should be supplemented (*e.g.* reactions of benzene, hexamethylradialene, Woodward-Hofmann rule). The book does not contain an alphabetic author index. The print and most of the formulae are clear, with only very few confusing printer's errors. *J. Sauer* [NB 507 IE]

**Atmospheric Oxidation and Antioxidants.** By *G. Scott*. Elsevier Publishing Company, Amsterdam-London-New York 1965. x, 528 pp., numerous illustrations, bound, Dutch fl. 72.50.

In recent years, autoxidative processes and their inhibition have been the subject of growing practical interest, particularly in connection with the development of petroleum, rubber, and plastics technology. The author presents an interim report on this fast-growing subject, ranging from the general reaction mechanisms of the autoxidation of organic compounds and the action of antioxidants, through the measuring techniques employed, to the description of special autoxidation reactions in industrial materials and their prevention by stabilizing additives.

The first chapter deals with the historical development of antioxidants, the second and third with the mechanisms and the energetic and kinetic fundamentals of autoxidation reactions, and the fourth and fifth with the general aspects of the action of antioxidants, both by free-radical chain termination and by prevention of chain initiation. The sixth chapter is devoted to the measurement of oxidation reactions and oxidative effects. The seventh chapter deals with the oxidative degradation of saturated organic materials, *i.e.* lubricating oils and plastics, and its inhibition by antioxidants, and in the eighth chapter the same treatment is given to unsaturated materials such as olefins, edible fats and oils, drying oils and their films, and raw rubber; the ninth chapter is concerned with the ageing of vulcanized rubber and its prevention, and the tenth with the ageing phenomena (ozone ageing and fatigue-cracking) produced by mechanical stresses and their prevention.

The main emphasis of the treatment which, owing to the volume of material discussed is highly concentrated although interspersed with numerous diagrams and tables, is laid on the reaction mechanism. Antioxidants are regarded mainly from the point of view of their structure-dependent modes of reaction and chemical effectiveness, and to a smaller extent from the point of view of their behavior under practical conditions and their technical importance. Thus the book is aimed predominantly at those who are interested in the scientific principles. It presents an exhaustively compiled and classified literature survey, supplemented by many of the author's own results. However, the literature is fully covered only up to and including 1960; a few publications from 1961 are also referred to. Consequently, a number of recent fundamental theoretical ideas (*e.g.* the critical antioxidant concentration in polymers) as well as some technically important additives (particularly light stabilizers) are not included in this edition.

The discussion of the stabilization of PVC touches on a field that is rather outside the scope of this book, and the description is therefore biased a little too much towards the inhibition of oxidation (organic phosphites are considered only as agents for the decomposition of peroxides), while no mention is made of the oxidative removal of chromophoric structures as a stabilizing factor. It should be stressed, however, that these are minor details which in no way detract from the value of the book.

*G. Scott*'s book is the first self-contained and uniformly presented monograph on autoxidation and antioxidants, and there is no doubt about its importance as a standard work.

*J. Voigt* [NB 506 IE]

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# Coupling Principles in Organic Dyes[1]

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*Dye molecules containing two or more polymethine structural units, or at least one polymethine and one polyene structural unit, generally exhibit coupling effects that determine the spectroscopic behavior and other physicochemical properties of the substance. The coupling concept can be used inter alia to fit the quinone dyestuffs, the indigoids, and the indanthrenes into a general polymethine color system and to predict new dye structures.*

## 1. Introduction

The hundred years of aromatic chemistry following *Kékulé's* proposal of the structure of benzene have also been a century of intensive research on the relation between color and structure in organic compounds [3]. As early as 1876, *Witt* [4] put forward his fundamental theory of chromophoric and auxochromic groups, which was extended by *Wizinger* in 1927 to include antiauxochromic groups [5], and which in this extended form still permits the description of the color properties of aromatic compounds [6].

It is mainly due to *König* that the polymethine structure was recognized in 1926 as the true cause of color. Organic compounds are always deeply colored [7] when they contain a polymethine structural unit *(1)* [2,8].

$$\cdots(p \pm 1)\pi\cdots$$
$$X\text{—}(CR)_n\text{—}X' \qquad (1)$$

$n = p - 2 = 1,3,5\ldots$

X,X′ = atoms from groups IV, V, or VI

R = any substituents

$(CR)_n$ = grouping that can be replaced by atoms of groups V or VI

A polymethine chain containing an odd number of carbon atoms, which may carry almost any substituents, and which has two atoms of elements from groups IV, V, or VI at its extremities [9], contains one $\pi$ electron more or, as has only recently been recognized, one $\pi$ electron less than the number of atoms in the chain (including the atoms at the ends of the chain). This particular electronic structure leads not only to the intense long-wavelength light absorption of the polymethines, but also to an alternating $\pi$-electron distribution with simultaneous equalization of the bond lengths in the polymethine chain. For a given chain length, the wavelength of the light absorption increases with decreasing electronegativity of the substituents at the ends of the chain and with increasing symmetry of the distribution of the $\pi$-electron system over the chain. To a first approximation, it is independent of the state of charge of the polymethines. Depending on the position of the terminal atoms in the periodic system and on the number of substituents, the polymethines may be electrically neutral or charged [2a].

The alternating $\pi$-electron density distribution associated with deep colors is equivalent to the alternating charge distribution in the polymethine chain proposed by *König*. This alternation follows from quantum-mechanical calculations, *e.g.* by the free electron (FE) method [10] or the LCAO–MO method [2b,11], and has been experimentally verified by proton magnetic resonance measurements [12,13]. The alternation of charge, *i.e.* of

[1] Second communication on general relationships between color and structure in organic compounds. 1st communication: [2a]; 3rd communication: [2b].

[2a] *S. Dähne*, Z. Chem. *5*, 444 (1965).

[2b] *S. Dähne* and *D. Leupold*, Ber. Bunsenges. physik. Chem. *70*, 618 (1966).

[3] Recent summaries: *K. Venkataraman*: The Chemistry of Synthetic Dyes. Academic Press, New York 1952, p. 323–400; *F. Klages*: Lehrbuch der organischen Chemie. Walter de Gruyter, Berlin 1958, Vol. III, p. 23–178; *H. R. Schweizer*: Künstliche organische Farbstoffe und ihre Zwischenprodukte. Springer, Berlin 1964, p. 228–238.

[4] *O. N. Witt*, Ber. dtsch. chem. Ges. *9*, 522 (1876); *21*, 325 (1888).

[5] *R. Wizinger*, Ber. dtsch. chem. Ges. *60*, 1377 (1927).

[6] *R. Wizinger*, Symposium over Kleur en Structuur van organische Verbindingen, Antwerpen 1956; Vlaamse Chemische Vereniging, Brussels 1956.

[7] The term "deeply colored" is used in this article to denote intense absorption at particularly long wavelengths.

[8] *W. König*, J. prakt. Chem. [2] *112*, 1 (1926).

[9] The replacement of the X,X′ atoms by hetero atoms while maintaining the polymethine electronic structure *(1)* is known as isologous substitution. Known examples with $(p + 1)\ \pi$ electrons to $p$ chain atoms are [2a]: cyanines: N....N, oxonols: O....O, merocyanines: O....N (generally "meropolymethines" for *(1)*, X≠X′), carbon polymethines: C....C (particularly carbeniate polymethines with $(p + 1)\pi/p$ atoms and carbonium polymethines with $(p-1)\pi/p$ atoms).

[10] *H. Kuhn*, Chimia *9*, 237 (1955); Angew. Chem. *71*, 93 (1959). Lectures at the international vacation course on the theory of $\pi$-electron systems, Constance (Germany) 1963.

[11] *D. Leupold*, Z. physik. Chem. *223*, 405 (1963).

[12] *G. Scheibe*, *W. Seiffert*, *H. Wengenmayr*, and *C. Jutz*, Ber. Bunsenges. physik. Chem. *67*, 560 (1963).

[13] *S. Dähne* and *J. Ranft*, Z. physik. Chem. *224*, 65 (1963); *232*, 259 (1966); Angew. Chem. *75*, 1175 (1963); Angew. Chem. internat. Edit. *2*, 740 (1963); *S. Dähne*, *D. Leupold*, *H.-E. Nikolajewski*, and *R. Radeglia*, Z. Naturforsch. *20b*, 1006 (1965); *R. Radeglia* and *S. Dähne*, Ber. Bunsenges. physik. Chem. *70*, 745 (1966).

π-electron density, occurs irrespective of whether or not the molecule as a whole is charged [*].

The definition of the polymethines essentially includes the color theories known so far. Thus in order to obtain $(p+1)$ or $(p-1)$ π electrons over a total of $p$ chain atoms, the chain ends X and X′ must, according to *König*, have the properties of an "aci-perichrome" and an "onium-perichrome", respectively. These terms coincide with the definitions of "auxochromic" and "antiauxochromic" substituents, or in more modern terminology with those of electron donors and acceptors. The definition also includes the idea proposed by *von Baeyer* [14] and *Willstätter* [15] that the color of meroquinoid [**] compounds is due to oscillation of valences between groups linked to one another [2a].

In addition to the polymethine dyes, there are many deeply colored organic radicals, which could not at first be rationalized by existing theories. On the basis of arguments advanced by *Weitz* [16], this difficulty could be overcome by an extension of the polymethine concept [2a, 17]. Free radicals are particularly deeply colored when they contain a polymethine structural unit having the formula *(1)* in which the number of chain atoms is even ($n = 0, 2, 4 \ldots$). Such radicals are therefore known as polymethine radicals.

Two other groups of organic compounds containing π electrons can with equal right stand alongside the polymethines; these are the aromatic compounds and the polyenes [2b]. Compounds of both groups can be colored if the molecule is sufficiently large. Aromatic compounds and polyenes always absorb at lower wavelengths than polymethines containing the same number of $sp^2$-hybridized atoms. Aromatic compounds contain $(4n+2)$ π electrons distributed over $4n+2$ atoms, *i.e.* in general, $p$ π electrons over a total of $p$ atoms. The polyenes *(2)* have the same electron distribution, but differ from the aromatic compounds in that the bond lengths alternate. In analogy to the polymethine radicals, polyene radicals *(3)* with an odd number, $p$, of π electrons on $p$ chain atoms are also known.

$X=(CH-CH=)_mX'$ *(2)* $m = 0, 1, 2 \ldots$

$\dot{X}-(\dot{C}H)_n-\dot{X}'$ *(3)* $n = 1, 3, 5 \ldots$

X,X′ = atoms of groups IV, V, or VI.

In the ideal state, the polyenes and aromatic compounds differ from the polymethines in that the π-electron densities do not alternate in compounds of the first two classes. The possibilities of transitions between the three types of compound are practically unlimited [2a,b]. A polymethine *(1)* becomes more polyene-like as the symmetry of the distribution of the π electrons over the chain decreases, *i.e.* as it approaches one of the possible limiting structures *(4a)* or *(4b)* as a result of differences in the donor and acceptor actions of the substituents X and X′ [18]; polymethines change directly to polyenes on uptake or loss of one electron, or to aromatic compounds on formation of rings containing 6 π electrons, and *vice versa* [*].

$X=(CH-CH=)_mCH-\ddot{X}'$ *(4a)*

$\cdots\cdots (2m+4)\,\pi \cdots\cdots$

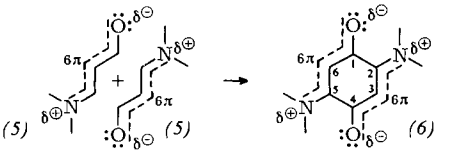
$X-(CH-CH-)_mCH-X'$

$\ddot{X}-(CH=CH-)_mCH=X'$ *(4b)* $m = 0, 1, 2 \ldots$

### 1.1. The Coupling Principle

For a general color system, it is found necessary to extend the term "polymethines" to include compounds that contain more than one polymethine structural unit having the general formula *(1)*. If these structural units can interact with one another across π bonds, this interaction leads to coupling effects, which determine the color and other physicochemical properties of the molecules. Compounds of this type are known as coupled polymethines. A special form of this coupling is the combination of two dipolar meropolymethine structural units *(1)* in which X = X′ and $n = 1,3,5 \ldots$. This necessarily gives rise to compounds having quadrupole character, which we have named quadrupole meropolymethines, the compounds obtained from *(1)* with X = $NR_2$ and X′ = O being quadrupole merocyanines [19].

For example, the physicochemical behavior of the 2,5-diamino-*p*-benzoquinones *(6)* can be fully understood only if the molecule is assumed to consist of two trimethine-merocyanine structural units *(5)*, which can couple *via* the $C^1-C^2$ and $C^4-C^5$ bonds.




[*] For this reason the expression "charge mesomerism" for the distribution of the charge of a dye ion over the chromophore system should be avoided, or should be used to denote an alternation of charge. For example, the electrically neutral meropolymethines and the non-alternant hydrocarbons (azulene, *etc.*) have a very pronounced charge alternation, though they are not ions themselves [2b].

[14] *A. v. Baeyer*, Liebigs Ann. Chem. *354*, 152 (1907).

[15] *R. Willstätter* and *J. Piccard*, Ber. dtsch. chem. Ges. *41*, 1467 (1908).

[**] "Meroquinones" are compounds, particularly di- and triphenylmethane dyes, that according to the conventional structure notation contain a quinoid and a hydroquinoid benzene ring.

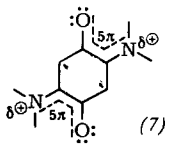
[16] *E. Weitz*, Z. Elektrochem. angew. physik. Chem. *34*, 538 (1928); Angew. Chem. *66*, 658 (1954).

[17] *S. Hünig* and *H. Quast*, Lecture at the 2nd International Color Symposium, Schloß Elmau (Germany), April 1964. Verlag Chemie, Weinheim/Bergstr. 1966.

[18] *L. G. S. Brooker*, Rev. mod. Physics *14*, 289 (1942) and in *C. E. K. Mees*: The Theory of the Photographic Process. MacMillan, 2nd Edit. New York 1954, p. 371–429.

[*] For example, the higher condensed aromatic compounds give polymethine-like, deeply colored radical-anions or -cations on uptake or loss of one electron. The aromatic *p*-phenylenediamines give the Wurster polymethine radical on uptake of one electron; on uptake of two electrons they give polyene-like quinonediimonium dications. Polymethine dyestuffs give less deeply colored polyene radicals *(3)* on gain or loss of one electron [2a].

The nature of the coupling can generally be seen from the structural formula [*(1)*, $n = 1, 3, 5 \ldots$]. In principle, however, coupling of two dimethine radicals in accordance with formula *(7)* would also be feasible in 2,5-diamino-*p*-benzoquinone. Nevertheless, experience has



*(7)*

shown that where there is a possibility of coupling either between two polymethine dyes [*(1)*, *n* odd] or between two polymethine radicals [*(1)*, *n* even], resonance within the odd chains, *i.e.* in the conventional terminology, within the "conjugated" carbonyl and amino groups, always predominates.

The coupling concept was first confirmed on the basis of spectroscopic data [19] (cf. Section 2.1.2). It also follows directly from quantum-mechanical calculations by the LCAO–MO method [19d]. If the calculation for the molecules is carried out in the usual manner [20] with equal values of the resonance integral $\beta$ for all the bonds involved, the wavelength found for the ligth absorption is too high, and a remarkably low $\pi$-bond order is found for the bonds that according to the structural formula effect the coupling of the polymethine structural units.

For the best approximation it is necessary to take into account this decrease in the $\pi$-bond orders in a second calculation step by reduction of the resonance integrals to about 0.5 $\beta$.

Conversely, if the coupling principle is known, the energy-level diagrams of the uncoupled parts of the molecule can be calculated first, and these parts of the molecule can then be brought together in steps, *i.e.* by gradually increasing the resonance integral for the coupling bonds to 0.5 $\beta$, to give the energy-level diagram of the coupled polymethine. In this way the changes in the energy levels of the individual systems on coupling can be followed directly. There is necessarily some resonance splitting of the levels, which may be regarded as the true cause of the long-wavelength absorption of the coupled polymethines [19d].

From the coupling concept, the bond lengths within the polymethine chains should be largely equalized, and the coupling bonds should be lengthened. The predicted interatomic distances [19d] in 2,5-diamino-*p*-benzoquinone have in fact been largely confirmed [19e].

On the basis of these experimental and theoretical results, some typical examples of dyes containing two or more polymethine structural units linked by $\pi$ bonds, so that coupling effects are to be expected, are described below.

The theoretical values given were calculated by an extended LCAO–MO method [11, 19d] using heteroatom Coulomb integrals ($\alpha_X$) and resonance integrals ($\beta$) also of non-adjacent atoms [*]. In a first calculation step, equal values were used, as usual [20], for the resonance integrals of all $\pi$ bonds. When the calculated and experimental wavelengths of the light absorption did not agree, a second calculation was carried out in which the resonance integrals of the bonds for which particularly low $\pi$-bond orders had been obtained in the first calculation were reduced to about 0.5 $\beta$. The substituent effects of the *N*-alkyl groups [21] were disregarded.

It is found that for many dyes, the light absorption and the $\pi$-bond orders [**] and electron densities [†] estimated from experimental results can be satisfactorily described even by this extended LCAO–MO method. The approximation can be further refined if instead of the overall reduction in the resonance integrals, the relations between calculated bond orders, bond lengths, and resonance integrals [22, 23] are used to find the optimum values of the integrals by an iteration method.

Since relatively high delocalization energies are found for the polymethines [2b, 19d], the preferred formulation of polymethine structural units in the molecule appears to be justified from the point of view of energy. However, it should not be expected that the polymethine structures will always be unambiguously defined as described above. The tendency to form polymethine systems, particularly in more extensive chromophore systems, is more or less strongly opposed by a tendency towards aromatization and the possibility of the formation of polyene structures. More detailed molecular-physical studies are therefore essential for a more accurate determination of the electronic structure of a dye. Even without molecular data, however, the coupling concept has shown itself to be a useful heuristic principle. Many dyes that formerly defied logical classification, such as the amino- and hydroxyquinone dyes, the indigoids, and the indanthrenes, can be readily fitted into a general system of polymethines, and the existence of new dyes can be predicted.

The coupling principle is not restricted to compounds with two polymethine structural units in the molecule. Similar coupling effects occur between a polymethine structural unit and a polyene-like structural unit (cf. Section 3), and even polyene-polyene coupling is conceivable.

[19a] *S. Dähne* and *H. Paul*, Contribution at the 2nd International Color Symposium, Schloß Elmau (Germany), April 1964.

[19b] *S. Dähne* and *H. Paul*, Chem. Ber. *97*, 1625 (1964).

[19c] *S. Dähne*, *J. Ranft*, and *H. Paul*, Tetrahedron Letters *1964*, 3355.

[19d] *D. Leupold* and *S. Dähne*, Theoret. chim. Acta *3*, 1 (1965); Mber. dtsch. Akad. Wiss. Berlin *7*, 46 (1965).

[19e] *S. Kulpe*, *D. Leupold*, and *S. Dähne*, Angew. Chem. *78*, 639 (1966); Angew. Chem. internat. Edit. *5*, 599 (1966).

[20] *C. Sandorfy*: Die Elektronenspektren in der theoretischen Chemie. Verlag Chemie, Weinheim/Bergstr. 1961; *A. Streitwieser*, Molecular Orbital Theory for Organic Chemists. Wiley, New York-London 1961.

[*] In contradiction to [20a] the resonance integrals of non-adjacent atoms cannot be neglected, either when Slater orbitals are used and the overlap is taken into account or when orthonormal Löwdin orbitals are used; *D. Leupold*, unpublished.

[20a] *M. Klessinger*, Theoret. chim. Acta *5*, 251 (1966).

[21] For substituent effects in polymethines see *D. Leupold* and *S. Dähne*, Z. physik. Chem. N.F. *48*, 24 (1966).

[**] Estimated *e.g.* from atomic distances, stretching frequencies, the activation energy of the restricted internal rotation (from the temperature dependence of the $^1$H-NMR spectrum), and the H–H coupling constants.

[†] Estimated from the chemical shifts in the NMR spectrum.

[22] *C. A. Coulson* and *A. Golebiewski*, Proc. physic. Soc. *78*, 1310 (1961).

[23] *D. Leupold* and *S. Dähne*, Lecture at the Conference of Chemistry Lecturers of the *Chemische Gesellschaft in der DDR*, Potsdam 1965.

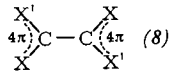
We shall not deal here with the well-known coupling effects *via* secondary valences, which occur *inter alia* in the association of dyes in concentrated solutions [24].

## 2. Coupled Polymethines

### 2.1. Coupling of Polymethines over One Bond Length

#### 2.1.1. Coupled Monomethines

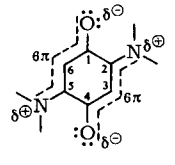
Coupling of two monomethinecyanines can be formulated in the dication *(8)*, X + X′ = $N\diagup$ + $\overset{\oplus}{N}\diagdown$ [25,26], that of two oxonols in the oxalate dianion *(8)*, X = X′ = O + $O^{\ominus}$, and that of two merocyanines in the electrically neutral oxamide derivative *(8)*, X = $N\diagup$, X′ = O. The tetracyanoethylene dianion *(8)*, X + X′ = C=N + C=$N^{\ominus}$ [27] may possibly also be regarded as a coupling product of two dicyanomonomethines [2a].



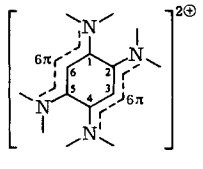
*(8)*

#### 2.1.2. Coupled Trimethines

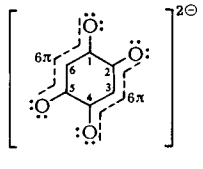
The coupling of two trimethinemerocyanines across two principal valences to give a quadrupole merocyanine *(6)* was described in Section 1. Similarly, two trimethinecyanines are coupled in *(9)* and two trimethinoxonols in *(10)*. Other isologously substituted compounds are known, *inter alia*, in the form of the 2,5-diaminodithio-*p*-benzoquinones. For a satisfactory LCAO–MO description of their absorption, π-bond orders, and π-electron densities, the resonance integrals for the coupling bonds $C^1$–$C^2$ and $C^4$–$C^5$ must be reduced to approximately 0.5 β.



*(6)*
$\lambda_{max}$(exp) = 336, 488 nm
(–$NH_2$, in $(CH_3)_2SO$) [28])
$\lambda_{max}$(theor) = 362, 485 nm
(resonance loss = 0.5 β)
[19d]



*(9)*
$\lambda_{max}$(theor) = 290, 501 nm
(resonance loss = 0.5 β)



*(10)*
$\lambda_{max}$(exp) = 315, 496 nm
(in 0.1 N NaOH)
$\lambda_{max}$(theor) = 319, 455 nm
(resonance loss = 0.5 β)

Figure 1, for example, shows the splitting of the energy levels for oxonol coupling, and Figure 2 shows the corresponding molecular diagram in the ground state. As mentioned earlier, the bond lengths calculated in this way have been confirmed by X-ray structure analysis of a 2,5-diamino-*p*-benzoquinone [19e].

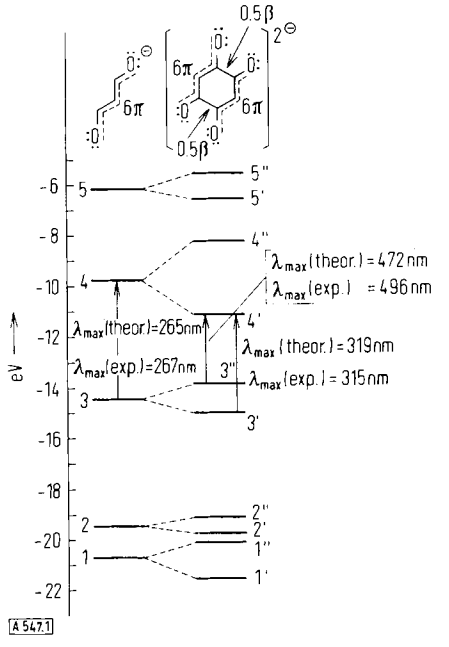


Fig. 1. LCAO–MO energy-level diagram of trimethinoxonol and of the 2,5-dihydroxy-1,4-benzoquinone dianion (term splitting on coupling). [Note: For the dianion *(10)* read $\lambda_{max}$(theor.) = 455 nm instead of 472 nm].

According to the calculations, the absorption band in the visible region of the spectra of *p*-benzoquinones with electron-donating substituents in positions 2 and 5 corresponds to a π→π* transition. Since the intensity of this band is low, it was formerly assigned to an n→π* transition of the quinone displaced to longer wavelengths. This contradiction could be resolved by symmetry considerations in the course of the LCAO–MO calculations, according to which the lowest energy transition of the coupled polymethines *(6)*, *(9)*, and *(10)* is forbidden [19d]; its occurrence as a band of low intensity is evidently due to a relaxation of the restriction on the transition as a result of mixing of the closely spaced highest occupied energy levels (levels 3′ and 3″ in Fig. 1) by participation of nuclear vibrations. This so-called Herzberg-Teller effect can in fact be detected experimentally in the 2,5-diamino-*p*-benzoquinones *(6)* [28]: as a result of *N,N′*-substituent effects the two bands of longest wavelength approach each other. The mixing then becomes stronger, and the intensity of the forbidden longest-wavelength transition

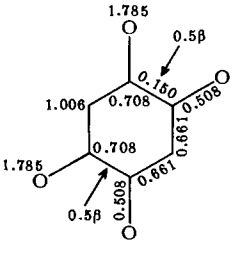


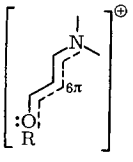
Fig. 2. 2,5-Dihydroxy-1,4-benzoquinone dianion *(10)*. Molecular diagram in the ground state (π-bond orders and π-electron densities).

[24] *Th. Förster*, Pure appl. Chem. *4*, 121 (1962).
[25] *N. Wiberg* and *J. W. Buchler*, Chem. Ber. *96*, 3223 (1963).
[26] *H. Wanzlick* and *F. Eßer*, Angew. Chem. *76*, 614 (1964).
[27] *O. W. Webster*, *W. Mahler*, and *R. E. Benson*, J. Amer. chem. Soc. *84*, 3678 (1962).
[28] *S. Dähne* and *D. Leupold*, Z. Naturforsch. *20b*, 76 (1965); *D. Leupold* and *S. Dähne*, J. molecular Spectroscopy *17*, 325 (1965).

consequently increases at the expense of the intensity of the next highest allowed transition. In agreement with its assignment as a forbidden $\pi \rightarrow \pi^*$ transition, the longest-wavelength band exhibits positive solvatochromism in many solvents. However, an $n \rightarrow \pi^*$ transition appears to be subjacent to it.

Corresponding to the behavior of the simple polymethine chains, the charge state of the coupled polymethines is of minor importance for the absorption. The distribution of the $\pi$ electrons over the individual polymethine chains must again be as symmetrical as possible. For example, 2,5-diamino-*p*-benzoquinones with NHR substituents dissolve in dilute alkali to form dianions, which differ only slightly in color from the undissociated quadrupole merocyanines *(6)* [29].

The existence of analogous dioxonium cations is to be expected, particularly in view of the recent preparation of the uncoupled cationic trimethinemerocyanines *(11)* [30]. Cou-

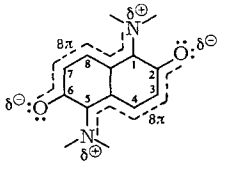


*(11)*

pling of electrically neutral cyanines may similarly be assumed in the diaminoquinonediimides [*(9)*−2H$^{\oplus}$] and coupling of electrically neutral oxonols in the dihydroxyquinones [*(10)*+2H$^{\oplus}$]. The absorption of these compounds is hypsochromically displaced relative to that of the doubly charged ions; for example, the longest-wavelength absorption band of [*(10)*+2H$^{\oplus}$] is displaced by 102 nm relative to *(10)* [*]. This is evidently due to the increase in the polyene character of the coupling structural units as a result of the less symmetrical $\pi$-electron distribution.

### 2.1.3. Coupled Penta- and Heptamethines

Coupling of two pentamethinemerocyanines occurs in 1,5-diamino-2,6-naphthoquinone *(12)*, prepared by *Paul* and *Zimmer* [30a]. This is a deep blue dye which, in agreement with spectroscopic measurements (solvatochromism, infrared, and $^1$H-NMR spectra), is to be



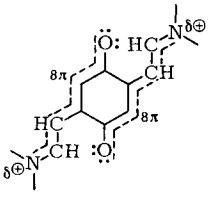
*(12)*

$\lambda_{max}$(exp) = 321, 581 nm
(−$NH_2$ in $(CH_3)_2SO$) [19b]

$\lambda_{max}$(theor) = 303, 572 nm
(resonance loss = 0.5 $\beta$) [19d]

formulated as a quadrupole merocyanine [19a, 19b]. To obtain a sufficiently accurate LCAO–MO approximation, the resonance integrals for the coupling bonds must again be reduced to 0.5 $\beta$. The transition of lowest energy is not forbidden by symmetry in this case, and the absorption band of longest wavelength is consequently several orders of magnitude more intense than that of the 2,5-diamino-*p*-benzoquinones [19b, 19d].

A similar coupling may be formulated for the blue dyes *(13)* prepared by *Henbest* [31]. Since the absorption may be affected by *cis-trans* isomerization, torsion in the



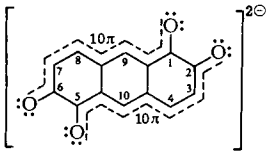
*(13)*

$\lambda_{max}$(exp) = 537, 645 nm
(−$N(C_2H_5)_2$ in dioxane) [31]

$\lambda_{max}$(theor) = 591 nm
(resonance loss = 0.5 $\beta$)

vinylene groups, and by the substituent effect of the ethyl groups the assignment of the calculated value to the two absorption bands observed is not yet certain.

Similarly coupled oxonols are also known. *Horner* [32] recently prepared the deep blue dianion of 1,5-dihydroxy-2,6-naphthoquinone, which may be formulated as a coupled pentamethinoxonol similar to *(12)*. *Boldt* [33] described the dark green di(?)anion of 2,6-dihydroxy-1,5-anthraquinone *(14)* in which, according to our



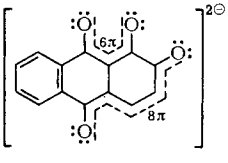
*(14)*

$\lambda_{max}$(exp) = 442, 700, (850) nm
(in NaOH/$CH_3OH$) [33]

notation, two heptamethinoxonols are coupled. The corresponding coupled cyanines have not yet been studied.

### 2.1.4. Coupling of Polymethines of Different Chain Lengths

In many polyhydroxy- and polyaminoquinone dyes it is possible to formulate two or more polymethine structural units of different chain lengths. Well known examples are alizarin and indanthrene blue. In alizarin, a trimethinoxonol apparently is coupled with a pentamethinoxonol, the well known electrically neutral form [*] again being less strongly colored, while the dianion *(15)* is deeply colored. Mention may be made of the naphthoquinone, anthraquinone, and phenanthrenequinone dyes, which can be formulated in a similar



*(15)*

$\lambda_{max}$(exp) = 245, 303, 520[**] nm
(in 2N NaOH)

[29] *K. Wallenfels* and *W. Draber*, Liebigs Ann. Chem. *667*, 55 (1963).

[30] *H. Bredereck*, *F. Effenberger*, and *D. Zeyfang*, Angew. Chem. *77*, 219 (1965); Angew. Chem. internat. Edit. *4*, 242 (1965).

[*] $\lambda_{max}$(exp) = 284, 394 nm (in methanol). Throughout this paper, wavelengths are expressed in nm (1 nm ≡ $10^{-9}$ m ≡ 1 m$\mu$).

[30a] *H. Paul* and *G. Zimmer*, J. prakt. Chem. [4] *18*, 219 (1962).

[31] *D. Buckley*, *H. B. Henbest*, and *P. Slade*, J. chem. Soc. (London) *1957*, 4891.

[32] *L. Horner* and *K.-H. Weber*, Chem. Ber. *98*, 1246 (1965).

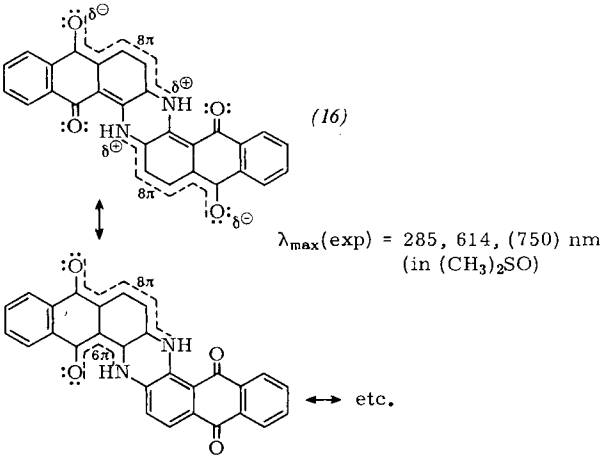
[33] *P. Boldt*, Habilitation Thesis, Universität Göttingen, 1964; Naturwissenschaften *51*, 137 (1964).

[*] [*(15)* + 2H$^{\oplus}$] $\lambda_{max}$(exp) = 272, 380, 445 (shoulder) nm (in dimethyl sulfoxide).

[**] Center of a structured band sequence with $\lambda_{max}$ at 480, 520, 556, and 585 nm.

manner. Earlier infrared measurements [34] showed that the carbonyl frequencies are greatly reduced in such dyes; on the basis of the polymethine concept, this is no longer surprising.

Indanthrene Blue *(16)* may be hypothetically represented as a combination either of two pentamethinemerocyanine or two trimethinemerocyanine structural units. However, information about the contribution of these units to the coupling will only be obtainable from quantum-mechanical calculations and more detailed experimental studies.



*(16)*

$\lambda_{max}$(exp) = 285, 614, (750) nm (in $(CH_3)_2SO$)

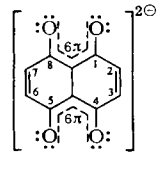


etc.

## 2.2. Coupling of Polymethine Dyes via Vinylene Groups

In some dyes the polymethine structural units are not linked by simple C–C bonds. According to the structural formula, coupling should take place across one or more vinylene groups. It is found that in such compounds it is not necessary, to a first approximation, to reduce the resonance integrals for the coupling bonds.

From the conceivable and known possibilities, it is again possible to select only a few interesting examples. In naphthazarin *(17)* and in quinizarin, coupling of two trimethinoxonols appears to take place across a central C–C bond and two outer vinylene groups. Similar couplings are known between two trimethinemerocyanines.



*(17)*

$\lambda_{max}$(exp) = 585, 614 nm (in 0.1 N NaOH) [35]

$\lambda_{max}$(theor) = 550, 653 nm (without resonance loss)

Since equal values of the resonance integral can be used for all the bonds in these substances in a rough LCAO–MO approximation, the preferred formulation of the trimethine structures and vinylene groups in *(17)* at first appears arbitrary. However, if the molecular diagram (Fig. 3) is considered in relation to the physicochemical properties of naphthazarin and similar compounds, it becomes clear that an approximately correct description of the molecule is given by the structural formula based on the coupling concept. Summation of the calculated π-electron densities within the polymethine

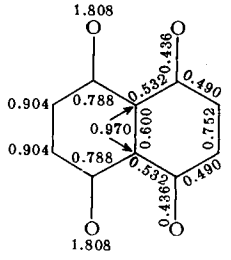



Fig. 3. 5,8-Dihydroxy-1,4-naphthoquinone dianion *(17)*. Molecular diagram in the ground state (π-bond orders and π-electron densities).

chains gives the characteristic polymethine like π-electronic structure with approximately six π electrons to a total of five atoms. The π-bond orders within the polymethine chains, including the C=O groups, are also found to be largely equalized. The double bonds of the vinylene groups are clearly distinguished by a remarkably high π-bond order and π-electron densities close to 1. In agreement with this, the frequency of the carbonyl stretching vibrations is greatly reduced, and such systems can be very readily hydrogenated on the $C^2=C^3$ bond, but not on the carbonyl oxygen [36].

The hypsochromic shift of the absorption of the electrically neutral dihydroxyquinone [*(17)* + $2H^{\oplus}$], which amounts to about 45 nm [35], is also understandable in view of the asymmetry of the π-electron distribution. This unsymmetrical bonding is confirmed by X-ray structure analysis in the case of the electrically neutral naphthazarin [37].

Coupling of two trimethine structural units *via* a vinylene bridge, as in *(18a)*, may also be assumed in the case of the indigoids, for which several isologous substitutions are known [19d]. Two intersecting trimethines having a common pair of π electrons, as in *(18b)* [38], may be considered as a second mesomeric structure; this will be discussed more fully in Section 2.3. The indigo structure can therefore be considered as a resonance hybrid of a total of four polymethine structures.

A more or less pronounced inclination towards polyene-like bonding is expected, depending on the donor strength of the X,X′ substituents. In the calculation for indigo [*(18)*, X = X′ = NH], the unreduced values are again required, to a first approximation, for the resonance integrals of the coupling bonds [19d].

Despite the simplicity of the quantum mechanical approximation used, the positions of the absorption bands

[34] *M. S. C. Flett*, J. chem. Soc. (London) *1948*, 1441; *M.-L. Josien, N. Fuson, J.-M. Lebas*, and *Th. M. Gregory*, J. chem. Physics *21*, 331 (1953).

[35] *R. A. Morton* and *W. T. Earlam*, J. chem. Soc. (London) *1941*, 159.

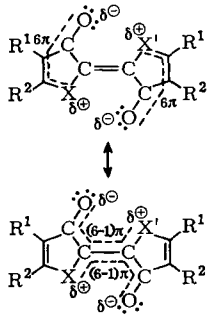
[36] *S. Bloom* and *R. Hutton*, Tetrahedron Letters *1963*, 1993.

[37] *C. Pascard-Billy*, Acta crystallogr. *15*, 519 (1962).

[38] Owing to the common pair of electrons, each of the polymethine structural units has one π-electron less. To demonstrate the polymethine-like electronic structure of the individual systems (6 π electrons to 5 chain atoms), this is indicated in *(18b)* by the expression (6 − 1) π. Structure *(18b)* corresponds to the resonance [19d] involving the non-polar structure and the two polar structures suggested by *F. Arndt* and *B. Eistert* [39].

[39] *B. Eistert*: Tautomerie und Mesomerie. G. Enke, Stuttgart 1938, p. 173.

of longest wavelength and the hypsochromic shifts both on *cis* isomerization and on vinylogous extension of the coupling –C=C– bridge are satisfactorily reproduced [19d]. The calculated π-bond order of the vinylene bridge is lower than in *(17)*, indicating increased resonance. The calculations confirm the quadrupole formulation of indigo, proposed by *Kuhn* as early as 1932 [19d,40].

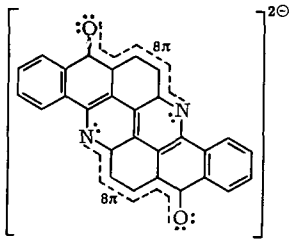


*(18a)*

*(18b)*

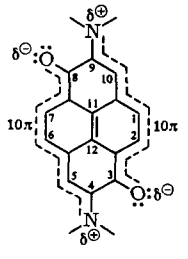
X = or ≠ X′ = NR, O, S, Se
$\lambda_{max}$(exp) = 350, 610 nm
(X = X′ = NH, $R_1 + R_2$ = annellated benzene ring [*] in ethanol [41])
$\lambda_{max}$(theor) = 368, 554 nm
(without resonance loss)
$R_{1,2}$ = H [19d]
Concerning the π electron numbers cf. [38].

Coupling of two pentamethinemerocyanines *via* several vinylene groups may be assumed in the deep blue vat of flavanthrene *(19)*.



*(19)*
$\lambda_{max}$(exp) = 630 nm
(in 2N NaOH)

Similarly, coupling of two heptamethinemerocyanines can be expected in 4,9-diamino-3,8-pyrenoquinone *(20)*.



*(20)*
$\lambda_{max}$(theor) = 481, 770 nm
(without resonance loss)

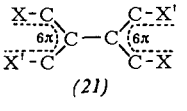
If in the calculations on this as yet unknown molecule the unreduced resonance integrals are used the two allowed longest-wavelength transitions should occur at 481 and 770 nm. The dye should therefore appear green and, as a quadrupole, should be sparingly soluble in non-polar solvents. Reduction of the resonance integrals for the $C^3$–$C^4$ and $C^{2a}$–$C^{12}$ bonds gives a hypsochromic shift for both transitions. However, the maintenance of maximum resonance is suggested by the possibility of coupling *via* the central vinylene group and the relatively high π-bond orders obtained for all the bonds involved from the first calculation step.

Another important property of the types of dyestuffs described here can be deduced directly from the concept of coupling: On gain or loss of one electron, the simple polymethines *(1)* are converted into substances of the polyene or aromatic types [2]. Accordingly, the gain or loss of two electrons in coupled polymethines should yield less strongly colored substances with aromatic or polyene-like behavior. An example is again indigo, the reduction and oxidation products of which (leuco- and dehydroindigo) have been studied in detail [41].

### 2.3. H-Chromophores

The term H-chromophore (linkage of conjugated systems in the form of an H) was proposed by *Klessinger* and *Lüttke* in connection with the indigo problem [42]. These chromophores merit special interest, since the coupling principle of two polymethine dyes is not always applicable to them in the form described above.

Coupled monomethines with an H-shaped structure have already been encountered in Section 2.1.1. H-shaped chromophores of the type *(21)* can be obtained by linkage of two trimethines *via* one principal valence [43]. The wavelength of the absorption of *(21)*, $X + X' = N\diagup + \overset{\oplus}{N}\diagdown$, calculated on the assumption of



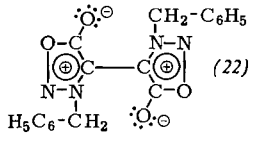
*(21)*

$\lambda_{max}$(exp) = 318 nm [44]
$X + X' = -N(CH_3)_2 + -N^{\oplus}(CH_3)_2$

$\lambda_{max}$(theor) = 404 nm
$X + X' = N\diagup + N\diagup^{\oplus}$
(resonance loss = 0.5 β)

partial coupling (0.5 β) is 100 nm lower in relation to the trimethinecyanines coupled *via* two principal valences *(9)*, and 90 nm too high in relation to the uncoupled trimethines. The experimental value essentially agrees with that of the uncoupled trimethinecyanines [*] [44].

One may mention here the striking red shift on linkage of two sydnones in 3,3′-dibenzyl-4,4′-bisydnonyl *(22)*, which



*(22)*

Sydnones: $\lambda_{max}$(exp) = 294 nm (in $C_2H_5OH$ [45])
Bisydnonyl: $\lambda_{max}$(exp) = 350 nm (in $CHCl_3$ [45])

[40] *R. Kuhn*, Naturwissenschaften *20*, 618 (1932).

[*] The removal of the two benzene rings in the transition from thioindigo (*(18)*, X = X′ = S; $R_1 + R_2$ = fused benzene rings; $\lambda_{max}$(exp) = 543 nm in ethanol) to bis-thiophenеindigo (*(18)*, X = X′ = S, $R_{1,2}$ = H) leads to a blue shift of the longest-wavelength absorption band by about 40 nm [41].

[41] *W. Lüttke* and *M. Klessinger*, Chem. Ber. *97*, 2342 (1964); *99*, 2136 (1966).

[42] *M. Klessinger* and *W. Lüttke*, Tetrahedron *19*, Suppl. *2*, 315 (1963).

[43] *Z. Arnold*, Collect. czechoslov. chem. Commun. *27*, 2993 (1962); *A. Holý*, *J. Krupička*, and *Z. Arnold*, *ibid. 30*, 4127 (1965).

[*] $\lambda_{max}$(theor) = 311 nm, $X + X' = N\diagup + N\diagup^{\oplus}$ [11];
$\lambda_{max}$(exp) = 308 nm ($X + X' = -N(CH_3)_2 + -\overset{\oplus}{N}(CH_3)_2$ in water).

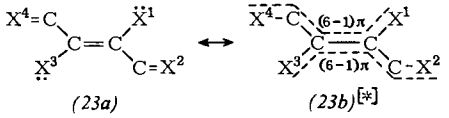
[44] *Z. Arnold*, personal communication. *A. Holý*, Chem. Listy *58*, 261 (1964).

[45] *F. H. C. Stewart*, J. chem. Soc. (London) *1963*, 701; Chem. Reviews *64*, 133 (1964).

was not to be expected by analogy with biphenyl[45]. The obvious interpretation of the bathochromism is as a coupling effect.

A stepwise reduction of the size of the indigo chromophore gives the H-shaped chromophore *(23)*. According to *Klessinger* and *Lüttke*[42,46] this still possesses indigoid properties, but smaller structural units do not. The chromophore lacks the isolated polymethine structural units required for coupling if one ignores the formal representation as two coupled dimethine radicals [*(23a)*, ($X^1$–C–C–$X^2$) and ($X^3$–C–C–$X^4$), each having 5 $\pi$ electrons to 4 atoms].

The relatively long-wavelength absorption of the H chromophore *(23)* and its vinylogues, as well as their other physicochemical properties (*e.g.* low C=O bond order for $X^2 = X^4 = O$[46]), can in our opinion be interpreted, in analogy with the indigoid mesomeric structural formula *(18b)*, by the assumption of two crossing polymethine units *(1)* with *n* odd, and in particular two trimethines in *(23b)*. On the basis of this interpretation,



*(23a)* *(23b)*[*]

$\lambda_{max}$(exp) = 450 nm for $X^1{=}X^3 = S$; $X^2{=}X^4 = O$ (*trans-s-cis-s-cis*, in cyclohexane) [46]

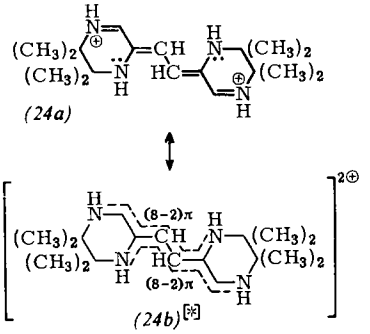
$\lambda_{max}$(theor) = 914 nm for $X^1{=}X^3 = N$; $X^2{=}X^4 = O$ (*trans-s-cis-s-cis*, no resonance loss)

$\lambda_{max}$(theor) = 743 nm for $X^1{=}X^3 = N$; $X^2{=}X^4 = N^{\oplus}$ (*trans-s-trans-s-trans*, no resonance loss)

$\lambda_{max}$(theor) = 473 nm (the same with alternation of resonance integral values)

if the X substituents at the ends of the individual systems are not the same ($X^1 \neq X^4$ and $X^2 \neq X^3$), the systems can again form a quadrupole structure, a possibility that cannot be reproduced with the aid of a single Kekulé structure[19d]. As with the simple polymethines, a transition to a bonding state similar to the polyene type is to be expected, together with a hypsochromic absorption shift, as the distribution of the $\pi$ electrons over the two individual polymethine chains becomes more unsymmetrical. Structure *(23a)* correponds to the pure polyene limiting structure with $X^1$ and $X^3$ as substituents.

Experimental values have been reported for the absorption of a number of H-chromophores with sulfur substituents [*(23)*, $X^1 = X^3 = S$, $X^2 = X^4 = O$][46]. A vinylogue of *(23)* (with $X^1 = X^3 = N$; $X^2 = X^4 = N^{\oplus}$) has been synthesized in the form of the deep red compound *(24)*[47]. The system may again be regarded as consisting of two crossing pentamethinecyanines having two common pairs of $\pi$ electrons[*], which more or less approximate to the polyene structure.



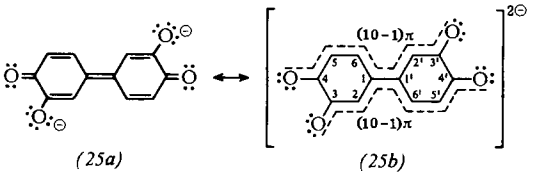
*(24a)* *(24b)*[**]

$\lambda_{max}$(exp) = 550 nm (in buffer solution, pH = 1 [47]

$\lambda_{max}$(theor) = 900 nm (no resonance loss)

$\lambda_{max}$(theor) = 491 nm (with alternation of resonance integral values)

3,3′-Dihydroxy-4,4′-diphenoquinone *(25)*, the dianion of which is deep green[48], may be formulated as an H-chromophore with further vinylogous extension. The limiting structures of a substituted polyene *(25a)* and of crossed polymethines, in this case crossed heptamethinoxonols *(25b)*, with one common pair of $\pi$ electrons[*], must again be taken into account. A $\pi$–$\pi$ interaction *via* the $C^3$–$C^4$ and $C^{3'}$–$C^{4'}$ bonds must also be expected in these compounds, so that it is not possible to distinguish between pure crossing and pure coupling of two heptamethines by means of the structural formula.



*(25a)* *(25b)*

Without additional assumptions, our quantum-mechanical approximation does not give good agreement with experiment for such systems of crossed polymethines. A better approximation can be obtained if the systems are assumed to have a structure of the polyene type. Thus with an alternating modification of the resonance integrals as described by *Coulson* and *Golebiewski*[22][**] the calculation for *(23)* and *(24)* gives much lower wavelengths for the absorptions, which are in better agreement with experiment. On the basis of this result, it should be expected that the polyene structures *(23a)* and *(24a)* are slightly favored in the H-chromophores. This tendency towards a polyene-like bonding state is also qualitatively understandable. Owing to the crossing of the polymethine chains, the polymethine-like alternating $\pi$-electron density distribution is interrupted over the common members of the two chains.

*Lüttke* and *Klessinger* obtained satisfactory agreement with experiment on calculation of the absorption of the H-chromophore *(23)* and of its *cis-trans*-isomeric derivatives with the aid of the Pariser-Parr-Pople approximation[42,46]. Since the H-shaped systems *(23)* absorb at relatively long wavelengths and are also similar to the indigoids in their

[46] *W. Lüttke, H. Hermann,* and *M. Klessinger,* Angew. Chem. *78*, 638 (1966); Angew. Chem. internat. Edit. *5*, 598 (1966).

[47] *M. Lamchen* and *T. Mittag,* Proc. chem. Soc. *1963*, 302.

[*] Concerning the numbers of $\pi$ electrons, compare [38].

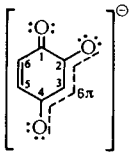
[48] *L. Horner* and *K. H. Weber,* Chem. Ber. *96*, 1568 (1963).

[**] About 0.8 $\beta$ for bonds with more single bond character and about 1.2 $\beta$ for bonds with more double bond character.

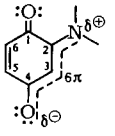
ease of reduction and of *cis*-isomerization, the authors believe that the formulation of indigoids as a mesomeric structure of coupled polymethines as in *(18a)* is disproved [46]. However, this discussion is not yet closed. For detailed molecular-theoretical considerations it is necessary to determine other physical properties, particularly the crystal structure of the systems under discussion.

## 3. Polyene-Polymethine Coupling

On the assumption that the coupling principle is of general validity as the cause of the color of complex dyes, it seemed impossible at first to understand the color of the monosubstituted quinone dyes, *e.g.* monohydroxy- and monoamino-*p*-benzoquinones *(26)* and *(27)*, which contain only one polymethine structural



*(26)*



*(27)*

$\lambda_{max}$(exp) = 258, 497 nm ($-N(CH_3)C_6H_5$, in $(CH_3)_2SO$)

$\lambda_{max}$(theor) = 280, 530 nm (resonance loss = 0.5 β [19d])

unit *(1)* (*n* odd) in the molecule. As can be seen from the formulae, this structural unit is linked, *via* the $C^1-C^2$ and $C^4-C^5$ bonds, to the polyene structural unit $-C=CH-C=O$, which is characterized by alternation of bond lengths and equal π-electron densities on all the atoms. It can again be shown by the LCAO–MO method that when these two structural units are brought together in steps, the individual energy levels change into those of the composite molecule. This conversion is shown in Figure 4 for *(27)* with coupling resonance integrals of 0.1, 0.3, and 0.5 β. Each coupling term receives components of both individual systems, as is indicated by the dotted levels. The optimum approximation is again obtained with a coupling resonance integral of about 0.5 β, *i.e.* the same as that required for polymethine-polymethine coupling *via* single bonds.

If, on the other hand, the calculation for the molecule *(27)* is carried out without application of the coupling concept, *i.e.* with equal values of the resonance integral for all bonds, the wavelength of the lowest-energy electron transition is found to be 500 nm too high, and particularly low π-bond orders are obtained for the bonds that form the coupling between the polyene and polymethine structural units ($C^1-C^2$ and $C^4-C^5$) and for the bond in the polyene having more single-bond character ($C^1-C^6$) [19d]. The lowering must then be taken into account in a second calculation by overall [19d] or iterative [23] modification of the resonance integrals. Thus the polyene-polymethine coupling principle also follows from the LCAO–MO calculations. The validity of this procedure is confirmed not only by the satisfactory description of the visible absorption, but also by infrared and proton magnetic resonance

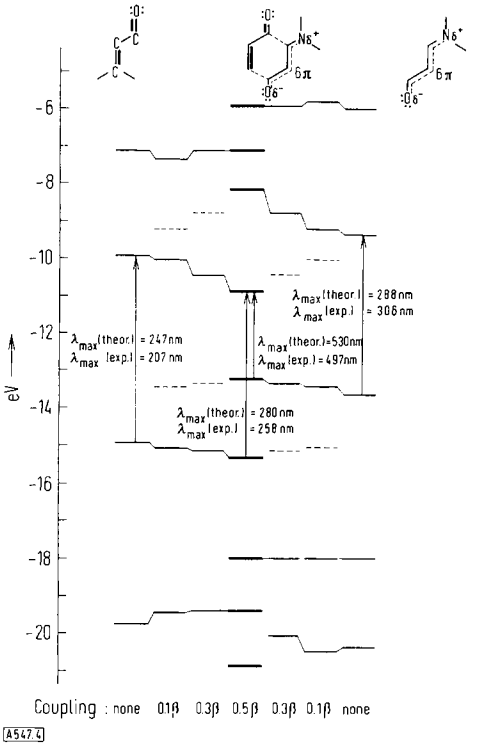



Fig. 4. LCAO–MO energy-level diagrams for the polyene-polymethine coupling in 2-amino-1,4-benzoquinone.

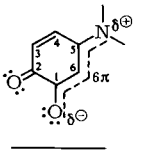
Polyene (acrolein): calculation to a rough approximation by the use of alternating resonance integrals: 1.0 β for $C^1-O$ and $C^2-C^3$; 0.5 β for $C^1-C^2$, Coulomb integrals [19d], experimental value in ethanol [49].

Trimethinemerocyanine and monoamino-*p*-benzoquinone: theoretical values without *N*-substituent effects after [19d], experimental values for $-N(CH_3)C_6H_5$ in dimethyl sulfoxide.

spectroscopy. The C=O stretching absorption of the polyene side is situated at higher frequencies than that of the polymethine side. The chemical shifts of the protons, after correction for the ring current, agree with those of the uncoupled polyene and of the uncoupled polymethine [50].

The bathochromism on coupling of the polyene with the trimethine in *(26)* and *(27)* is comparable to that arising on coupling of two trimethines in *(10)* and *(6)*. However, the fact that owing to asymmetry, the transition is not forbidden in the polyene-polymethine coupling provides a simple explanation for the remarkable observation that the *mono*substituted *p*-benzoquinones absorb much more intensely in the visible region than the 2,5-*di*substituted derivatives.

Similar coupling should occur in the 4-amino-*o*-benzoquinones *(28)*, in which the polyene structural unit is linked in the opposite direction with the trimethine structural unit. In fact, calculation to a simple approximation (reduction of the resonance integrals to 0.5 β



*(28)*

$\lambda_{max}$(exp) = 266, 314, 503 nm ($-N(CH_3)C_6H_5$ in $(CH_3)_2SO$)

$\lambda_{max}$(theor) = 309, 510 nm (resonance loss = 0.5 β)

[49] *W. F. Forbes* and *R. Shilton*, J. Amer. chem. Soc. *81*, 786 (1959).

[50] *S. Dähne, D. Leupold, H. Paul*, and *J. Ranft*, Angew. Chem. *77*, 1017 (1965); Angew. Chem. internat. Edit. *4*, 970 (1965).

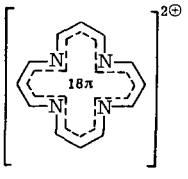
for the bonds $C^1-C^2$, $C^2-C^3$, and $C^4-C^5$) gives a similar long-wavelength absorption, which agrees closely with the experimental value.

Many other colored systems with polyene-polymethine coupling are to be found among the monosubstituted naphthoquinones, anthraquinones, and higher condensed quinones.

For consistent application of the polymethine system one should also mention here the dye radicals formed from coupled polymethines by the uptake of *one* electron. In this case only *one* polymethine structural unit should formally be converted into a polyene unit, and the actual coupling state probably will exhibit pronounced resonance equalization. The relatively long wavelength absorption of the indigo and 5,8-diamino-1,4-naphthoquinone radicals[51] appears to substantiate this procedure.

## 4. Other Possibilities of Coupling

The intense long-wavelength absorption of the porphyrins, whose essential chromophore *(29)* contains 18 $\pi$ electrons to 16 chain atoms, can be formally explained by *cyclic* linkage of pairs of polymethine structural units that merge into one another.

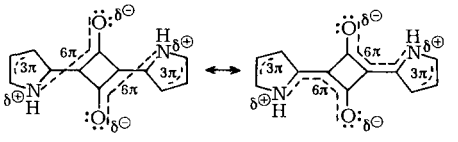



*(29)*

A similar polymethine-like $\pi$-electron distribution, with $2(n+1)$ $\pi$ electrons to $2n$ atoms is evidently also to be found in the interesting colored polyhydroxyquinone dianions of general formula $C_nO_n^{2\ominus}$ ($n = 4,5,6$)[17].

In general, the branching of a polymethine system leads to splitting of the absorption bands of longest wavelength. The only exceptions are higly symmetrical molecules. "Classic" examples of substances exhibiting this splitting of the band are the triphenylmethane dyes. However, similar effects are known with the neocyanine, flavone, and anthocyanin dyes, which can also be interpreted as branched polymethines (with more or less strong polyene or aromatic character)[2a]. It seems obvious to interpret the spectra of these dyes on the basis of coupling effects.

The formulation is problematic when this apparently leads to biradicals, *e.g.* in *(30)*. Owing to intramolecular spin




*(30)*

$\lambda_{max}$(exp) = 550 nm (in $CHCl_3$ [52])

saturation, the compound is diamagnetic. There is a possibility of a decrease in stability, expressed in the biradical notation.

It must also be checked whether it is justifiable to speak of polyene-polyene coupling as well as of polymethine-polymethine and polyene-polymethine couplings. As we have seen, the polymethine structural unit becomes increasingly polyene-like as the $\pi$-electron distribution becomes more unsymmetrical, *e.g.* in the electrically neutral hydroxyquinone and quinone imide dyes. Pure polyene-polyene coupling is to be expected in *p*-benzoquinone and in its derivatives with electron-accepting substituents in positions 2 and 5. Further studies will be necessary in this connection.

This discussions should, however, give some idea of the large number of possible polymethines. The possible coupling variations have by no means been exhausted. The synthesis of coupled polymethines with isologous chain substituents opens a large new field for investigation.

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Translated by Express Translation Service, London

[51] *W. Luck* and *H. Sand*, Angew. Chem. *76*, 463 (1964); Angew. Chem. internat. Edit. *3*, 570 (1964).

[52] *A. Treibs* and *K. Jakob*, Angew. Chem. *77*, 680 (1965); Angew. Chem. internat. Edit. *4*, 694 (1965).

# Polymers Containing Lactone Groups

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*Polymers containing intact lactone groups are a new class of macromolecules with reactive groups, which are relatively easy to obtain by polymerization, polycondensation and polyaddition, as well as by reactions on existing macromolecules. Polymers with β-lactone groups in particular can enter into numerous addition reactions, which can be used, for example, to obtain macromolecules containing hydroxy acid or amino acid groupings. The reactions proceed under mild conditions, and can even be carried out in aqueous media, frequently giving water-soluble polymers. The polymers can be cross-linked at low temperatures, even from the aqueous phase, by the addition of bifunctional or oligofunctional reagents. Polymers containing β-lactone groups can also be used as a basis for graft copolymers; polyester or polyether branches can be grafted on, depending on whether monomeric lactones or monomeric epoxides are used.*

Macromolecules containing reactive groups have been intensively studied in recent years [1], but little is known about polymers containing intact lactone groups. Though a few studies have been carried out on the introduction of γ-lactone groups into existing polymers (see Section I.2.c), the only method reported so far for the preparation of macromolecules having high contents of β-lactone groups is exposure of liquid diketene to high-energy radiation at high temperatures [2]. Polymers of this type are of interest in view of the special readiness of the β-lactone group to undergo additions. The following sections describe the synthesis of suitable monomers, the preparation of polymers containing β- or γ-lactone groups, and the reactions of these polymers.

## I. Preparation of Polymers Containing Lactone Groups

The principal methods for the preparation of macromolecules containing intact lactone groups are:

1. polymerization of lactones containing another polymerizable group, *e.g.* a double bond or an epoxy group;

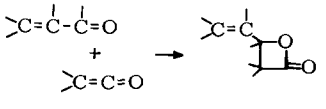
2. polycondensation or polyaddition of lactones containing functional groups, *e.g.* dihydroxylactones; and

3. reactions on suitable macromolecules, *e.g.* intramolecular lactonization or addition of dihydropyran β-lactones to polymeric hydroxy compounds.

### 1. Polymers Containing β-Lactone Groups

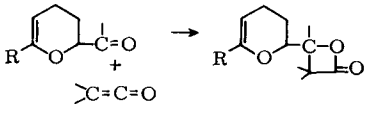
#### a) Polymerization of β-Lactones Containing a C=C Double Bond

β-Lactones *(1)* with a vinyl group in the β-position are obtained by the addition of ketene or dimethylketene to acrolein or α-methylacrolein [3]. Though such β-lactones can be selectively polymerized across the



*(1)*

lactone ring to give unsaturated polyesters [4], satisfactory polymerization across the C=C double bond, with retention of the lactone ring, has not yet been achieved. However, the addition of ketene or dimethylketene to dimeric acrolein or dimeric methacrolein by conventional methods [3] yields β-(2,3-dihydropyran-2-yl)-β-lactones *(2)*, which contain a lactone group and a cyclic vinyl ether group.



*(2)*, R = H, $CH_3$

The β-(2,3-dihydropyran-2-yl)-β-lactones *(2)* can be selectively polymerized across the vinyl ether double bond [*], for example by Lewis acids or alkylaluminum

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[***] New address: Kunststoff-Forschung, Farbwerke Hoechst, Frankfurt/Main-Höchst (Germany).

[1] *W. Kern* and *R. C. Schulz*, Angew. Chem. *69*, 153 (1957); *W. Kern*, *R. C. Schulz*, and *D. Braun*, Chemiker-Ztg. *84*, 385 (1960); *G. Smets*, Angew. Chem. *67*, 57 (1955).

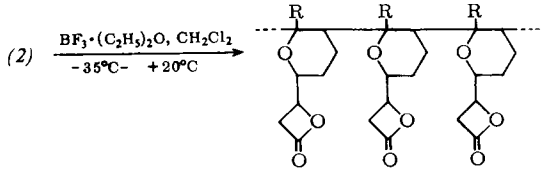
[2] *S. Okamura*, Chimia *1*, 9 (1963).

[3] For summary see *H. Kröper* in Houben-Weyl: Methoden der organischen Chemie. Vol. VI/2, Thieme, Stuttgart 1964.

[4] *H. Ohse* and *H. Cherdron*, Makromolekulare Chem. *95*, 283 (1966).

[*] Selective polymerization across the lactone ring to obtain polyesters with intact vinyl ether groups is also possible [4].

halides, without attack on the lactone ring [5], as can be shown *e.g.* by IR spectroscopy (the β-lactone absorption at 1820 $cm^{-1}$ is retained, the absorption of the C=C double bond at 1675 $cm^{-1}$ disappears, and no open-chain ester absorption appears at 1720 $cm^{-1}$) or by gas-chromatographic determination of the $CO_2$ liberated on heating (see Section II.1).



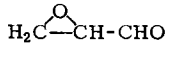

*(3)*, R = H, $CH_3$

Owing to a transfer reaction to the monomer, the molecular weights obtained under these conditions do not exceed 10000. The resulting polymers *(3)* are solid, high-melting substances [poly-β-(2,3-dihydropyran-2-yl)-β-lactone melts at 180–200 °C with decomposition], which dissolve in chlorinated hydrocarbons and in tetrahydrofuran, and can be precipitated with ether or petroleum ether.

Copolymerization across the vinyl ether group with other vinyl monomers, *e.g.* styrene [5], is also possible, and in this way the number of intact lactone groups per macromolecule can be controlled.

The polymers *(3)* change on storage in the solid state in the presence of catalytic quantities of protonic acids or Lewis acids. Even at room temperature, the spectrum shows the following changes after a few days: the absorption of the β-lactone band at 1820 $cm^{-1}$ becomes weaker, while a γ-lactone band occurs first at 1765 $cm^{-1}$, followed by an open-chain ester absorption at 1720 $cm^{-1}$. The formation of open-chain esters is probably due to an intermolecular reaction (cross-linking); such a reaction also explains the fact that the polymers become insoluble and infusible. This rearrangement of the polymers *(3)*, which probably involves both the β-lactone ring and the pyran ring, can be suppressed by the addition of amines (*e.g.* 0.1–1 % of β-naphthylamine).

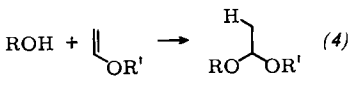
Macromolecules containing intact lactone groups are also obtained by selective polymerization of monomers that contain an epoxy group as well as a lactone group, *e.g.* β-oxiranyl-β-propiolactone, which can be prepared by addition of ketene to glycidaldehyde *(3a)* [6].




*(3a)*

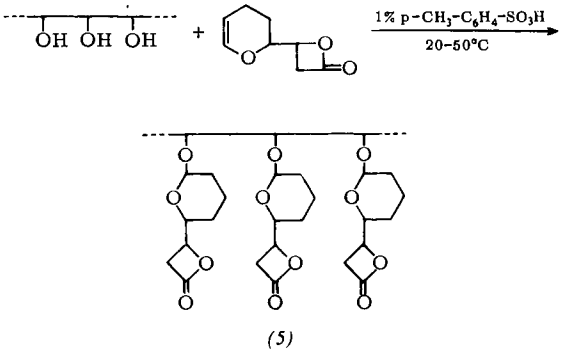
### b) Addition of β-(2,3-Dihydropyran-2-yl)-β-lactones to Polymers Containing Free Hydroxyl Groups

Alcohols add to vinyl ethers in the presence of acidic catalysts to give acetals *(4)*. It has been found that β-(2,3-dihydropyran-2-yl)-β-lactones can be added in




*(4)*

the same manner to polymers containing free hydroxyl groups. The lactone ring is not cleaved during this reaction, though lactones can normally be readily transesterified under these conditions; instead, the




*(5)*

reaction leads to polymers of the type *(5)*. This route to polymers containing intact lactone groups is very versatile, since the starting material may be any of a wide variety of polyhydroxy compounds (*e.g.* polyalkylene glycols, polyvinyl alcohol, alkyd resins, and natural polymers such as starch and cellulose); it is particularly suitable for the preparation of water-soluble polymers, which can subsequently be cross-linked in two ways. The lactone group of a water-insoluble adduct (*e.g.* starch containing more than 20 mole-% of lactone groups) may be treated with *e.g.* a monoamine until the adduct becomes water-soluble; the adduct can then be cross-linked from the aqueous phase *via* the remaining lactone groups, *e.g.* by treatment with a diamine. Alternatively, just enough β-(2,3-dihydropyran-2-yl)-β-propiolactone may be added to a water-soluble polymer containing hydroxyl groups to retain solubility in water; the polymer is then cross-linked *via* the lactone groups introduced, by treatment with bifunctional reagents. Thus the latter method can be used for the additive cross-linking of polymers containing hydroxyl groups under mild conditions similar to those used for cross-linking with diisocyanates; this cross-linking can even be carried out in aqueous media.

The reaction of ketene with polymers containing intact carbonyl groups, which should also lead to macromolecules containing β-lactone groups, has not yet been tried as far as we know.

## 2. Polymers Containing γ-Lactone Groups

### a) Polymerization of Unsaturated γ-Lactones

The first attempts to polymerize unsaturated γ-lactones were made by *Marvel* and *Levesque* [7]. From the lactone of γ-hydroxyangelic acid with $BF_3$·ether as the initiator, these authors obtained a dark red, tacky mass having

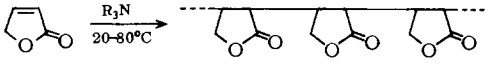
[5] *H. Cherdron* and *H. Ohse*, unpublished.

[6] *P. H. Williams, G. B. Payne, W. J. Sullivan*, and *P. R. van Ess*, J. Amer. chem. Soc. *82*, 4883 (1960).

[7] *C. S. Marvel* and *C. L. Levesque*, J. Amer. chem. Soc. *61*, 1682 (1939).

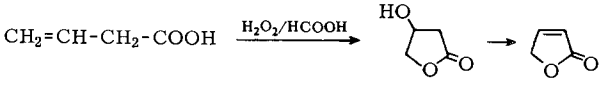
a molecular weight of 800–900 (ebullioscopic). In addition to γ-lactone groups, this polymer still contained about 25 % of its hydroxyl and carboxyl groups.

The only data available on the lactone *(6)* of γ-hydroxycrotonic acid, which is the simplest unsaturated γ-lactone, deal with its free-radical induced copolymerization with styrene [8]; according to this report, the free-radical polymerization of this monomer proceeds only with great difficulty. On the other hand, with a number of tertiary amines (*e.g.* triethylamine) as initiators, we readily obtained solid polymers (softening points about 150 °C), which are soluble only in strongly polar solvents (dimethylformamide or formic acid). On the basis of the IR spectrum (the γ-lactone absorption at 1765 $cm^{-1}$ is retained and the absorption of the C=C double bond at 1675 $cm^{-1}$ disappears) and of the titration with aqueous NaOH and HCl, these polymers must be




*(6)* *(7)*

assigned the structure *(7)*. They depolymerize quantitatively at 250 °C to the monomer. The lactone of γ-hydroxycrotonic acid can be conveniently prepared as follows:



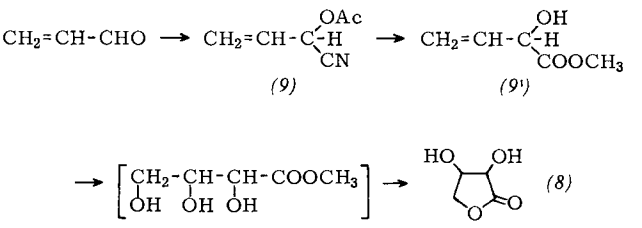

*(6')* *(6)*

*Lactone of γ-Hydroxycrotonic Acid (6)*: 470 g of 30 % (or 140 g of 100 %) hydrogen peroxide is added dropwise to a mixture of 344 g (4 mole) of vinylacetic acid and 840 ml of formic acid at 40–45 °C. This temperature is maintained until all the $H_2O_2$ has been consumed, catalytic quantities of platinum (*e.g.* platinum black) are added to decompose any remaining performic acid, and the formic acid is distilled off under vacuum. Concentrated HCl (20 ml) and water (600 ml) are added to the residue, and the mixture is refluxed for 2 hours. The hydrochloric acid and the water are then evaporated off under vacuum, and the crude product is dried by azeotropic distillation with chloroform. Fractional distillation of the residual solution yields 357 g (88 %) of pure β-hydroxy-γ-butyrolactone *(6')* (b.p. 133 °C/0.35 mm Hg; $n_D^{20}$ = 1.4652). After addition of two drops of polyphosphoric acid, this product is heated to 160 °C/13 mm Hg. A mixture of water and the lactone *(6)* distils, and most of the water is removed from the mixture as described above. Fractional distillation yields 288 g (98 %) of the pure lactone of γ-hydroxycrotonic acid (b.p. 90–92 °C/13 mm Hg; $n_D^{20}$ = 1.4682).

### b) Polycondensation and Polyaddition of Dihydroxy-γ-lactones

An example of a suitable diol component for the synthesis of polymers containing γ-lactone groups by polycondensation or polyaddition is α,β-dihydroxy-γ-butyrolactone *(8)*, which can be readily prepared from acrolein *via* 1-cyano-2-propenyl acetate *(9)*.

[8] *J. M. Judge* and *C. C. Price*, J. Polymer Sci. *41*, 435 (1959).




*(9)* *(9')* *(8)*

*1-Cyano-2-propenyl Acetate (9)*: 79 g (0.77 mole) of acetic anhydride is quickly added dropwise to a mixture of 150 ml of benzene and 43.3 g (0.77 mole) of acrolein cooled to −10 °C, and a solution of 55 g (1.12 mole) of sodium cyanide in 280 ml of water is then added. The mixture is stirred for 2 hours at −10 °C, then warmed to 0 °C, and the benzene layer is removed. The aqueous layer is extracted with benzene, and the organic phases are combined and washed first with a little acetic acid, then with $NaHCO_3$, and finally with water. The solution is dried over $MgSO_4$, the benzene is evaporated off, and the residue is fractionated under vacuum. Yield: 84 g (87 %); b.p. 63–65 °C/10 mm Hg; $n_D^{20}$ = 1.4240.

*Methyl 2-Hydroxy-3-butenoate (9')*: A mixture of 250 g (2 moles) of 1-cyanoprop-2-enyl acetate and 215 ml of anhydrous methanol is heated until it boils gently. The heating bath is then removed, and a mixture of 215 ml of methanol saturated with HCl and 55 ml of concentrated hydrochloric acid (36.4 %) is gradually added at such a rate that the reaction mixture just continues to boil. When the exothermic reaction has stopped, the mixture is refluxed for a further 2 hours and then allowed to cool, and the ammonium chloride is filtered off. The methanol solution is then concentrated, diluted with ether, washed with $NaHCO_3$ and then with water, and dried over $MgSO_4$. When the ether has been evaporated off, the residue is fractionated under vacuum. Yield: 174 g (75 %); b.p. 60 °C/13 mm Hg; $n_D^{20}$ = 1.4392.

*α,β-Dihydroxy-γ-butyrolactone (8)*: 59 g (0.517 mole) of 30 % hydrogen peroxide is added dropwise over a period of 3 hours to a solution of 58 g (0.5 mole) of *(9)* in 105 ml of 98–100 % formic acid at 40–45 °C. This temperature is maintained until performic acid can no longer be detected iodometrically, then any traces still remaining are decomposed with catalytic quantities of platinum, and the mixture is filtered. The formic acid and water are distilled off, and the residue is refluxed for 2 hours with a mixture of 75 ml of water and 0.5 ml of concentrated hydrochloric acid. The water is distilled off and the residue is diluted with 50 ml of dioxane, dried over $MgSO_4$, and distilled. Yield: 32.7 g (55.5 %); b.p. 164–166 °C/0.03 mm Hg; $n_D^{20}$ = 1.4900.

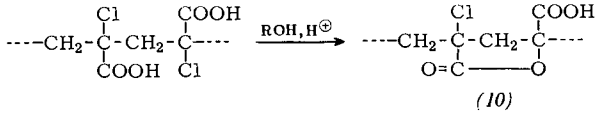
The polycondensation of α,β-dihydroxy-γ-lactones such as *(8)* with dicarboxylic acids or their derivatives, *e.g.* dichlorides of dicarboxylic acids, in the melt or in solution, leads only to low molecular weight products, since the lactone ring is partially cleaved under the reaction conditions. On the other hand, with diisocyanates (polyaddition in the melt or in toluene) such as toluene diisocyanate (mixture of 2- and 4-methyl-1,3-phenylenediisocyanate (1:4); "Desmodur T" produced by Farbenfabriken Bayer), high molecular weight polyurethanes with intact γ-lactone groups are obtained. These polyurethanes dissolve in polar solvents.

### c) Introduction of γ-Lactone Groups by Reactions on Macromolecules

By refluxing poly-α-chloroacrylic acid with water, *Marvel* [9] obtained polymers containing γ-lactone groups, but these polymers were cross-linked as a result of

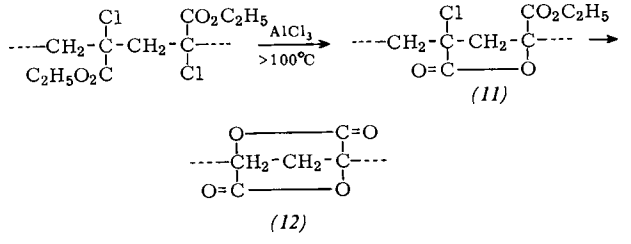
[9] *C. S. Marvel, J. Dec, H. G. Cooke*, and *J. C. Cowan*, J. Amer. chem. Soc. *62*, 3495 (1940).

simultaneous intermolecular esterification. On the other hand, when poly-α-chloroacrylic acid is boiled in alcohol,soluble polymers of the type *(10)* are formed [10].



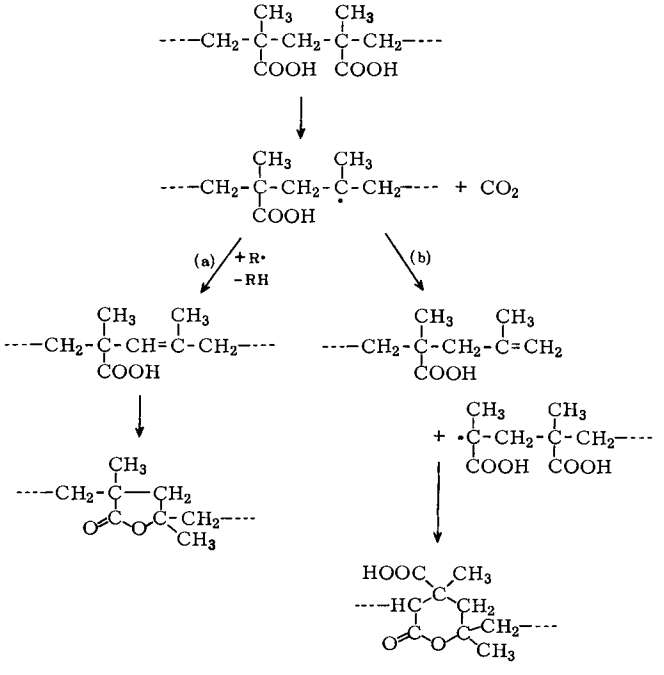
*(10)*

Polymers containing γ-lactone groups can also be obtained from esters of poly-α-chloroacrylic acid by rearrangement with Friedel-Crafts catalysts [11]. In this reaction, up to 80 % of the ester groups may be in the monolactone *(11)* or dilactone form *(12)*.

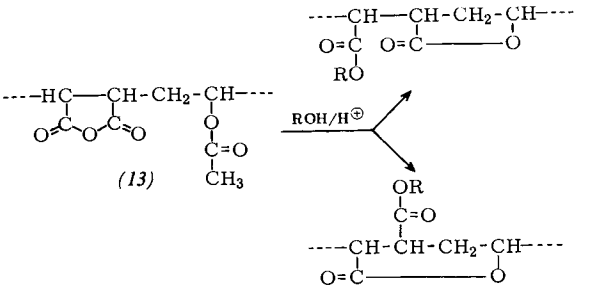


*(11)* *(12)*

Lactonization was observed by *Smets* [12] during electrolysis of polymethacrylic acid. Macroradicals are first formed by decarboxylation; double bonds are then introduced into the macromolecules by disproportionation (a) or degradation (b), and these can react with the remaining carboxyl groups with cyclization to form γ-lactones or δ-lactones. Depending on the electrolysis, the content of lactone groups can amount to 35–40 %.

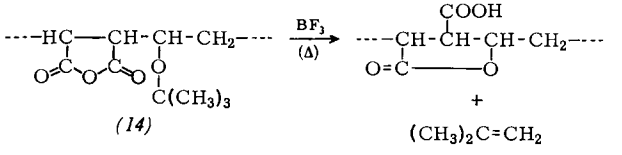


Maleic anhydride-vinyl acetate copolymers *(13)* can also be converted into polymers containing intact lactone groups [13]; polymers containing both γ- and δ-lactone rings are obtained.



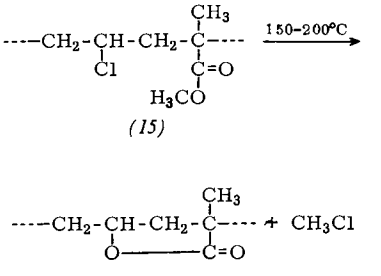
*(13)*

Copolymers *(14)* of t-butyl vinyl ether and maleic or citraconic anhydride react in the presence of $BF_3$ to form polymers containing δ- and β-lactone groups as well as γ-lactone groups [14]; the same rearrangement takes place on heating.



*(14)*

Finally, polymers containing intact γ-lactone groups can be obtained by thermal elimination of methyl chloride from 1:1-copolymers *(15)* of methyl methacrylate and vinyl chloride [15].



*(15)*

## II. Reactions of Polymers Containing Lactone Groups

Reactions of polymers containing intact lactone groups are distinguished above all by the following characteristics:

1. With few exceptions, they are addition reactions, most of which (particularly in the case of polymers containing β-lactone groups) proceed under very mild conditions.
2. The reactions can often be carried out in aqueous media, and they then give water-soluble polymers.

As in low molecular weight compounds, β-lactone groups react more readily than γ-lactone groups.

### 1. Reactions of Polymers Containing β-Lactone Groups

These reactions were carried out with poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone as a model substance;

[10] *L. M. Minsk* and *W. O. Kenyon*, J. Amer. chem. Soc. *72*, 2650 (1950).

[11] *G. Smets* and *P. Flore*, J. Polymer Sci. *35*, 519 (1959).

[12] *G. Smets*, *X. van der Borght*, and *G. van Haeren*, J. Polymer Sci. A *2*, 5187 (1964).

[13] *L. M. Minsk*, *G. P. Waugh*, and *W. O. Kenyon*, J. Amer. chem. Soc. *72*, 2646 (1950).

[14] *R. J. Kern*, Makromolekulare Chem. *79*, 122 (1964).

[15] *N. L. Zutty* and *F. J. Welch*, J. Polymer Sci. A *1*, 2289 (1963).

however, it has been found that they can also be applied directly to other polymers containing intact β-lactone groups.

Reactions of compounds containing β-lactone groups can be conveniently followed by IR spectroscopy (β-lactone absorption at 1820 $cm^{-1}$). Titration with base can be used for quantitative analysis in only a few cases.

The gas-chromatographic determination (by the ampoule technique) of the carbon dioxide liberated on heating (see Scheme 1, a) is very accurate and free from perturbing influences[16]: 5 mg of polymer is decomposed in a glass ampoule during 2 hours at 250 °C; the $CO_2$ is then quantitatively determined at 50 °C and 0.3 atm on a 2 m di-n-decyl phthalate column.

### a) Thermal Elimination of Carbon Dioxide

Polymers containing β-lactone groups quantitatively lose $CO_2$ at high temperatures; in the case of poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone *(3)*, this occurs above 180 °C with formation of a polymeric 2-vinyl-dihydropyran (see Scheme 1,a). If this reaction is allowed to proceed above the softening point of the polymer, porous foams are obtained.

### b) Reaction with Acids

According to *Gresham*[17], the reaction of β-lactones with hydrohalic acids leads to β-halogenopropionic acids. This reaction does not occur with poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone *(3)*, which instead is cross-linked by Brönsted or Lewis acids, even at room temperature, *via* the lactone groups. Carboxylic acids open the lactone ring at high temperatures to form the esters of the (substituted) β-hydroxypropionic acid, the alkali metal salts of which are water-soluble (see Scheme 1,$b_2$).

### c) Reaction with Alcohols

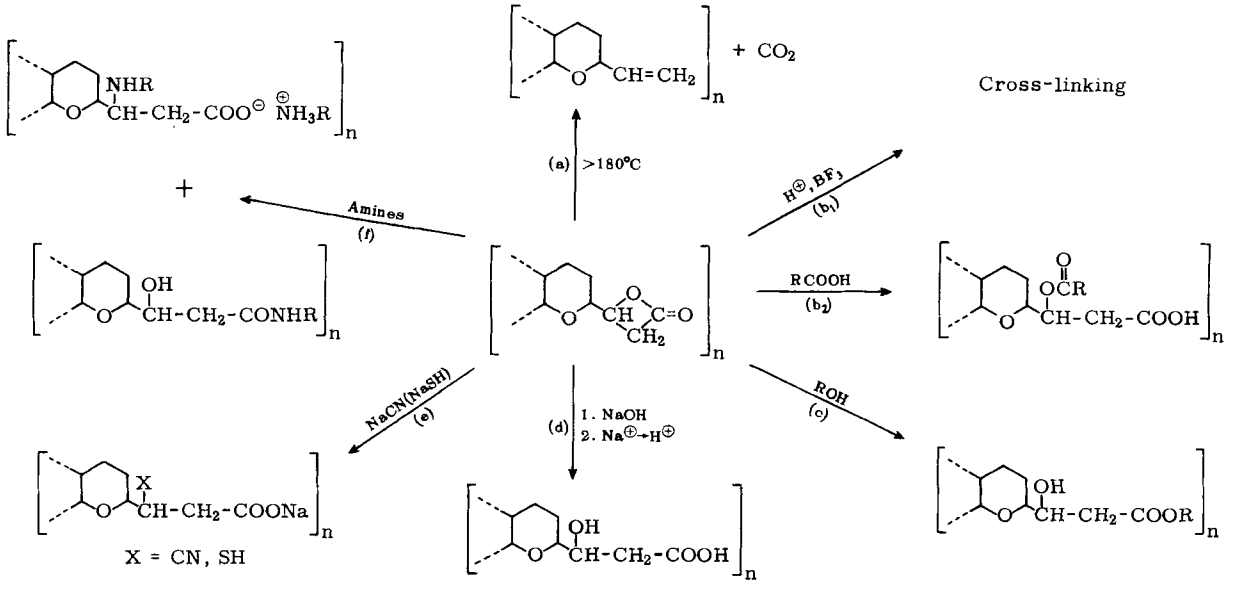
The acid-catalysed reaction of poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone *(3)* *e.g.* with ethanol leads to the polymeric (substituted) β-hydroxypropionate (see Scheme 1,c). A suspension of the polymer in an excess of methanol is heated, the product gradually going into solution. Attempts to catalyse this reaction with alkali have been unsuccessful.

### d) Reaction with Alkali Metal Hydroxides

Poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone *(3)* dissolves in 1N NaOH, even in the cold, to give a clear solution which contains sodium poly-β-(2,3-dihydropyran-2-yl)-β-hydroxypropionate, which can be converted into the free acid with cation exchange resins or by acidification and extraction of the concentrated residue with ethanol (see Scheme 1,d).

### e) Reaction with Salts

Whereas the reaction corresponding to that of β-propiolactone with sodium chloride to give sodium β-chloropropionate[17] does not take place, poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone reacts with salts of weak acids, such as NaCN and NaSH, in aqueous media at 20 to 50 °C. The reaction leads to water-soluble polymeric Na salts of (substituted) β-cyano- and β-mercaptopropionic acids (see Scheme 1,e). Hydrolysis of β-lactone groups takes place at the same time, so that in addition to the desired groups, the polymeric products contain also β-hydroxypropionic acid groups.




Scheme 1. Reactions of poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone.

### f) Reactions with Amines

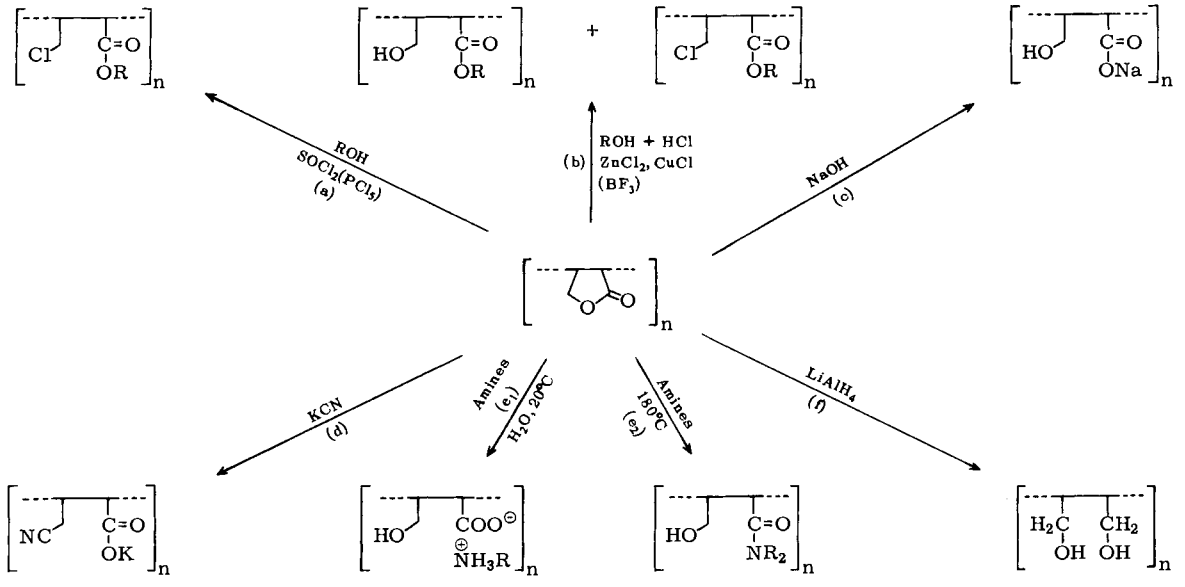
Amines react with β-propiolactone[18] to give either the β-hydroxypropionamide or the β-aminopropionic acid, depending on the reaction conditions. The reaction of

[16] *H. Cherdron, L. Höhr,* and *W. Kern,* Angew. Chem. *73*, 215 (1961).

[17] *T. L. Gresham,* J. Amer. chem. Soc. *70*, 999 (1948); *74*, 1223 (1952); *76*, 486 (1954).

[18] *T. L. Gresham,* J. Amer. chem. Soc. *73*, 3, 168 (1951).

poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone with ammonia or primary or secondary amines in water at 20 to 50 °C leads to water-soluble products containing both β-hydroxypropionamide and β-aminopropionic acid groups, or possibly their ammonium salts (Scheme 1,f). To obtain water-soluble polymers, only some of the β-lactone groups in the insoluble polymer need react with a monoamine; cross-linking from the aqueous solution can then be achieved by reaction of the remaining β-lactone groups with diamines or polyamines at 20 to 50 °C. In organic solvents, *e.g.* in an excess of the reagent, the reactions of poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone *(3)* with amines are much slower.




Scheme 2. Reactions of poly-γ-hydroxycrotonolactone.

### g) Preparation of Graft Copolymers

The intact lactone groups *e.g.* in poly-β-(2,3-dihydropyran-2-yl)-β-propiolactone can also be used for the preparation of graft copolymers. Thus polyester branches can be grafted on by dissolution of *(3)* in monomeric lactones, such as β-propiolactone, and addition of an initiator. Polyether branches can also be grafted on, since lactones copolymerize with epoxides [19]. This graft copolymerization can be initiated by cationic or anionic initiators under conditions similar to those used in the homopolymerization of lactones [20]. Ethylene oxide and propylene oxide have been used as epoxide components.

## 2. Reactions of Polymers Containing γ-Lactone Groups

The model substance used for reactions of polymers containing γ-lactone groups was polymeric γ-(hydroxycrotono)lactone. All the reactions of γ-lactone groups, except the alkaline hydrolysis and the reaction with amines in water, require higher temperatures than those of β-lactone groups, so that considerable chain degradation occurs in many cases. The reactions can be followed quantitatively by IR spectroscopy (γ-lactone absorption at 1770 $cm^{-1}$).

### a) Reaction with Inorganic Acid Halides

Inorganic acid halides (*e.g.* $PCl_5$ or $SOCl_2$) react with poly-γ-(hydroxycrotono)lactone to give polymeric γ-halogenoacyl halides, from which the esters of the γ-halogeno acids can be directly obtained by treatment with alcohol (see Scheme 2,a).

### b) Reaction with Alcohols

When gaseous hydrogen chloride is led into an ethanolic suspension of poly-γ-hydroxycrotonolactone in the presence of $ZnCl_2$, the polymer dissolves, but is precipitated unchanged on addition of ether. However, if the solution is heated for several hours under reflux, the polymeric ester of the γ-hydroxycarboxylic acid and a little of the ester of the γ-chlorocarboxylic acid are formed (see Scheme 2,b).

### c) Reaction with Alkali Metal Hydroxides

Polymeric γ-hydroxycrotonolactone dissolves in aqueous sodium hydroxide solution on gentle heating to give the Na salt of the corresponding polymeric γ-hydroxy acid (see Scheme 2,c). The original polymer is recovered quantitatively on acidification.

### d) Reaction with Salts

When a suspension of poly-γ-hydroxycrotonolactone in aqueous potassium cyanide solution is heated, the polymer dissolves within two hours; the only product is the salt of the γ-hydroxycarboxylic acid, from which the original polymer can be recovered by acidification. However, the salt of the γ-cyanocarboxylic acid can be

[19] *H. Cherdron* and *H. Ohse*, Makromolekulare Chem. *92*, 213 (1966).

[20] *H. Cherdron*, *H. Ohse*, and *F. Korte*, Makromolekulare Chem. *56*, 179, 187 (1962).

obtained in anhydrous dimethylformamide at 150 °C (Scheme 2,d).

e) Reaction with Amines

Poly-γ-hydroxycrotonolactone reacts with amines in aqueous media at 20 to 50 °C to give the ammonium salt of the polymeric γ-hydroxy acid (see Scheme 2,$e_1$). In organic solvents, *e.g.* in an excess of the amine, higher reaction temperatures are required, and the polymeric γ-hydroxy carboxamide is then formed (Scheme 2,$e_2$).

f) Reduction with Lithium Tetrahydridoaluminate

Polymeric crotonolactone can be smoothly reduced with $LiAlH_4$ in tetrahydrofuran to give a water-soluble polymer of 2-butene-1,4-diol (Scheme 2,f).

*We are grateful to Professor Korte for his interest in this work.*

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# Conformational Aspects of Many-Membered Rings[*]

BY PROF. J. DALE

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*The stereochemistry of the various chemical groupings which constitute the structural units of ring systems is first reviewed. It is then shown that the strain-free possibilities even of large rings are restricted, and that the ring conformations theoretically derived generally correspond to those found by physical methods. Variations of physical properties and of cyclization yield in homologous series are explained on a conformational basis.*

## Introduction

Although the conformational analysis of aliphatic six-membered rings has had a remarkable development [2,3] over the twenty years following *Hassel*'s demonstration [1] by electron diffraction that the chair is the normal stable form and that axial and equatorial substituents can be distinguished, the development has been much slower in other ring systems. In larger rings the understanding of conformational details was virtually lacking until *Dunitz*'s recent demonstration [4] by X-ray diffraction of a unique conformation of the ten-membered ring skeleton in a variety of cyclodecane derivatives. It is true that synthetic difficulties, certain anomalies in physical properties, and abnormal transannular reactions of medium (eight- to eleven-membered) rings had been rationalized vaguely as being due to compression in the interior of the ring and to the proximity of atoms across the ring, but the conformational details remained obscure.

The nature of the unique Dunitz conformation of cyclodecane (see below) is such that, as in the cyclohexane chair, the carbon skeleton follows quite closely the diamond lattice; however, since this involves too close an approach between some of the hydrogen atoms, a compromise is reached between angle opening, torsion of bonds, and hydrogen repulsion.

As shown in Fig. 1, a C–C–C angle opening of 5 ° demands only an energy of 0.5 kcal/mole, of 10 °, 1.9 kcal/mole, while eclipsing a single bond in saturated hydrocarbons costs 2.8 kcal/mole [5]. Oscillation of the C–C–C angle in a $CH_2$ chain (normally 112 °) between 100 and 124 °, therefore, is as easy as rotation about a single C–C bond.

Crystal structures of some other medium and large ring compounds have been determined [6] and have confirmed the view that the angular (Baeyer) and torsional (Pitzer) strain are well balanced and, if physically possible, are both totally absent. Knowledge of the most stable orientation about single bonds thus becomes particularly important, since the shape of a large ring depends much more on the orientation of the chain members about each bond than on the exact value of the bond angles.

[*] For previous reviews see *J. Sicher* in: Progress in Stereochemistry. Butterworths, London 1962, Vol. 3, p. 202; *R. A. Raphael*, Proc. chem. Soc. (London) *1962*, 97; *V. Prelog*, Pure appl. Chem. *6*, 545 (1963).

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[2] *D. H. R. Barton* and *R. C. Cookson*, Quart. Rev. *10*, 44 (1956).

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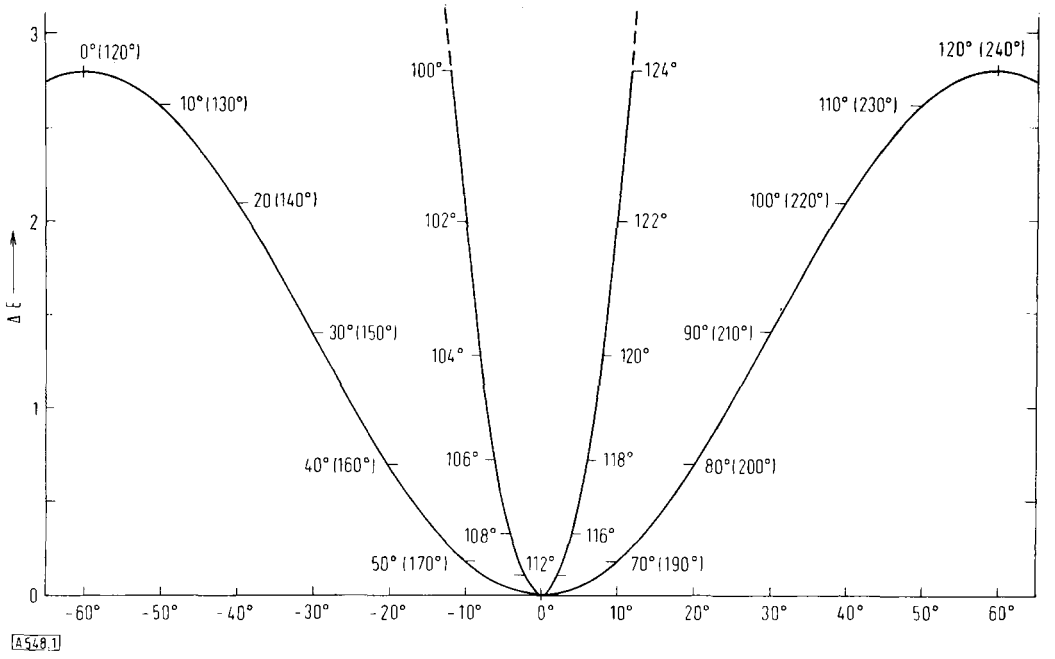


Fig. 1. Change in the potential energy (ΔE, in kcal/mole) of polymethylene chains with deviations from the equilibrium values of the valency angle (inner curve) and the dihedral angle (outer curve). The numbers on the curves are the actual angles.

## Some Basic Stereochemical Facts

The most reliable information about the basic stereochemistry of the various molecular units comes from direct physical methods such as X-ray diffraction, electron diffraction, and microwave spectroscopy (rotational spectra). Other spectroscopic methods, such as electronic spectra (ultraviolet and visible), vibrational spectra (infrared and Raman), and nuclear magnetic resonance spectra, can also yield useful information but are rarely of comparable precision. Conclusions have also been drawn from dipole moments and thermodynamic data.

The stable conformations of a C–C single bond in a saturated carbon chain are illustrated in Fig. 2 [7], which shows the potential wells for the staggered positions,

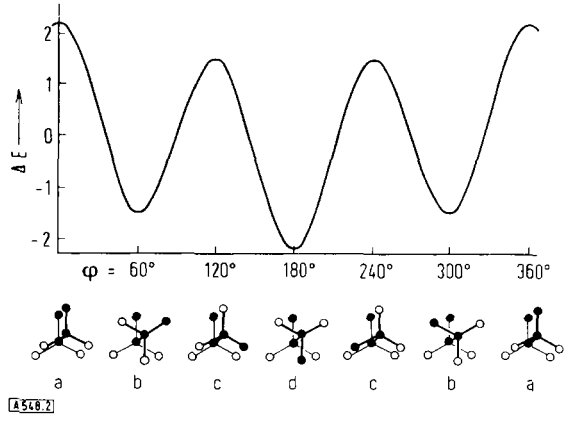


Fig. 2. Dependence of the potential energy (in kcal/mole) of a tetramethylene chain on the conformation of the central C–C bond [7]. The dihedral angle is denoted by φ.
*a* and *c*, eclipsed conformations; *b gauche* conformation; *d*, *anti* conformation.

[7] *M. Kobelt, P. Barman, V. Prelog*, and *L. Ruzicka*, Helv. chim. Acta *32*, 256 (1949).

separated, even in the case of ethane, by surprisingly high and theoretically unsatisfactorily explained barrier peaks at the eclipsed positions [8]. The lower energy of the *anti* (or *trans*) as compared to the two *gauche* conformations leads to a tendency for long paraffin chains to be essentially all-*anti* and extended at low temperatures, and this is unfavorable for cyclization. If the chain carries an alkyl branch, the adjacent C–C bond does not distinguish between the branch and the main chain, so that the probability of having a "kink" in the main chain, necessary for cyclization, increases; this is the simplest explanation for the *gem*-dimethyl effect [9] in cyclization processes. Carbon-carbon single bonds next to almost any group other than $CH_2$, $CH_3$, or heavy atoms (higher halogens), take up *gauche* as easily as *anti* conformations; thus a bend of the main chain becomes more probable next to double bonds, triple bonds, carbonyl groups, hetero-atoms, *etc.*, and cyclization is facilitated [10].

Fig. 3 shows how the stereochemistry of most of the structural elements and the adjoining atoms occurring in ring systems can be derived from that of saturated hydrocarbons by assuming that hydrogen atoms can be replaced with no essential stereochemical change by a lone electron pair in atoms like oxygen, nitrogen, and sulfur, and that double bonds can be considered as two bent bonds [11]. The barriers of rotation (kcal/mole) in the illustrated or in similar compounds are given at the bond in question. It is remarkable how similar they are, except those next to multiple bonds or to hetero-atoms engaged in partial conjugation (ester, amide), where the

[8] *D. J. Millen* in: Progress in Stereochemistry. Butterworths, London 1962, Vol. 3, p. 138.

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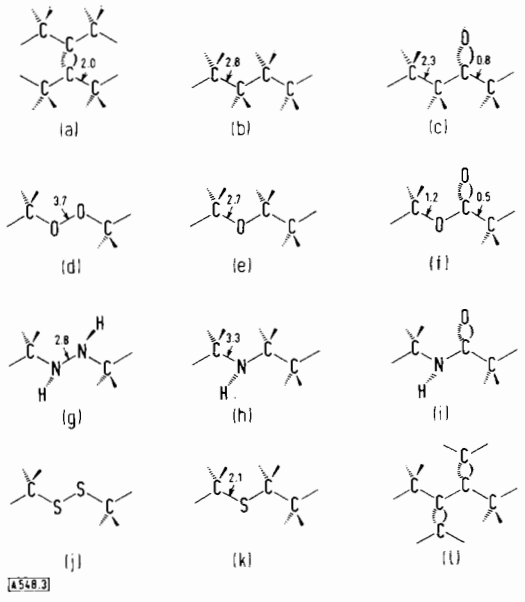


Fig. 3. Derivation of the stereochemistry of some structural elements from that of a saturated hydrocarbon. The numbers are energy barriers (kcal/mole) for rotation about the respective bonds.

values become much lower so as to make the chain more flexible. For the ether linkage (Fig. 3,e) both the rotational barrier and the conformation have been determined on dimethyl ether [12]; for the sulfide linkage (k) on dimethyl sulfide [13]; and the barrier in secondary amines (h) on dimethylamine [14].

Although only the *anti* conformation is shown in Fig. 3, it is likely that the *gauche* and *anti* conformations of the bond between carbon and hetero-atom in homologous compounds have comparable energies. Thus in crystalline polyoxymethylene [15] all C—O bonds are *gauche*: in polyethylene glycol [15] they are all *anti* (and the C—C bond *gauche*). The situation is less clear when two hetero-atoms are adjacent (Fig. 3; d, g, j). Thus it has been assumed generally that the torsional angle in hydrogen peroxide is 90 to 100 °. However, the observation that one of the possible values for the dihedral angle in hydrogen peroxide dihydrate [16] is 68 ° and that in sodium oxalate perhydrate [17] it is 180 ° indicates that it is a normal *anti-gauche* system; this is supported by the presence of perfectly chair-shaped six-membered tetraoxa rings in sodium peroxoborate [18] and in various dimeric cycloalkanone peroxides [19]. With hydrazine [20] there is agreement about a three-fold barrier and that *gauche* and *anti* forms coexist; even in bishydrazinezinc chloride [21] the torsional angle is 74 °. The situation is similar in tetrafluorohydrazine [22], but no conclusions could be reached for dimethylhydrazine [23]. For the disulfide group it has been assumed [24,25] that the normal dihedral angle is 90 °, although in some carbon-substituted open-chain systems like L-cystine [26] and its hydrochloride [27] it is as low as 74 and 79 °. In a six-membered 1,2-dithiane derivative, a perfect *gauche* value of 60 ° was found [25]. In linear polysulfides [28], too, the dihedral angles are all close to *gauche*, varying from 61 to 82 °.

Both hydrogens of a $CH_2$ group can be replaced by one bivalent group to form a double bond without disturbing the stereochemistry of the carbon chain, as shown for the ketone in Fig. 3,c. This basic carbon skeleton is the predominant one in methyl ethyl and diethyl ketone [29], and the same stereochemistry and low rotational barrier next to the carbonyl group has been established in numerous other carbonyl compounds, like aldehydes [30–32], acetyl derivatives [33,34], and acyl halides [30,33]. The barrier next to the carbonyl group (Fig. 3,c) was determined on acetone [14,35], that of the α,β bond on propionaldehyde [32]. For a double bond between two carbon atoms, the situation is similar (Fig. 3,a), but the torsional barrier in adjacent single bonds is only moderately reduced in mono- and *trans*-disubstituted [36] and 1,1-disubstituted [37] olefins, whereas it is much lower (0.6 to 1.4 kcal/mole) in *cis*-disubstituted olefins [36]. It is noteworthy that even in *cis*-2-butene [38] the conformation derived from Fig. 3,a is strictly obeyed even if this implies the closest possible hydrogen-hydrogen distance; conformers of higher 1-alkenes [39] follow the same pattern. Next to a C=N double bond the basic stereochemistry is the same, as is shown in the case of *N*-methylenemethylamine [40], with a torsional barrier for the adjoining single bond of 1.97 kcal/mole.

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[30] *E. B. Wilson*, Proc. nat. Acad. Sci. U.S.A. *43*, 816 (1957).

[31] *R. J. Abraham* and *J. A. Pople*, Molecular Physics *3*, 609 (1960).

[32] *S. S. Butcher* and *E. B. Wilson*, J. chem. Physics *40*, 1671 (1964).

[33] *L. C. Krisher* and *E. B. Wilson*, J. chem. Physics *31*, 882 (1959); *33*, 304 (1960).

[34] *O. L. Stiefvater* and *J. Sheridan*, Proc. chem. Soc. (London) *1963*, 368.

[35] *J. D. Swalen* and *C. C. Costain*, J. chem. Physics *31*, 1562 (1959).

[36] *R. A. Beaudet*, J. chem. Physics *38*, 2548 (1963); *40*, 2705 (1964).

[37] *V. W. Laurie*, J. chem. Physics *34*, 1516 (1961); *39*, 1732 (1963).

[38] *T. N. Sarachmann*, quoted in [36].

[39] *A. A. Bothner-By* and *C. Naar-Colin*, J. Amer. chem. Soc.*83*, 231 (1961); *A. A. Bothner-By, C. Naar-Colin*, and *H. Günther*, *ibid. 84*, 2748 (1962).

[40] *J.T. Yardley, J. Hinze*, and *R. F. Curl*, J. chem. Physics *41*, 2562 (1964).

If an oxygen atom is next to the double bond, enol ethers are obtained whose conformation should be as in Fig. 3,f. Esters show a strong preference for the planar *anti* conformation (unfortunately often referred to as *cis* in formates) [41–43], and it seems reasonable to attribute this to partial double bond character in the C–O bond next to the carbonyl group. Except for formic acid [44] and its ethyl ester [45], there is no evidence for another conformation in open chains; a planar *cis*-ester would give eclipsed single bonds, and a non-planar *gauche*-ester would not be able to acquire double-bond character. It has been pointed out [46] that in lactones with a six-membered ring the ester group is *cis*-planar, but the examples quoted are all fused-ring systems favoring a boat conformation. In methyl vinyl ether a second (unstable) form has been observed [43], presumably because resonance stabilization in the planar *anti* form is less important in a C=C–O than in an O=C–O system; it is interesting that the latter is not planar *cis*, but nonplanar *gauche*. The partial double-bond character is probably also responsible for the lowered torsional barriers in the adjacent single bonds of esters (Fig. 3,f), although these were not determined on higher esters, but on acetic acid [30] and methyl formate [42]. The crystal structures of aliphatic carboxylic acids [47] and dicarboxylic acids [48,49] also demonstrate that torsion of the C–C bond next to the carbonyl group is particularly easy; the carboxyl group is usually oriented as shown in Fig. 3,f, in or close to the plane of the methylene chain, but sometimes it is twisted by up to 30° by packing forces [48].

The *N*-monosubstituted amide group (Fig. 3,i) is completely analogous to the ester group. The *anti*-conformation is strongly favored [50,51], and again only in formamides is there evidence [51] for another less stable isomer, supposed to be planar *cis*. The torsional barriers are not known, but they seem to be low in the single bonds on both sides. Thus there are small deviations from the ideal *anti* and *gauche* values (180° and 60°) in the N–C(α) bond of acetamide-like compounds [52,53] and in the α-helix of proteins [54], and a stronger deviation in the C–C(α) bond of the α-helix [54]. In less stable protein structures the deviations are much greater [54]. Since the double-bond character of the C–N bond (of formamide [55]) is only 25 %, the *cis*-hydrogen on nitrogen (Fig. 3,i) is not expected to be coplanar with N–C=O; deviations from planarity have been observed in *N*-acetylglycine [53] and formamide [55].

A similar situation arises in conjugated diolefins in which the central single bond has a preference for the *transoid* (s-*trans* or s-*anti*) conformation shown in Fig. 3,l, since it has double bond character. "Resonance" being no doubt less important here than in amides and esters, the "other form" may even be non-planar *gauche* instead of planar *cis*. Only the *transoid* (*anti*) conformer has been found in butadiene itself by electron diffraction [56] and vibrational spectra [57], and a vain search for the *cis*-conformer by microwave spectroscopy has been reported [58]. Similarly, fluoroprene [58] and isoprene [59] are planar *anti*, and the well-known linear shape of all-*trans*-polyenes and carotenoids implies also *anti*-conformation of the single bonds. Isomerization of hydrocarbons having two double bonds in a 1,3-dimethylcyclohexane [60] or a decalin [61] skeleton shows a preference for positions where the conjugated diene can assume an *anti*-conformation. On the other hand, when in rings of more than five members a *cisoid* conformation is structurally imposed, there exists no evidence that the diene is planar; on the contrary, the low intensity of ultraviolet absorption of 1,2-dimethylenecyclohexane [62] suggests a non-planar "*gauchoid*" conformation. The crystal structure of calciferol [63] shows that an analogous "*cis*"-diene system is non-planar with a torsional angle of 54°, close to the *gauche* conformation, but here, of course, steric hindrance may play a role [*]. Steric hindrance also blurs the picture in the β-ionone ring of vitamin A acid [64] and lower homologues [65,66], but it is interesting that in one of the crystal structures the ring double bond is *anti* and almost coplanar with the polyene system of the chain [65], whereas in the other cases [64,66] it is *gauchoid* with torsional angles of *ca.* 35 and 80°. When a C=C double bond is conjugated with an aldehyde group, as in acrolein, *anti*-preference for the enclosed single bond has been established [67], but when it is conjugated with a carboxyl group, almost planar *cisoid* conformations have been observed [64,65], presumably because the torsional barrier is further reduced by resonance in the hydrogen-bonded carboxyl group. Delocalization of the double bonds

[41] *J. K. Wilmshurst*, J. molecular Spectroscopy *1*, 201 (1957).

[42] *R. F. Curl*, J. chem. Physics *30*, 1529 (1959).

[43] *N. L. Owen* and *N. Sheppard*, Proc. chem. Soc. (London) *1963*, 265.

[44] *T. Miyazawa* and *K.S.Pitzer*, J.chem.Physics *30*, 1076 (1959).

[45] *D.Tabuchi*, J. chem. Physics *28*, 1014 (1958).

[46] *A. M. Mathieson*, Tetrahedron Letters *1963*, 81.

[47] *F. J. Strieter, D. H.Templeton, R. F. Scheuermann*, and *R.L. Sass*, Acta crystallogr. *15*, 1233, 1240, 1244 (1962).

[48] *C. H. MacGillavry, C. Hoogschagen*, and *F. L. J. Sixma*, Recueil Trav. chim. Pays-Bas *67*, 869 (1948).

[49] *J. D. Morrison* and *J. M. Robertson*, J. chem. Soc. (London) *1949*, 980, 987, 993, 1001.

[50] *S. I. Mizushima, T. Simanouti, S. Nagakura, K. Kuratani, M.Tsuboi, H. Baba*, and *O. Fujioka*, J. Amer. chem. Soc. *72*, 3490 (1950), *J. E. Worsham* and *M. E. Hobbs, ibid. 76*, 206 (1954).

[51] *L. A. LaPlanche* and *M.T. Rogers*, J. Amer. chem. Soc. *86*, 337 (1964).

[52] *M. Bailey*, Acta crystallogr. *8*, 575 (1955).

[53] *J. Donohue* and *R.E.Marsh*, Acta crystallogr. *15*, 941 (1962).

[54] *T. Miyazawa*, J. Polymer Sci. *55*, 215 (1961).

[55] *C. C. Costain* and *J. M. Dowling*, J. chem. Physics *32*, 158 (1960).

[56] *A. Almenningen, O. Bastiansen*, and *M.Traetteberg*, Acta chem. scand. *12*, 1221 (1958).

[57] *D. J. Marais, N. Sheppard*, and *B. P. Stoicheff*, Tetrahedron *17*, 163 (1962).

[58] *D. R. Lide*, J. chem. Physics *37*, 2074 (1962).

[59] *R.J.W.LeFèvre* and *K.M.S.Sundaram*, J. chem. Soc. (London) *1963*, 3547; *D. R. Lide* and *M. Jen*, J. chem. Physics *40*, 252 (1964).

[60] *O. H. Wheeler*, J. org. Chemistry *20*, 1672 (1955).

[61] *R. B. Bates, R. H. Carnighan*, and *C. E. Staples*, J. Amer. chem. Soc. *85*, 3030 (1963).

[62] *W. J. Bailey* and *H. R. Golden*, J. Amer. chem. Soc. *75*, 4780 (1953); *A.T.Blomquist* and *D.T.Longone, ibid. 79*, 3916 (1957).

[63] *D. Crowfoot Hodgkin, B. M. Rimmer, J. D. Dunitz*, and *K.N. Trueblood*, J. chem. Soc. (London) *1963*, 4945.

[*] *Added in proof*: A recent microwave investigation led to a non-planar diene system also for 1,3-cyclohexadiene itself. The dihedral angle is only 18°. *S. S. Butcher*, J. chem. Physics *42*, 1830 (1965).

[64] *C. H. Stam* and *C. H. MacGillavry*, Acta crystallogr. *16*, 12 (1963).

[65] *E. L. Eichhorn* and *C. H. MacGillavry*, Acta crystallogr. *12*, 872 (1959).

[66] *B. Koch* and *C. H. MacGillavry*, Acta crystallogr. *16*, A 48 (1963).

[67] *J. Fine, J. H. Goldstein*, and *J.W.Simmons*, J. chem. Physics *23*, 601 (1955).

must also be held responsible for the free or nearly free internal rotation of methyl substituents in aromatic systems, *e.g.* in methylpyridines[68]. Similarly, methyl groups next to trigonal boron, as in trimethylboron[69], and to cylindrically symmetrical sp carbon atoms, as in dimethylacetylene[70], are essentially free to rotate.

## Cycloalkanes and Simple Substituted Derivatives

The only strain-free saturated carbon skeletons are those which can be derived from the diamond lattice[10]. This means that only even-membered carbon rings $C_6$ and higher can have skeletons without torsional strain, but the 8-, 10-, and 12-membered (medium) rings are strained because of repulsion between hydrogen atoms pointing "inwards" (Fig. 4 and 5).

In rings larger than the 14-membered ones, many of the strain-free skeletons that can be derived using space-filling models, which do not allow torsional or angular strain[10], are supposedly unstable because they either contain more *gauche*-bonds than the necessary minimum or have too open structures that do not fill space efficiently. Adopting this *horror vacui* postulate, one arrives at the conclusion[10] that only the 14-, 18-, 22-, 26-, *etc.* membered rings can have the ideal "rectangular" conformation shown in Fig. 4, with two parallel long chains roughly at van der Waals distance linked at each end by $C_2$ bridges. The 16-, 20-, 24-, *etc.* membered rings must have $C_3$ bridges if they are to be without torsional strain, or may prefer to collapse, adopting some strain in order to have $C_2$ bridges and better internal van der Waals contacts (Fig. 5). Cyclododecane may change similarly to avoid the three hydrogen-hydrogen repulsions (Fig. 5).

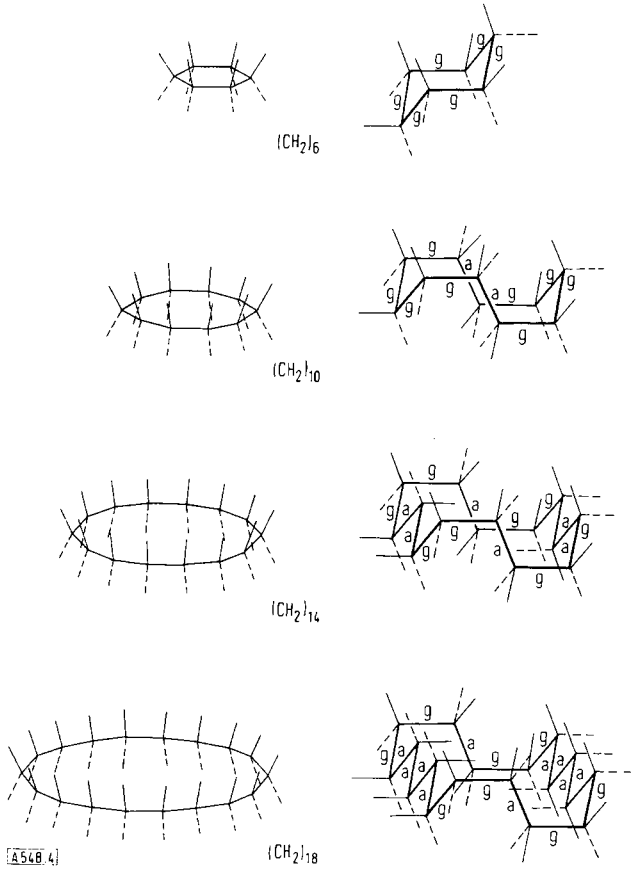



Fig. 4. Conformations of strain-free and compact cycloalkanes of general formula $(CH_2)_{4n+2}$. Right: actual conformation; left: hypothetical planar conformation. D and L substituents are indicated by —— and - - -, respectively. *g*, Bond, with *gauche* conformation; *a*, bond with *anti* conformation.

Structural determinations have confirmed the first three conformations in Fig. 4. The ring conformations of several derivatives of cyclodecane have been found to be almost identical and close to the ideal skeleton shown in Fig. 4. The crystal structures determined so far include two different modifications of *trans*-1,6-cyclodecanediammonium dichloride[71], the corresponding *cis*-isomer[72], cyclodecylammonium chloride[73], and *trans*-1,6-dibromocyclodecane[74]. The observed maximum C–C–C angle opening (to 120°) and deviation from a staggered position (up to 29°) both represent strains of about 1.3 kcal/mole (Fig. 1) and are therefore balanced. The crystal structure found for cyclotetradecane[75], as well as for the structurally equivalent 1,8-diazacyclotetradecane dihydrobromide[76], is very close to the quasi-rectangular one derived in Fig. 4, third row; in the latter compound, the cationic nitrogen atoms occupy the corner positions. For several higher cycloalkanes, early X-ray results[77] suggested two parallel straight polymethylene chains at van der Waals distance, but gave no details of the folding at each end. The recently determined crystal structure of cyclotetratriacon-

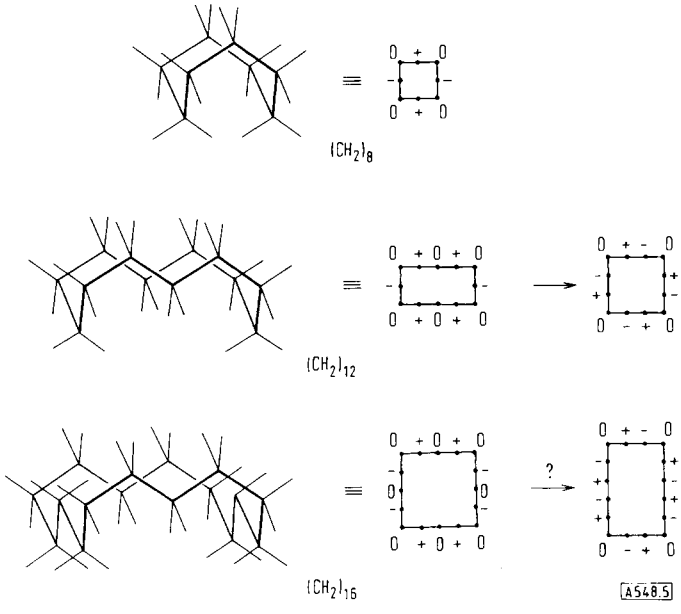



Fig. 5. Conformational possibilities of cycloalkanes $(CH_2)_{4n}$. The carbon atoms in the projections on the right-hand side are marked with reference to a plane through the corner atoms; + denotes above, — denotes below the plane.

[68] *D. W. Scott et al.*, J. physic Chem. *67*, 680, 685 (1963).

[69] *L. S. Bartell, B. L. Carroll*, and *J. P. Guillory*, Tetrahedron Letters *1964*, 705.

[70] *R. Kopelman*, J. chem. Physics *41*, 1547 (1964).

[71] *E. Huber-Buser* and *J. D. Dunitz*, Helv. chim. Acta *43*, 760 (1960); *44*, 2027 (1961).

[72] *J. D. Dunitz* and *K. Venkatesan*, Helv. chim. Acta *44*, 2033 (1961).

[73] *M. H. Mladeck* and *W. Nowacki*, Helv. chim. Acta *47*, 1280 (1964).

[74] *J.D.Dunitz* and *H.P.Weber*, Helv. chim. Acta *47*, 951 (1964).

[75] *B. A. Newman* (Bristol), unpublished.

[76] *J. D. Dunitz* and *E. F. Meyer* (Zürich), unpublished.

[77] *A. Müller*, Helv. chim. Acta *16*, 155 (1933).

tane ($C_{34}$) has confirmed this[75] and established that the folding consists of the bond sequence

... *gauche, gauche, anti, gauche, gauche*, ...

as shown in Fig. 4. Since the cycloalkanes of the series $(CH_2)_{4n+2}$, therefore, seem to possess well-defined centrosymmetrical conformations, L and D substituents (on either side of the hypothetical flat ring which the Fischer and Haworth projections are based upon) have been marked in Fig. 4 in order to facilitate the discussion of steric relationships.

In the series of cycloalkanes $(CH_2)_{4n}$ (Fig. 5) the situation is less clear. Only for cyclododecane are conclusive X-ray results available[78]. Its approximately square conformation (Fig. 6,a) although deviating systematically from the diamond lattice, seems to be typical for this ring size, since it is also found in azacyclododecane

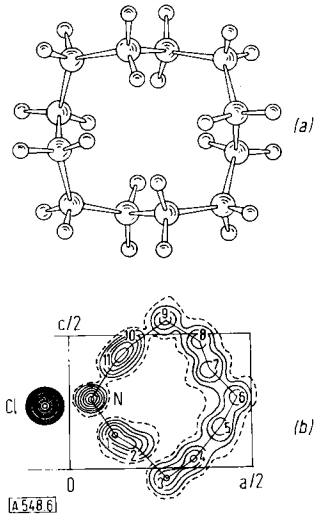



Fig. 6. Crystal structure of (a) cyclododecane [94] and (b) azacyclododecane hydrochloride [95].

hydrochloride[79], with the cationic $\overset{\oplus}{N}H_2$ group at a corner position (Fig. 6,b). In both compounds the torsional strain is similar to that found in cyclodecane derivatives, but the maximum bond angle is smaller (116–117°). In higher homologues $(CH_2)_{4n}$ the same amount of strain might be distributed over more bonds, and the regular increase of the longest period in the crystal lattice[77] suggests that the torsionally strained $C_2$ bridged compact conformations are preferred to the unstrained $C_3$ bridged open conformations.

For cyclooctane the conformational situation is still undecided; evidence has been obtained both for the saddle form[10,80] derived from the diamond lattice (shown in Fig. 5), and for a crown form[81]. In the isoelectronic cation of azacyclooctane hydrobromide, a twisted crown is indicated[6]. Machine computation, taking into account bond angle, torsional strain, and hydrogen repulsion, showed[82] that several cyclooctane conformations have comparable energies[*], and electron diffraction data on the gas could not be explained by any one single model, but fairly well with a mixture of several models[83][*].

The lowest member, cyclobutane, provides a striking demonstration of the necessity of the C–C single bonds to get away from the completely eclipsed conformations of a planar structure even at the expense of further reduction of the already very strained C–C–C angles to below 90°. Thus cyclobutane itself[84] is non-planar, and the angle between the planes of the two halves is 29° in bromocyclobutane[85].

The inherent strain in odd-membered cycloalkanes can be distributed in various ways without, or with only little, difference in energy. This uncertainty, or travelling of an "imperfection", has been termed pseudo-rotation and was first recognized in cyclopentane[86]. When substituents are introduced, certain symmetries, "envelope" and "half-chair"[86,87] are preferred. The detailed calculations by *Hendrickson* have led to a deeper understanding of pseudo-rotation also in the cyclohexane flexible form[5] (between "classical" and "twisted" boat), in the two conformational families ("boat" and "chair") of cycloheptane[5], and in medium rings[82]. The undetermined nature of odd-membered rings is also reflected in the crystal structure of cyclononylammonium bromide[88], which contains two similar conformers with C–C–C, angles up to 124° and deviations up to 44° from the staggered position of the bonds.

The alternation in conformational stability between even- and odd-membered rings is reflected in the melting points (sometimes a transition point), particularly of the larger rings[10]. Singly substituted cycloalkanes as well as saturated macro-heterocycles behave similarly[10].

## Cyclic Ketones

The cycloalkanones show a remarkable similarity with the cycloalkanes in melting point behavior[10]. The $CH_2$-scissoring vibration also follows the same splitting pattern through the medium ring region in the two series[89], and the higher symmetrical cyclic diketones ($C_{24}$, $C_{28}$) show the same feature of two parallel long

[78] *J. D. Dunitz* and *H. M. M. Shearer*, Helv. chim. Acta *43*, 18 (1960).

[79] *J. D. Dunitz* and *H. P. Weber*, Helv. chim. Acta *47*, 1138 (1964).

[80] *J. Dale, I. Laszlo*, and *W. Ruland*, Proc. chem. Soc. (London) *1964*, 190.

[81] *N. L. Allinger, S. P. Jindal*, and *M. A. DaRooge*, J. Amer. chem. Soc. *27*, 4290 (1962).

[82] *J. B. Hendrickson*, J. Amer. chem. Soc. *86*, 4854 (1964); cf. also *K. B. Wiberg*, *ibid. 87*, 1070 (1965).

[*] If the value 112°, instead of 109.5°, for the preferred C–C–C angle had been used, the result might have been different.

[83] *O. Bastiansen* and *H. Jensen* (Oslo), unpublished.

[*] *Added in proof*: Recently, a hybrid saddle-crown conformation (boat-chair form) has been established for the eight-membered ring in dimeric cyclooctanone peroxide (*P. Groth*, Acta chem. scand. *19*, 1497 (1965)) and in cyclooctane-1,2-*trans*-dicarboxylic acid (*J. D. Dunitz* and *A. Mugnoli*, Chem. Commun. *1966*, 166). On the other hand, the low-temperature NMR-data reported for perfluorocyclooctane (*A. Peake, J. A. Wyer*, and *L. F. Thomas*, Chem. Commun. *1966*, 95) can, in the writer's opinion, only be accounted for by a saddle conformation.

[84] *A. Almenningen, O. Bastiansen*, and *P. N. Skancke*, Acta chem. scand. *15*, 711 (1961).

[85] *W. G. Rothschild* and *B. P. Dailey*, J. chem. Physics *36*, 2931 (1962).

[86] *K. S. Pitzer* and *W. E. Donath*, J. Amer. chem. Soc. *81*, 3213 (1959).

[87] *F. V. Brutcher, T. Roberts, S. J. Barr*, and *N. Pearson*, J. Amer. chem. Soc. *81*, 4915 (1959).

[88] *R. F. Bryan* and *J. D. Dunitz*, Helv. chim. Acta *43*, 3 (1960).

[89] *G. Chiurdoglu, T. Doehard*, and *B. Tursch*, Bull. Soc. chim. France *1960*, 1322.

chains at van der Waals distances in the crystal [77], although details of the end folding and the location of the carbonyl groups are not known. In medium rings one would expect the carbonyl groups to occupy positions where transannular hydrogen repulsion could be relieved. In fact, the ultraviolet absorption of cyclodecane-1,2-dione indicates an *anti*-planar dicarbonyl system [90], which only fits the cyclodecane skeleton when two "interior" hydrogen atoms are removed (Fig. 7).

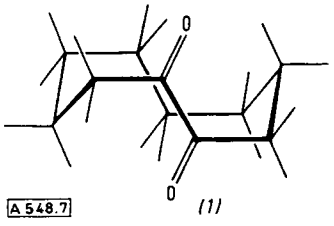



Fig. 7. Suggested conformation of cyclodecane-1,2-dione [90].

In view of the low torsional barrier in bonds adjacent to carbonyl groups, eclipsed bonds occur more easily; thus cyclobutanone is planar [91], cyclopentanone should prefer the "half-chair" and not the "envelope" conformation [87], and even 3,3,5,5-tetramethylcyclopentane 1,2-dione is planar [92]. In cyclohexanone the chair form should be of lowest enthalpy [86,93], having the single bonds adjoining the C=O group in their preferred conformation. However, the flexible boat form will be less Pitzer-strained than in cyclohexane, and since its entropy is favorable [94], the equilibrium may contain the boat form [95]. Most of the established cases of cyclohexane boat forms in non-condensed systems are ketones [95]. Neither *cis*- nor *trans*-2,5-dimethylcyclohexane-1,4-dione occur in the chair form [96]. Cyclohexane-1,4-dione itself has a substantial dipole moment in solution [97], and occurs as a distorted boat in the solid [98].

In larger rings, however, the flexibility introduced with the keto-group does not seem to manifest itself. When there is more than one carbonyl group in the ring, dipole interaction may stabilize or destabilize particular conformations [10].

## Lactones and Cyclic Polyesters

The planar *anti*- or *trans*-ester system can only be accommodated in rings of ten and more members by replacement of two $CH_2$ groups of the cycloalkane skeleton (Fig. 4). In fact, the 10-membered lactone is the first of the series of saturated monolactones [99] to be solid at room temperature (m.p. 32 °C). The discontinuities in boiling point, dipole moment, and rate of hydrolysis as function of ring size indicate that the transition from the less stable *cis*-ester configuration is completed in the 10-membered ring [100]. The low melting point (2 °C) [101] of the 12-membered monolactone is probably due to the considerable departure from planarity (155–163 ° instead of 180 °) in the *anti*-bonds. These bonds, where most of the Pitzer strain is concentrated, are the only places where the *anti*-ester group can be fitted into the molecule. In the 14-membered monolactone (m.p. 28 °C) [101] there are three possibilities of accommodating a strictly planar *anti*-ester group (Fig. 4).

The simplest ring systems containing two ester groups are the dilactones *(2)* (Fig. 8) and, with one ester group

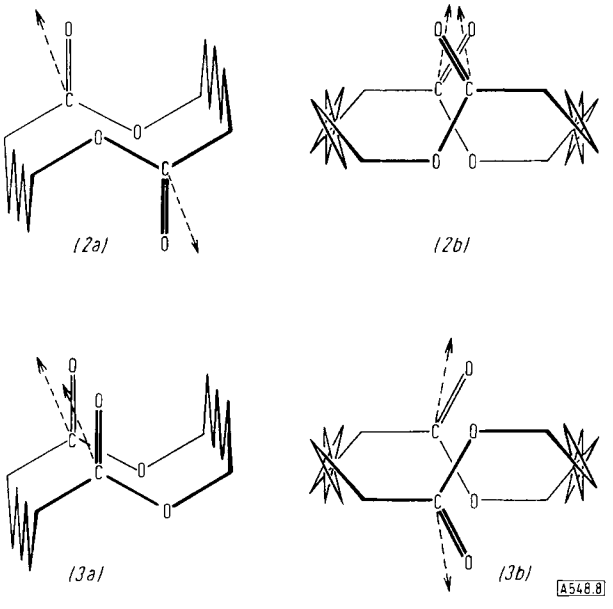



Fig. 8. Conformations of dilactones (top) and cyclic diesters (bottom). Left: odd number of $CH_2$ groups between ester groups; right: even number of $CH_2$ groups [102].

turned around, the symmetrical diesters *(3)*. In both series, the ester groups should tend to form the bridges between two parallel polymethylene chains at van der Waals distance, as the necessary *gauche* bonds at the corners are then obtained at no extra expense. When the number of $CH_2$ groups in each half is odd, there is no strain, but when it is even, there must be skeletal strain except if three-atom bridged open (hence unstable) conformations are adopted. The alternation of melting points (Fig. 9) of the dilactones [99] confirms this conclusion; the alternation may be accentuated in this case by dipole interaction [10]. In the series of symmetrical diesters *(3)* [102], the alternation has disappeared or become inverted (Fig. 9); although it is expected [10] that dipole interaction should in this case counteract

[90] *W. H. Urry, D. J. Trecker*, and *D. A. Winey*, Tetrahedron Letters *1962*, 609.
[91] *A. Bauder, F. Tank*, and *H. H. Günthard*, Helv. chim. Acta *46*, 1453 (1963).
[92] *L.C.G. Goaman* and *D.F. Grant*, Tetrahedron *19*, 1531 (1963).
[93] *W. D. Cotterill* and *M. J. T. Robinson*, Tetrahedron *20*, 765, 777 (1964).
[94] *N. L. Allinger* and *L. A. Freiberg*, J. Amer. chem. Soc. *82*, 2393 (1960).
[95] *J. Dale*, J. chem. Soc. (London) *1965*, 1028.
[96] *R. D. Stolow* and *M. M. Bonaventura*, Tetrahedron Letters *1964*, 95.
[97] *O. Hassel* and *E. Naeshagen*, Tidsskr. Kjemi, Bergves. Metallurgi *10*, 81 (1930).
[98] *P. Groth* and *O. Hassel*, Acta chem. scand. *18*, 923 (1964).
[99] *M. Stoll* and *A. Rouvé*, Helv. chim. Acta *18*, 1087 (1935).
[100] *R. Huisgen* and *H. Ott*, Tetrahedron *6*, 253 (1959).
[101] *H. Hunsdiecker* and *H. Erlbach*, Chem. Ber. *80*, 129 (1947).
[102] *J. Dale*, J. chem. Soc. (London) *1965*, 72.

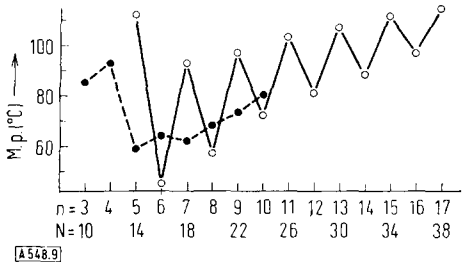



Fig. 9. Melting points of (o) dilactones and (●) symmetrical cyclic diesters [102].

Abscissa: Upper row number of $CH_2$ groups between ester groups in one half of the molecule, $n$; lower row, total number of ring members, $N$.

the alternation, the effect should be noticeable only in the lower members where the dipoles are close. The dipole moments [102] of the dilactones and symmetrical

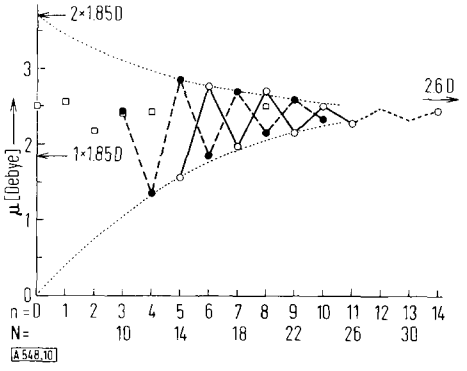



Fig. 10. Dipole moments of (o) dilactones, (●) symmetric cyclic diesters, and (□) open-chain diesters $H_5C_2O_2C-(CH_2)_n-CO_2C_2H_5$ [102].

Abscissa: Upper row, number of $CH_2$ groups between two ester groups, $n$; lower row, total number of ring members, $N$.

diesters (Fig. 10) are in agreement with the predictions from the models *(2)* and *(3)*. Also, X-ray results on the dilactones [103] show that, apart from the lowest members (number of $CH_2$ groups, $n$, five or six in each chain), they form two series, $n$ odd and $n$ even, in each of which there is a fixed increment of one unit cell dimension, corresponding to the increasing length of straight polymethylene chains as the series is ascended. The crystal structure of jacobine bromhydrin *(4)* [104], which contains a 12-membered diester ring, confirms the similarity with the parent hydrocarbon and the orientation of the

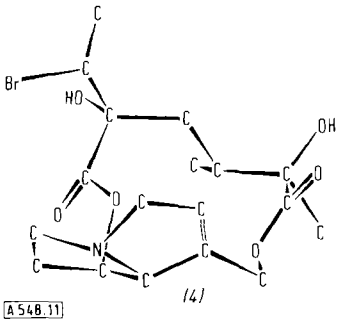



Fig. 11. Crystal structure of jacobine bromhydrin [104].

planar *anti*-ester groups (Fig. 11), although at one corner the ring is heavily strained by fusion with two 5-membered rings.

## Lactams, Cyclic Amides, Peptides, and Depsipeptides

The introduction of one or more amide groups into a cycloalkane should have the same conformational consequences as discussed for the ester group, but the intramolecular dipole interactions are expected to be more pronounced. Intermolecular hydrogen bonding should increase the heat of fusion and obscure subtle variations in the conformational part of the entropy of melting and, consequently, in the melting point alternation [101]. The smallest of the simple monolactams which has a

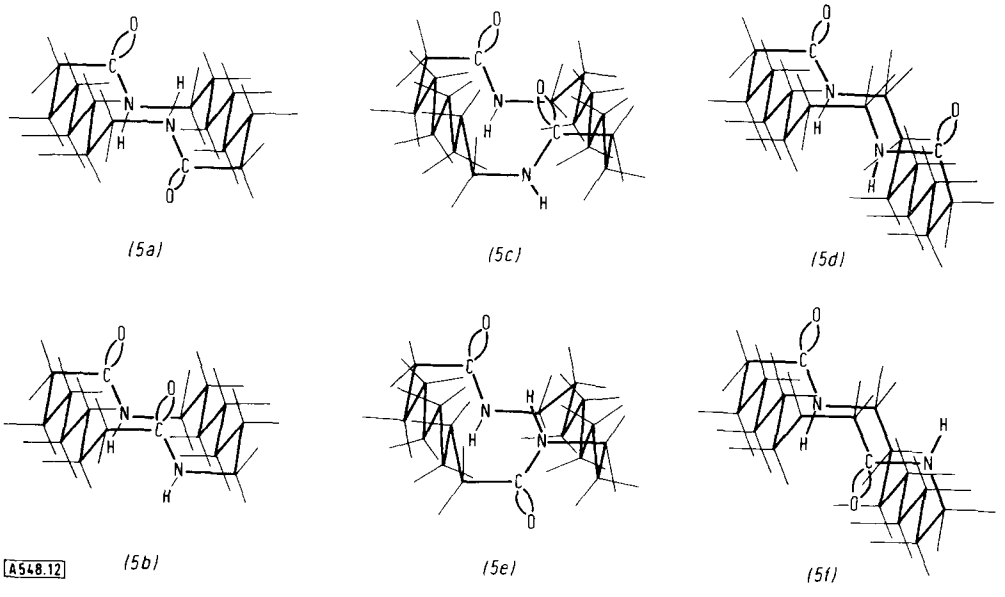



Fig. 12. Conformations of dilactams (top) and cyclic diamides (bottom) with odd (left) and even (middle and right) number of $CH_2$ groups between the amide groups in each half of the molecule [109].

[103] *G. S. D. King* (Brussels), unpublished.

[104] *J. Fridrichsons, A. M. Mathieson,* and *D. J. Sutor,* Acta crystallogr. *16*, 1075 (1963).

high melting point[105,106] is the nine-membered ring, which is also the first to allow the stable *anti*- (or *trans*-) amide configuration in the solid[106]; however, no melting point alternation is observed[105] in higher monolactams. Dielectric constants[107] and infrared and ultraviolet spectra[106] show that the ten-membered ring is the smallest one present exclusively with an *anti*-amide group in solution, as was also observed for the *anti*-ester group.

The accentuated melting point alternation predicted[10] for the series of macrocyclic dilactams of the type *(5a)*

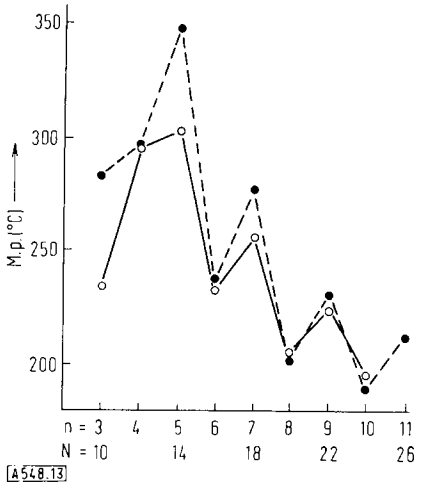
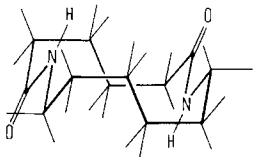



Fig. 13. Melting points of (●) dilactams [108] and (o) symmetrical cyclic diamides [109]. The figure differs from that in [109] in that the melting point of the highest dilactam (212 °C) [110] has been included, and the melting point of the lowest diamide (233—234 °C) [111] has been corrected.

Abscissa: Upper row, number of $CH_2$ groups between the amide groups in each half of the ring, *n*; lower row: total number of ring members, *N*.

and *(5c)* (Fig. 12) has been confirmed[108] (Fig. 13), as has the attenuated alternation expected for the symmetrical cyclic diamides, *(5b)* and *(5e)*,[109] (Fig.13); the difference between the two series disappears as the amide dipoles become separated by longer saturated chains. By studying the $CH_2$-scissoring infrared bands assigned[112] to the *gauche*- and *anti*-conformations on either side of the amide group, and by using polarized infrared radiation, it was shown[113] not only that the 14-, 18-, and 26-membered dilactams have *gauche* bonds in both the N and C=O vicinal positions and, therefore, have conformations of the type *(5a)*, but also that this holds for the 12- and 16-membered dilactams, so that these have the compact strained conformations *(5c)*, and not the open strain-free ones *(5d)*. The same result was obtained[109] from an infrared study of association of cyclic diamides in dilute solution. Whereas the very stable 14-membered caprolactam dimer showed conformational homogeneity at least up to its melting point (348 °C), the 18-membered homologue has also an unstable crystal modification with C=O vicinal *anti* bonds[113]. This increasing flexibility with ring size is likewise seen in the 26-membered dilactam, which seems to contain not exclusively *anti* bonds within the polymethylene chains[113].

In the higher cyclic caprolactam oligomers the number of *anti* bonds increases[113], as is expected for stretched double chains, and the same is true for the cyclic oligoamides of adipic acid and hexamethylenediamine (Nylon 6,6). The lowest member of this latter series, the 14-membered diamide, has the C=O vicinal bonds only in *gauche* orientation[113]. At 150 °C the N-vicinal bonds are also *gauche*, but become increasingly *anti* at lower temperatures, so that at very low temperatures the only strain-free conformation, *(6)* (Fig. 14), is

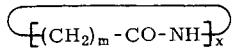



*(6)*

Fig. 14. Suggested low-temperature conformation of hexamethylene adipamide.

adopted. The inherent well-known instability[114] of this isomer, compared with the caprolactam dimer of the same size, seems to stem from the presence of two extra non-vicinal *gauche* bonds and a less favorable dipole orientation.

Melting point alternations in homologous series of oligolactams have already been interpreted in detail[10] for the case of ε-aminocaproic acid[115] and ω-aminoundecanoic acid[116]. Recently, data have become available also for β-alanine[108], γ-aminobutyric acid[108], and δ-aminovaleric acid[117], and the following generalization can be made: In the general series




*(6a)*

high conformational stability, hence high melting points and high synthetic yields are expected when the number of ring atoms, $x(m + 2)$, is 14, 18, 22, 26, 30, *etc.* In addition, it is advantageous when the *gauche* bonds forming corners are not from the interior of the polymethylene chains, but those adjoining the amide groups, and this is only possible when *m* is odd (both "bridges" consist then of amide groups) or with $m = 4$ (one "bridge" only is an amide group). It can be seen from

[105] *L. Ruzicka, M. Kobelt, O. Häfliger*, and *V. Prelog*, Helv. chim. Acta *32*, 544 (1949).

[106] *R. Huisgen, H. Brade, H. Walz*, and *I. Glogger*, Chem. Ber. *90*, 1437 (1957).

[107] *R. Huisgen* and *H. Walz*, Chem. Ber. *89*, 2616 (1956).

[108] *M. Rothe*, Angew. Chem. *74*, 725 (1962).

[109] *J. Dale* and *R. Coulon*, J. chem. Soc. (London) *1964*, 182.

[110] *H. Zahn, H. D. Stolper*, and *G. Heidemann*, Chem. Ber. *98*, 3251 (1965).

[111] *G. I. Glover* and *H. Rapoport*, J. Amer. chem. Soc. *86*, 3397 (1964).

[112] *G. Heidemann* and *H. Zahn*, Makromol. Chem. *62*, 123 (1963).

[113] *G. Heidemann et al.* (Aachen), unpublished.

[114] *D. Heikens, P. H. Hermans*, and *H. A. Veldhoven*, Makromol. Chem. *30*, 154 (1959).

[115] *H. Zahn* and *J. Kunde*, Liebigs Ann. Chem. *618*, 158 (1958).

[116] *H. Zahn, H. Roedel*, and *J. Kunde*, J. Polymer Sci. *36*, 539 (1959).

[117] *M. Rothe* and *R. Hossbach*, Makromol. Chem. *70*, 150 (1964).

Table 1. Melting points (°C) of oligolactams *(6a)* and of cyclic peptides ($m = 1$). Number of ring atoms, $N = (m + 2)x$. The underlining signifies conformational stability (——, *anti*-amide; - - - -, *cis*-amide).

| $m$ | 1 | | 2 | | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| x | M.p. (°C) | (N) | M.p. (°C) | (N) | M.p. (°C) | (N) | M.p. (°C) | (N) | M.p. (°C) | (N) |
| 1 | | (3) | | (4) | 24 | (5) | 40 | (6) | 69 | (7) |
| 2 | | (6) | 299 | (8) | 283 | (10) | 296 | (12) | 348 | (14) |
| 3 | | (9) | >360 | (12) | 243 | (15) | 331 | (18) | 244 | (21) |
| 4 | | (12) | >360 | (16) | 255 | (20) | 267 | (24) | 257 | (28) |
| 5 | | (15) | | (20) | | (25) | | (30) | 254 | (35) |
| 6 | | (18) | | (24) | 295 | (30) | | (36) | 260 | (42) |
| 7 | | (21) | | (28) | | (35) | | (42) | 237 | (49) |
| 8 | | (24) | | (32) | | (40) | | (48) | 230 | (56) |
| 9 | | (27) | | (36) | | (45) | | (54) | 226 | (63) |
| 10 | | (30) | | (40) | | (50) | | (60) | | (70) |

Table 1 that the melting points of conformationally favored compounds are in fact higher than those of their immediate neighbors.

The cyclic peptides ($m = 1$) decompose at or before the melting point. The remarkable stability of cyclohexaglycyl[118], and the general preference[10, 119] for the formation, sometimes by doubling reactions, of hexa- and deca-peptides, thus finds a surprisingly simple explanation without the usual assumptions of intramolecular hydrogen bonding and dipole interaction. In the recently determined crystal structure of cyclohexaglycyl hemihydrate[120] the pseudo-cell contains two different centrosymmetrical molecules with planar *anti*-amide groups (Fig. 15). In one molecule (a) there

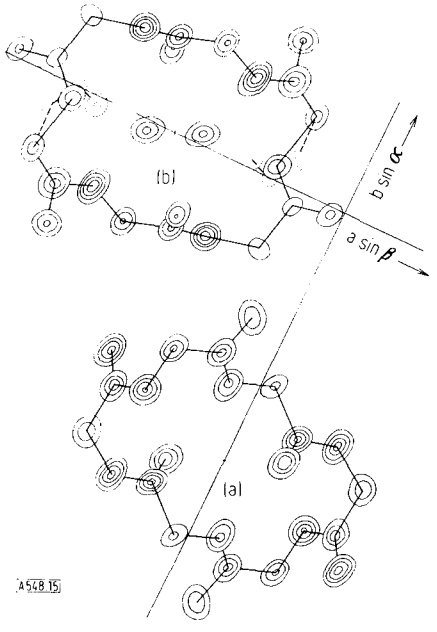



Fig. 15. Crystal structure of cyclohexaglycyl hemihydrate [120].
(a) Conformation with two weak intramolecular hydrogen bridges; (b) conformation without intramolecular hydrogen bridge. The two regions of high electron density in the center are water molecules above and below the ring.

are two weak internal hydrogen bonds, and the conformation is intermediate between the "crowded", flat, Pitzer-strained molecule and the "rectangular" puckered cyclooctadecane conformation (Fig. 16), and is quite different from other

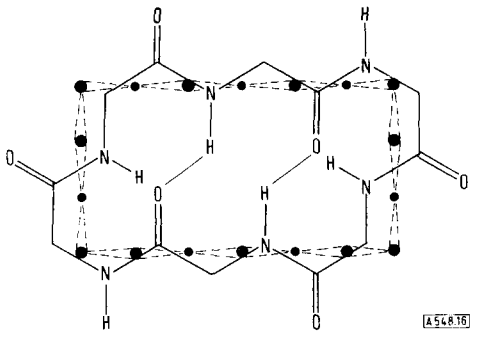



Fig. 16. The hypothetical flat cyclohexaglycyl molecule (full line) compared with the puckered cyclooctadecane conformation (broken line).

proposed[119] conformations. The second molecule (b) has no internal hydrogen bonds, but instead is hydrogen-bonded with water molecules. It may perhaps be concluded that in aqueous solution no internal hydrogen bonds exist, in accord with the finding[121] that *N*-methylacetamide is not associated in aqueous solution.

When α-amino acid residues other than glycine occur in cyclic peptides, size and orientation (D or L) of the substituents must also be considered. Fig. 17, formula

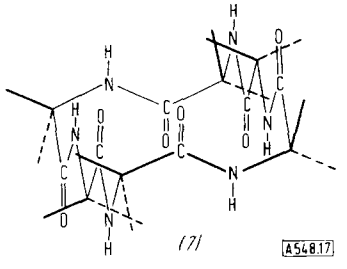



Fig. 17. Idealized conformation of a cyclic hexapeptide with D and L substituents marked —— and - - - -, respectively.

*(7)*, shows the idealized conformation of a cyclic hexapeptide with D- and L-substituents indicated; in the corners bulky substituents of any configuration can be accommodated, but the two remaining substituents must have opposite configuration if they are bulky. The frequent occurrence of D-amino acids in natural cyclic polypeptides[119] and depsipeptides[122], in contrast to their absence in open-chain polypeptides, and the high synthetic yield obtained in the cyclization of oligopeptides with mixed configuration, may, in part, be linked with this conformational feature.

The strong tendency for doubling in the cyclization of tri- and pentapeptides with formation of cyclic hexa- and decapeptides was explained by *Schwyzer*[119] as being due to a preceding hydrogen-bond association of two molecules. However, a concerted reaction of both ends of two peptide chains seems unlikely, and it has already been shown[121] that peptide association is insignificant in water solution and weak in tetrahydrofuran and dioxane, while doubling occurs even in water and methanol[123]. Recently, it has been demon-

[118] *C. H. Bamford* and *F. J. Weymouth*, J. Amer. chem. Soc. *77*, 6368 (1955).

[119] *R. Schwyzer*, Record chem. Progr. *20*, 147 (1959).

[120] *I. L. Karle* and *J. Karle*, Acta crystallogr. *16*, 969 (1963).

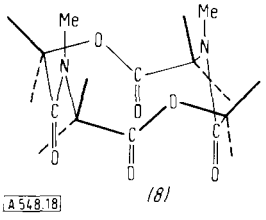
[121] *I. M. Klotz* and *J. S. Franzen*, J. Amer. chem. Soc. *82*, 5241 (1960); *84*, 3461 (1962).

[122] *Yu. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryushkin*, and *M. M. Shemyakin* in *G. T. Young*: Peptides. Proc. 5. Europ. Symp. Oxford, Sept. 1962. Pergamon Press, London 1963, p. 207.

[123] *Yu. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryushkin*, and *M. M. Shemyakin*, Doklady Akad. Nauk SSSR *153*, 122 (1963).

strated [123–125] that tripeptides and tridepsipeptides, which cannot associate lengthwise, nevertheless undergo doubling on cyclization. Thus, glycyl-L-prolyl-glycine [124,125] gives the cyclic hexapeptide as easily as does diglycyl-L-proline [124], although the prolyl unit carries no NH group; further, the tridepsipeptide glycyl-glycolyl-glycine, having an ester linkage instead of one of the amide links [125], and even *N*-methylated tridepsipeptides [123], cyclize with formation of double molecules. Doubling (and tripling) occurs also with tetradepsipeptides [123], *N*-methylated or not, but the yields of tetra-, octa- and dodeca-depsipeptides are generally lower and not significantly different [123], presumably because none of these compounds can have strain-free conformations (Table 1). *Shemyakin* [123] proposed on this basis a reaction sequence with a dilution-dependent final cyclization step.

The configurational sequence of the amino acids in oligopeptides (and of hydroxy acids in depsipeptides) has a profound influence on the cyclization yield. Thus, *Schwyzer* has reported [126] that while gramicidin S itself, which contains two D-phenylalanyl residues, was synthesized in good yield, the corresponding all-L-cyclodecapeptide, with two L-phenylalanyl residues, could not be obtained. Similarly, the cyclic pentapeptide was obtained in 57 % yield from glycyl-L-leucyl-glycyl-D-leucyl-glycine as against 41 % for the L,L-isomer [127], and in 39 % yield from glycyl-D-leucyl-L-leucyl-glycyl-glycine compared with 12 % for the L,L-isomer [128]. The cyclic hexapeptide, cyclophenylalanyl-glycyl-glycyl-phenylalanyl-glycyl-glycyl was mainly the *meso*-form, whether obtained from racemic tripeptides or diastereomeric hexapeptides [129]; when synthesized separately [129], the yield of the *meso*-form (D,L) was higher than for the optically active isomers (D,D and L,L). The same phenomenon was observed in the cyclization of glycyl-tyrosyl-glycyl-glycyl-benzylhistidyl-glycine [130]; when both asymmetric centers had the L-configuration, the yield of cyclic hexapeptide was 31 %, whereas it was 58 % (2/3 containing D-tyrosyl) when the tyrosine was racemic. In these cases there is enough room for the few bulky substituents at corner positions [cf. *(7)*], so that the yield variation must be due to differences in shape of the peptide chain before the final cyclization step. Such differences are indicated by the observation [128] that open-chain peptides containing both L- and D-amino acids have a smaller dielectric increment, hence a smaller distance between $-NH_3^+$ and $-COO^-$, than sterically homogeneous peptides. Although attempts have been made at a conformational analysis of such peptide (and depsipeptide) chains [128,131], these are not convincing because of admitted arbitrary assumptions, and lack of data for the conformational preferences about the C(α)-CO bond, and especially the C(α)-N and C(α)-O bonds. The only conclusion that seems certain is that the extended chain is favored by steric homogeneity, and that each opposite configuration introduces a bend, which cannot be clearly specified. This is particularly well demonstrated by a series of cyclization experiments [131] with diastereomeric tetradepsipeptides (*N*-methylvalyl-α-hydroxyisovaleryl-*N*-methylvalyl-α-hydroxyisovaleric acid); seven sterically heterogeneous isomers gave the cyclotetradepsipeptide in yields from 40 to 75 %, while the sterically homogeneous isomer gave only 8 %, accompanied by the doubling product (13 %). From Fig. 18, *(8)*, it is seen that the isopropyl side groups must all be at "corners" and have enough room in any of these isomers, so that the ring-strain in the end products can hardly differ.



*(8)*

Fig. 18. Proposed conformation of cyclic tetradepsipeptides, based on the conformation of cyclododecane. D and L substituents are marked —— and - - -, respectively.

## Cyclic Olefins and Annulenes

The introduction of a double bond into a cycloalkane makes strain-free conformations impossible for any ring size, and it has been pointed out [10] that almost all known cycloalkenes are liquids, reflecting their conformational instability. The exact stereochemistry of the cycloalkenes is not known, except for derivatives of cyclohexene and for cyclopentene [132]; the latter is not planar, but has the 4-$CH_2$ group bent out of the plane, presumably to avoid totally eclipsed 3,4- and 4,5-bonds, although some eclipsing in the 2,3- and 1,5-bonds is thereby introduced. Dihedral angles in single bonds adjoining the double bond have been calculated from NMR coupling constants for *cis*-cycloalkenes up to $C_{10}$ and for *trans*-cyclodecene [133]; the considerable deviations from the "correct" angles of 60 and 180 ° in 7 to 10 membered rings suggests that the departure from ideality is concentrated in these bonds with their lower torsional barrier. Since three-membered rings approach the stereochemistry of the double bond, the

[124] *M. Rothe, K. D. Steffen,* and *I. Rothe,* Angew. Chem. *75,* 1206 (1963); Angew. Chem. internat. Edit. *3,* 64 (1964).

[125] *R. Schwyzer, J. P. Carrión, B. Gorup, H. Nolting,* and *A. Tun-Kyi,* Helv. chim. Acta *47,* 441 (1964).

[126] *R. Schwyzer* in: Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity. Churchill, London 1958, p. 171.

[127] *G. W. Kenner, P. J. Thomson,* and *J. M. Turner,* J. chem. Soc. (London) *1958,* 4148.

[128] *P. M. Hardy, G. W. Kenner,* and *R. C. Sheppard,* Tetrahedron *19,* 95 (1963); *J. Beacham, V. T. Ivanov, G. W. Kenner,* and *R. C. Sheppard,* Chem. Commun. *1965,* 386.

[129] *R. Schwyzer* and *A. Tun-Kyi,* Helv. chim. Acta *45,* 859 (1962).

[130] *K. D. Kopple, R. R. Jarabak,* and *P. L. Bhatia,* Biochemistry *2,* 958 (1963).

[131] *Yu. A. Ovchinnikov, V. T. Ivanov, A. A. Kiryuskin,* and *M. M. Shemyakin,* Doklady Akad. Nauk SSSR *153,* 1342 (1963).

[132] *G. W. Rathjens,* J. chem. Physics *36,* 2401 (1962).

[133] *G. V. Smith* and *H. Kriloff,* J. Amer. chem. Soc. *85,* 2016 (1963).

crystal structures of cycloalkenimine derivatives [134,135] (Fig. 19 and 20) may give an indication of the conformations of *cis*-cyclooctene and *trans*-cyclododecene,

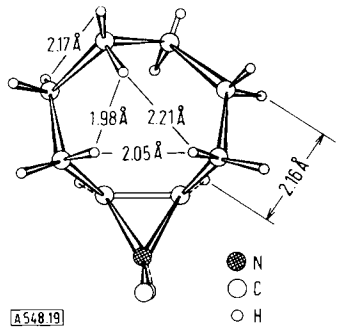



Fig. 19. The crystal structure of *cis*-9,9-dimethyl-9-azoniabicyclo-[6.1.0]nonane iodide [134].

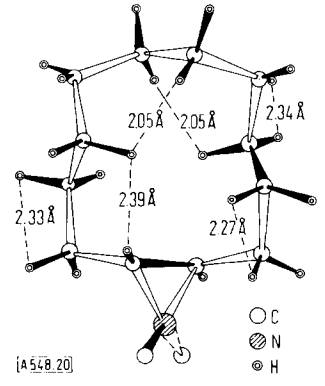



Fig. 20. The crystal structure of *trans*-13,13-dimethyl-13-azoniabicyclo-[10.1.0]tridecane iodide [135].

respectively [*]. In the latter case, *trans*-13,13-dimethyl-13-azoniabicyclo[10.1.0]tridecane iodide (Fig.20) [135], it is interesting to note the strong resemblance of the 12-membered ring to the conformation of cyclododecane itself.

The heat of hydrogenation gives an idea of the relative strain in a cycloalkene compared with that of the corresponding cycloalkane, and also of the relative stabilities of *cis*- and *trans*-isomers. The data [136] in Table 2 show that in cyclooctene the *trans*-isomer is much more strained than the *cis*-isomer and higher *trans*-olefins; this strain is also reflected in the notable dipole moment [137] (0.82 D), as compared with that of *trans*-cyclodecene (0.15 D). The strain renders the molecule rigid as is demonstrated by the resolution into optical isomers [138]. Up to cyclodecene the *cis*-isomers have lower enthalpies than the *trans*-isomers; however, in

Table 2. Heats of hydrogenation [136] and thermodynamic data for *cis,trans*-equilibria [141] of cycloalkenes.

| | Heat of hydrogenation (kcal/mole) at 25 °C | | | Isomerization *trans* → *cis* (100 °C) | | |
|---|---|---|---|---|---|---|
| | $\Delta H_{trans}$ | $\Delta H_{cis}$ | $\Delta H_{cis}-\Delta H_{trans}$ | $\Delta F$ (kcal/mole) | $\Delta H$ (kcal/mole) | $\Delta S$ (e.u.) |
| Cyclohexene | | 27.1 | | | | |
| Cycloheptene | | 25.9 | | | | |
| Cyclooctene | 32.2 | 23.0 | −9.2 | | | |
| Cyclononene | 26.5 | 23.6 | −2.9 | −4.04 | −2.9 | 3.0 |
| Cyclodecene | 24.0 | 20.7 | −3.3 | −1.86 | −3.6 | −4.7 |
| 4.4,7,7-Tetramethyl-cyclodecene | 25.4 | 22.0 | −3.4 | | | |
| 5,5,8,8-Tetramethyl-cyclodecene | 26.0 | 28.7 | 2.7 | | | |
| Cycloundecene | | | | 0.67 | 0.1 | −1.5 |
| Cyclododecene | | | | 0.49 | −0.4 | −2.4 |

the symmetrical tetramethyl derivative (Table 2) this situation is reversed [139]. An explanation on the basis of the Dunitz conformation of cyclodecane, with all the methyl groups at two corners, has been proposed [139]; a *trans* double bond fits into the symmetrical position better (although not at all well!) than a *cis* double bond, which becomes highly strained (Table 3). This is also borne out by the observation [140] that the corresponding acetylene is reduced by sodium in liquid ammonia to a *cis*-olefin, with the double bond shifted to the neighboring position.

The enthalpy differences between *cis*- and *trans*-cycloalkenes are in good agreement with values obtained by equilibration of medium size cycloalkenes (Table 2) [141].

In the 11- and 12-membered rings the *trans*-isomer is preponderant, but surprisingly in the latter case this is not due to a lower enthalpy, but to the more favorable entropy of the *trans*-isomer. In larger rings the equilibrium is largely on the *trans*-side [142].

When two double bonds are present, strain-free skeletons become possible in particular cases, namely when the two double bonds are diametrically placed, have the same configuration, and are linked by odd-membered polymethylene chains [10] (Fig. 21). In the larger rings,

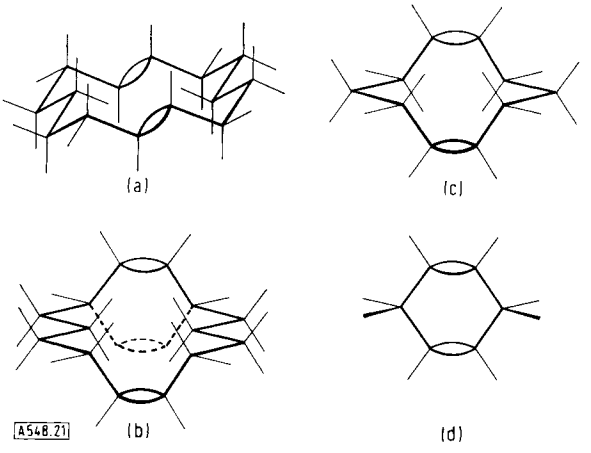



Fig. 21. Conformations of *trans,trans*- and *cis,cis*-cyclotetradeca-1,8-diene (a and b), of *cis,cis*-cyclodeca-1,6-diene (c), and of cyclohexa-1,4-diene (d).

[134] *L. M. Trefonas* and *R. Majeste*, Tetrahedron *19*, 929 (1963).

[135] *L. M. Trefonas* and *J. Couvillion*, J. Amer. chem. Soc. *85*, 3184 (1963).

[*] *Added in proof*: That such an analogy does indeed hold has now been demonstrated by the crystal structure of laurencin (*A. F. Cameron, K. K. Cheung, G. Ferguson*, and *J. M. Robertson*, Chem. Commun. *1965*, 638). In this molecule a substituted 5-oxa-*cis*-cyclooctane ring has a conformation very close to that shown in Fig. 19.

[136] *R. B. Turner* and *W. R. Meador*, J. Amer. chem. Soc. *79*, 4133 (1957).

[137] *N. L. Allinger*, J. Amer. chem. Soc. *79*, 3443 (1957); *80*, 1953 (1958).

[138] *A. C. Cope, C. R. Ganellin, H. W. Johnson, T. V. Van Auken*, and *H. J. S. Winkler*, J. Amer. chem. Soc. *85*, 3276 (1963).

[139] *P. Goebel, J. Sicher, M. Svoboda*, and *R. B. Turner*, Proc. chem. Soc. (London) *1964*, 237.

[140] *M. Svoboda, J. Sicher*, and *J. Závada*, Tetrahedron Letters *1964*, 15.

[141] *A. C. Cope, P. T. Moore*, and *W. R. Moore*, J. Amer. chem. Soc. *82*, 1744 (1960).

[142] *A. J. Hubert*, unpublished.

like the 14-membered ring, the *trans,trans*-isomer (a) is favored because hydrogen interactions destabilize the *cis,cis*-isomer (b). In the 10-membered ring, the *trans, trans*-isomer of type (a) would have too formidable a $\pi$-electron repulsion, which can be avoided in the *cis,cis*-isomer (c); the 6-membered ring necessarily has a planar conformation. As no absolutely perfect conformation is possible for the conjugated cycloalkadienes (see below) one might expect that these at least partially deconjugate on equilibration to give preferentially diametric isomers in the case of (4 *n* + 2)-membered rings.

The experimental facts support these deductions. The melting points of diametrical *cis,cis*-cycloalkadienes

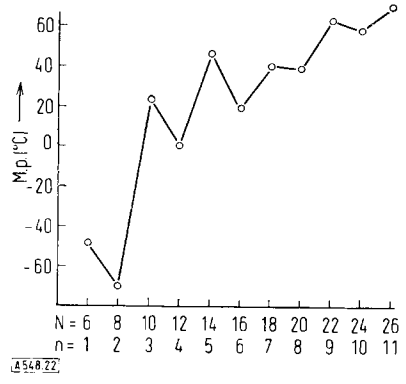



Fig. 22. Melting points of the *cis,cis*-cycloalkadienes

$$\text{C}(\text{CH}_2)_n\text{-CH=CH-}(\text{CH}_2)_n\text{-CH=CH}\text{C}$$

Abscissa: Upper row, total number of ring members, *N*; lower row, number of $CH_2$ groups between two vinylene groups, *n* [143].

(Fig. 22) show the required alternation [143], and the corresponding *trans,trans*-isomers are alternately solids and liquids [144]. Equilibration of cyclohexadiene [61,145] gives 31 % of the 1,4-isomer, which shows that its energy is comparable with that of the statistically favored conjugated isomer. The vibrational spectra of the 1,4-isomer indicate a planar structure [146]. Equilibration of cycloocta-1,5-diene gives almost quantitatively the conjugated isomer [147] since all *cis,cis*-isomers must be Pitzer-strained; the *cis,trans*-1,5-isomer is also strongly Baeyer-strained and so rigid that it preserves its asymmetry even under pyrolytic conditions [148]. The 9-membered ring approaches the behavior expected for the 10-membered ring; equilibration of cyclononadienes thus gives 94 % of the most "diametrical" *cis,cis*-1,5-isomer and only 6 % of the 1,3-isomer [147], while equilibration of cyclodecadienes gives almost quantitatively the "diametrical" *cis,cis*-1,6-isomer [142], even though this position is disfavored statistically. The rigid, torsionally strain-free conformation in Fig. 21,c has been proposed for *cis,cis*-cyclodeca-1,6-diene [149] and for the *cis,cis*-1,6-dioxocyclodeca-3,8-diene [150]. The 1,5-isomers, on the other hand, must be strained, as evidenced by the fact that both the *trans,trans*- [151] and *cis,trans*-1,5-isomers [152] undergo valence isomerization to divinylcyclohexane. In cyclonona-1,5-diene even the *cis,cis*-isomer undergoes this kind of valence isomerization [153]. Higher cyclic diolefins have been isomerized at 200 °C with triethylborane [154]. Extensive deconjugation does take place; there remains only 10 % of conjugated isomer in the 12-membered ring, 25 % in the 13-membered, and in higher rings up to the 22-membered it never surpasses 50 %. Among the non-conjugated isomers the expected preference for the diametrical isomer in 14- and 18-membered, and lack of preference in 12- and 16-membered rings was confirmed [154]. The situation is complicated by the concurrent *cis,trans*-isomerization. With strong bases at room temperature the result is similar, but the preferences are more accentuated [142]. The much simpler problem of *cis,trans*-isomerization without migration of positional isomers has recently been studied [144] at room temperature. The results confirm (Table 3) the

Table 3. *Cis,trans*-isomer equilibria of cycloalkadienes

$$\text{C}(\text{CH}_2)_n\text{-CH=CH-}(\text{CH}_2)_n\text{-CH=CH}\text{C}$$ brought about by U.V. irradiation in the presence of diphenyl disulfide [144].

| *n* | Ring atoms (2*n* + 4) | Temp. (°C) | Distribution of isomers (%) *trans-trans* | *cis-trans* | *cis-cis* |
|---|---|---|---|---|---|
| 3 | 10 | 25 | — | 3.8 | 96 |
| | | 75 | — | 8.0 | 92 |
| 4 | 12 | 25 | — | 30 | 70 |
| | | 75 | 8.3 | 35 | 57 |
| 5 | 14 | 25 | 92 | 6.4 | 2.0 |
| | | 75 | 85 | 12 | 2.8 |
| 6 | 16 | 25 | 29 | 58 | 13 |
| | | 75 | 38 | 51 | 11 |
| 7 | 18 | 25 | 71 | 22 | 6.9 |
| | | 75 | 68 | 27 | 5.1 |
| 8 | 20 | 25 | 42 | 48 | 10 |
| | | 75 | 47 | 45 | 7.8 |
| 9 | 22 | 25 | 66 | 31 | 2.8 |
| | | 75 | 57 | 37 | 5.9 |

strong preference for the *trans,trans*-isomer (although *cis,trans* is statistically favored) in the 14-, 18-, and 22-membered and the lack of preference in 16- and 20-membered rings. By comparing the equilibria at 25 and 75 °C (Table 3) it also becomes clear that these preferences are due to a low enthalpy in spite of an unfavorable entropy, hence indicate rigid, stable conformations.


[143] *J. Dale, A. J. Hubert*, and *G. S. D. King*, J. chem. Soc. (London) *1963*, 73.

[144] *J. Dale* and *C. Moussebois*, J. chem. Soc. (London) [C] *1966*, 264.

[145] *B. Franzus*, J. org. Chemistry *28*, 2954 (1963).

[146] *H. Gerding* and *F. A. Haak*, Recueil Trav. chim. Pays-Bas *68*, 293 (1949); *H. D. Stidham*, Spectrochim. Acta 21, 23 (1965).

[147] *D. Devaprabhakara, C. G. Cardenas*, and *P. D. Gardner*, J. Amer. chem. Soc. *85*, 1553 (1963).

[148] *A. C. Cope, C. F. Howell*, and *A. Knowles*, J. Amer. chem. Soc. *84*, 3190 (1962).

[149] *C.A.Grob* and *P.W.Schiess*, Helv. chim.Acta *47*, 558 (1964).

[150] *C. A. Grob* and *P. W. Schiess*, Helv. chim. Acta *43*, 1546 (1960).

[151] *C. A. Grob, H. Link*, and *P. W. Schiess*, Helv. chim. Acta *46*, 483 (1963).

[152] *P. Heimbach*, Angew. Chem. *76*, 859 (1964); Angew. Chem. internat. Edit. *3*, 702 (1964).

[153] *E. Vogel, W. Grimme*, and *E. Dinné*, Angew. Chem. *75*, 1103 (1963); Angew. Chem. internat. Edit. *2*, 739 (1963).

[154] *A.J. Hubert* and *J.Dale*, J.chem. Soc. (London) *1963*, 4091.

The macrocyclic conjugated cycloalkadienes have been isolated from equilibrium mixtures of various positional isomers [155] and shown to have exclusively the *cis,trans*-configuration from the 12- to the 16-membered ring; in the 18-membered and higher rings the *trans,trans*-isomer occurs also. Models show that a relatively strain-free conformation with a planar *transoid cis,trans*-diene system first becomes possible in the 14-membered ring (Fig. 23,a); experimentally, cyclotetradeca-1,3-diene is

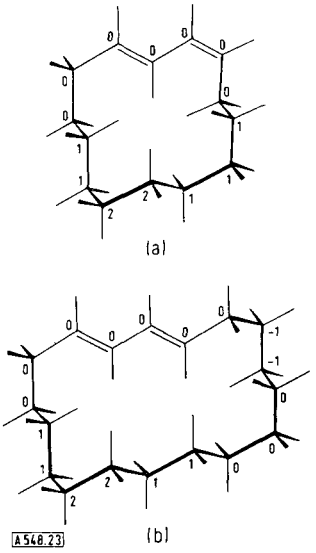



Fig. 23. Suggested conformations for (a) *cis,trans*-cyclotetradeca-1,3-diene and (b) *trans,trans*-cyclooctadeca-1,3-diene [155]. Atoms marked 0 are situated in the plane of the diene system, those marked 1 above, those marked 2 further above, while atoms marked -1 lie below the plane.

found to be the first to have a full intensity ultraviolet absorption [155]. Similarly, the 18-membered ring is the smallest which can accommodate a planar *transoid trans,trans*-diene system in an essentially strain-free conformation (Fig. 23,b) [155].

With three double bonds in a ring, "trigonal" ideal conformations with symmetrically placed *trans* double bonds, *(9)* (Fig. 24), become possible, but only for the

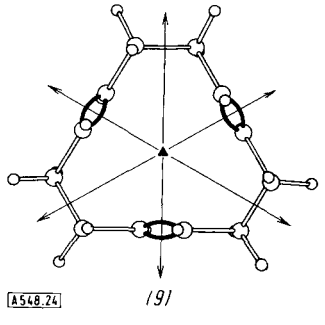



Fig. 24. Crystal structure of all-*trans*-cyclododeca-1,5,9-triene [156].

first member, all-*trans*-cyclododeca-1,5,9-triene, has such a strain-free conformation been established [156] by X-ray methods. Higher rings ($C_{18}$, $C_{24}$, *etc.*) would have intolerably large holes in the interior. The fact that among the known cyclododeca-1,5,9-triene isomers, the all-*trans* is by far the highest melting [157], may be a reflection of its particular conformational stability. A related structure with three *trans* double bonds in an 11-membered ring is present in humulene, and the conformation found [158] in its silver nitrate adduct,

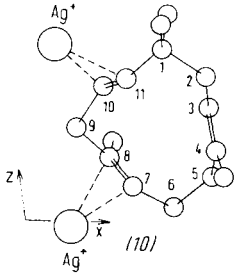



Fig. 25. Crystal structure of humulene (all-*trans*-1,1,4,8-tetramethyl-cycloundeca-3,7,10-triene) [158].

*(10)*, (Fig. 25), has main features in common with the 12-membered ring, *(9)*; most of its inherent strain is located in that part of the ring where one $CH_2$-group is missing.

Among the cyclononatrienes the all-*cis*-1,4,7-isomer seems to be the most stable [159] and its conformation has been proposed [159] to be a rigid crown (Fig. 26),

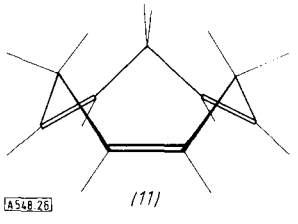



Fig. 26. Crystal structure of all-*cis*-cyclonona-1,4,7-triene [160].

subsequently confirmed by X-ray methods [160]. The single bonds must contain some Pitzer strain and the crystal structure [160] reveals that some strain is also introduced by transannular hydrogen repulsion; this is manifested in the heat of hydrogenation [160]. Equilibration of cyclooctatriene, on the other hand, shows that the conjugated all-*cis*-1,3,5-isomer is by far more stable than the 1,3,6-isomer [161], but it is not known whether the triene chromophore is planar. In cycloheptatriene it has been shown by spectral methods that not only are the protons of the $CH_2$ group non-equivalent [162], but that the molecule has a boat conformation [163] with a non-planar triene system, *(12)* (Fig. 27), as was confirmed recently by electron diffraction [164]; X-ray

[155] *A.J. Hubert* and *J. Dale*, J.chem.Soc. (London) *1965*, 6674.

[156] *G. Allegra* and *I.W. Bassi*, Atti Acad. naz. Lincei, Rend. Cl. Sci. fisiche, mat. natur. *38*, 72 (1962).

[157] *H. Breil, P. Heimbach, M. Kröner, H. Müller*, and *G. Wilke*, Makromol. Chem. *69*, 18 (1963).

[158] *A.T. McPhail, R. I. Reed*, and *G. A. Sim*, Chem. and Ind. *1964*, 976; *J. A. Hartsuck* and *I. C. Paul, ibid. 1964*, 977.

[159] *P. Radlick* and *S. Winstein*, J. Amer. chem. Soc. *85*, 344 (1963); *K. G. Untch, ibid. 85*, 345 (1963).

[160] *W. R. Roth, W. B. Bang, P. Goebel, R. L. Sass, R. B. Turner*, and *A. P. Yü*, J. Amer. chem. Soc. *86*, 3178 (1964).

[161] *D. S. Glass, J. Zirner*, and *S. Winstein*, Proc. chem. Soc. (London) *1963*, 276; *W. R. Roth*, Liebigs Ann. Chem. *671*, 25 (1964).

[162] *C. laLau* and *H. deRuyter*, Spectrochim. Acta *19*, 1559 (1963).

[163] *F. R. Jensen* and *L. A. Smith*, J. Amer. chem. Soc. *86*, 956 (1964).

[164] *M. Traetteberg*, J. Amer. chem. Soc. *86*, 4265 (1964).

diffraction on a derivative has led [165] to the same result. The dihedral angle between planes of adjacent double bonds, 54°, calculated from electron diffraction data [164], is so close to 60° that it must be concluded

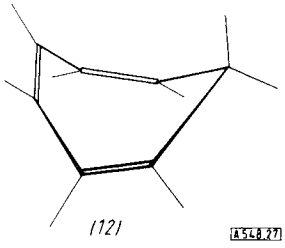
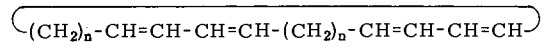



Fig. 27. Conformation of cycloheptatriene in the gas phase [164].

that the 2,3 and 4,5 single bonds prefer *gauchoid* to planar *cisoid* conformations. That this is not caused by angle strain is shown by the fact that the ring is strictly planar [166] as soon as the double bonds become delocalized (*e.g.*, 6 $\pi$-electrons on 7 atoms in the cycloheptatrienylium cation).

The cycloalkatetraenes of general formula




with two *cis,cis*-diene chromophores placed diametrically, show again melting point alternation with the number, *n*, of methylene groups in the connecting saturated chains [155]; the more rigid conformations of the high-melting members with odd *n* are also manifested by the sharper vibrational structure of the ultraviolet absorption bands.

Longer conjugated double bond systems, other than the annulenes (see below), have only been encountered as part of macrocyclic lactones, both natural (macrolide antibiotics [167]) and synthetic [168]. If one extrapolates from the model of Fig. 23,b, one is led to expect that an extended all-*trans* triene requires a 22-membered, a tetraene a 26-membered, and a pentaene a 30-membered ring in order to be "comfortable". It is interesting that all macrolide polyene antibiotics have ultraviolet spectra indicating an all-*trans* all-*anti* structure [167]. In only a few cases, however, is the ring size known; thus pimaricin [169] has a tetraene in a 26-membered ring, and lagosin [170], filipin [171], and fungichromin [172] have pentaene chromophores in 28-membered rings. The latter must therefore have a certain tension. Similar tensions must exist also in simple synthetic polyene macrolides [168] containing an all-*trans* triene in a 19-membered ring and an all-*trans* tetraene in a 24-membered ring.

In rings consisting of a closed loop of conjugated double bonds, like benzene and the annulenes, the main interest has centered on problems of aromaticity [173], or double bond localization *versus* delocalization (alternating or identical bond lengths). In addition to electronic factors, formulated in the well-known (and sometimes abused) *Hückel* rule, and steric factors, such as the possibility of having a planar structure with correct bond angles, conformational factors may also play a role. Thus in benzene, as well as in the flat [173,174] molecule of [18]annulene, *(14)* (Fig. 28), the localized structure

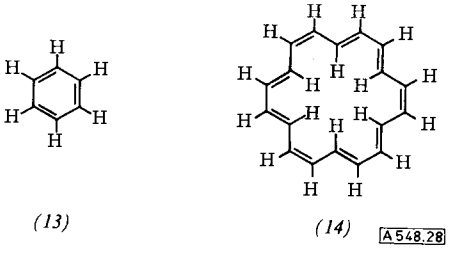



Fig. 28. Hypothetical planar localized double bond structures of benzene and [18]annulene.

(Kekulé structure) would have three eclipsed planar *cisoid* single bonds; since non-planar strain-free conformations with *gauchoid* single bonds are not possible here, the above bonds can only be avoided by delocalization. This may constitute an additional driving force for delocalization in the [4 *n* + 2] annulenes which also are aromatic according to *Hückel*. For cyclooctatetraene ([8]annulene), [16]-, and [24]annulene *(15)*, *(16)*, *(17)*, (Fig. 29), *etc.*, strain-free non-planar conformations with perfect *anti* and *gauche* single bonds linking localized double bonds are possible, so that there is no tendency for delocalization; just these rings happen

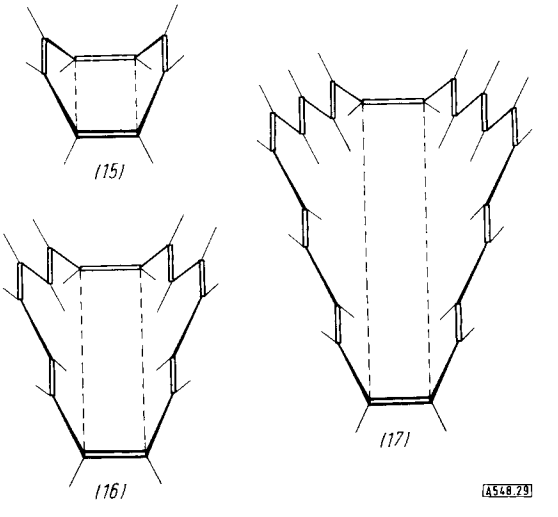



Fig. 29. Tub-shaped conformations of [8n]annulenes; *(15)* established for gaseous cyclooctatetraene [175]; *(16)* suggested for [16]annulene and *(17)* for [24]annulene.

[165] *R. E. Davis* and *A. Tulinsky*, Tetrahedron Letters *1962*, 839.

[166] *W. G. Fateley* and *E. R. Lippincott*, J. Amer. chem. Soc. *77*, 249 (1955).

[167] *W. Oroshnik* and *A. D. Mebane*, Fortschr. Chem. org. Naturstoffe *21*, 17 (1963).

[168] *L. D. Bergelson* and *Yu. G. Molotkovsky*, Izvest. Akad. Nauk SSSR, otdel khim. Nauk *963*, 105.

[169] *O. Ceder*, Acta chem. scand. *18*, 126 (1964).

[170] *M. L. Dhar*, *V. Thaller*, and *M. C. Whiting*, J. chem. Soc. (London) *1964*, 842.

[171] *O. Ceder* and *R. Ryhage*, Acta chem. scand. *18*, 558 (1964).

[172] *A. C. Cope*, *R. K. Bly*, *E. P. Burrows*, *O. J. Ceder*, *E. Ciganek*, *B. T. Gillis*, *R. F. Porter*, and *H. E. Johnson*, J. Amer. chem. Soc. *84*, 2170 (1962).

[173] *F. Sondheimer*, Pure appl. Chem. *7*, 363 (1963).

[174] *J. Bregman*, *F. L. Hirshfeld*, *D. Rabinovich*, and *G. M. J. Schmidt*, Acta crystallogr. *19*, 227 (1965).

also to be non-aromatic according to *Hückel*. For cyclooctatetraene the structure *(15)* has been established by electron diffraction [175], and from the data a dihedral angle of 57° between adjacent double bonds can be calculated, which is close to the perfect *gauche* conformation. The same dihedral angle is found also in the crystal structure of the carboxylic acid derivative [176]. That angle strain in the planar structure cannot be decisive for the non-planarity is indicated by the fact that when the electronic situation requires delocalization of the double bonds, as in the radical anion [177] and the dianion [177, 178], the ring becomes planar. X-ray data [179] show that [14]annulene does not have alternating bonds and that the carbon atoms are arranged in such a way that overcrowding in the interior is relieved, mainly by a serious in-plane distortion of the pyrene-like skeleton (Fig. 30). The relatively high melting point [180], 136 °C, indicates that this may be a

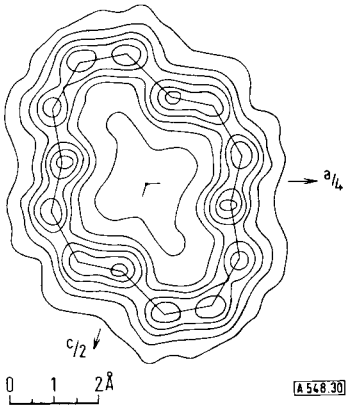



Fig. 30. Crystal structure of [14]annulene [179].

unique conformation, and the NMR spectrum below −40 °C shows the presence of a ring current [181], generally taken as a sign of aromaticity [173]. The coalescence of all NMR signals to one line at 20 °C indicates that the ring is nevertheless flexible enough to interconvert "inner" and "outer" hydrogen atoms [181].

For [18]annulene the X-ray data [173, 174] indicate a coronene-like, practically flat conformation (Fig. 31) and again no alternation in bond length. In [18]annulene trisulfide [182] there seems to be no ring current; the three *cisoid* single bonds are now part of "aromatic" thiophene rings, and delocalization of the double bonds over the large ring is no longer necessary.

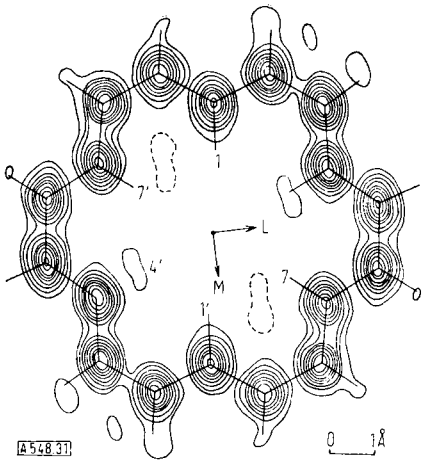



Fig. 31. Crystal structure of [18]annulene [173,174].

The melting point of [18]annulene is over 230 °C [183] and thus still higher than that of [14]annulene. A more rigid conformation of [18]annulene is suggested also by the higher temperature, 110 °C, required for the NMR signals of outer and inner protons, strongly split by the ring current at room temperature, to coalesce to one sharp line [181]. [16]Annulene [173, 184] melts already at 93 °C, and its single NMR line [173], indicating a "flexible" structure, is at the position observed for conjugated polyenes. The non-planar conformation *(16)* with alternating bonds is in accord with its properties, and the mixing of *cis* and *trans* double bond protons in the NMR spectrum can be explained by valence isomerization. For [20]annulene, not even non-planar conformations can be strain-free and accordingly this is a liquid [185]. The NMR spectrum of [24]annulene [186] is similar [173] to that of [16]annulene, indicating conjugated localized double bonds. The structure *(17)* seems to fit the ultraviolet spectrum, the chromophore being considered as two weakly coupled planar halves.

## Cyclic Acetylenes

One triple bond alone introduces the same conformational disorder into an even-membered cycloalkane as does one double bond, and it has been pointed out [10] that all known cycloalkynes are liquid. The requirement of the acetylenic grouping that four carbon atoms lie on a straight line evidently leads to a rapid increase of tension with diminishing ring size. Thus in the equilibrium at 100 °C between a cyclic acetylene and the corresponding cyclic allene (with only three collinear atoms) the percentage of acetylene changes from 74 % for the 11-membered, to 35 % for the 10-membered, and to only 7 % for the 9-membered ring [187].

[175] *O. Bastiansen, L. Hedberg*, and *K. Hedberg*, J. chem. Physics *27*, 1311 (1957).

[176] *D. P. Shoemaker, H. Kindler, W. G. Sly*, and *R. C. Srivastava*, J. Amer. chem. Soc. *87*, 482 (1965).

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[178] *H. P. Fritz* and *H. Keller*, Z. Naturforsch. *16b*, 231 (1961).

[179] *J. Bregman*, Nature (London) *194*, 679 (1962).

[180] *F. Sondheimer* and *Y. Gaoni*, J. Amer. chem. Soc. *82*, 5765 (1960).

[181] *Y. Gaoni, A. Melera, F. Sondheimer*, and *R. Wolovsky*, Proc. chem. Soc. (London) *1964*, 397.

[182] *G. M. Badger, J. A. Elix*, and *G. E. Lewis*, Proc. chem. Soc. (London) *1964*, 82.

[183] *F. Sondheimer, R. Wolovsky*, and *Y. Amiel*, J. Amer. chem. Soc. *84*, 274 (1962).

[184] *F. Sondheimer* and *Y. Gaoni*, J. Amer. chem. Soc. *83*, 4863 (1961).

[185] *F. Sondheimer* and *Y. Gaoni*, J. Amer. chem. Soc. *83*, 1259 (1961); *84*, 3520 (1962).

[186] *L. M. Jackman, F. Sondheimer, Y. Amiel, D. A. Ben-Efraim, Y. Gaoni, R. Wolovsky*, and *A. A. Bothner-By*, J. Amer. chem. Soc. *84*, 4307 (1962).

[187] *W. R. Moore* and *H. R. Ward*, J. Amer. chem. Soc. *85*, 86 (1963).

Cyclooctyne has been isolated [188], and the enormous strain manifests itself in an explosive reaction with phenyl azide; nevertheless, the triple-bond character is essentially retained since the infrared absorption is at 4.53 $\mu$ as in higher homologues. The transient existence of lower-membered cycloalkynes ($C_7$, $C_6$, $C_5$) has been inferred from reaction products [189], but such intermediates may perhaps involve non-linear excited "acetylenes" having no triple bond character.

More subtle conformational details are revealed by the heats of hydrogenation of some tetramethyl derivatives of cyclodecyne [139]. Again, an explanation is possible on the basis of the Dunitz conformation of cyclodecane with *gem*-dimethyl groups at two corners; the symmetrically located triple bond in 5,5,8,8-tetramethylcyclodecyne is more easily accommodated and gives a smaller heat of hydrogenation than the asymmetrically placed triple bond in the 4,4,7,7-tetramethyl derivative.

Two acetylenic bonds diametrically placed in 14-, 18-, 22-membered rings *etc.* can give strain-free ring conformations, whereas in 12-, 16-, and 20-membered rings this is not possible, and a strong melting-point alternation (Fig. 32, lower curve) is observed [143]. By application of the postulate that a minimum of *gauche* bonds are accepted, conformations of the type *(18)* (Fig. 33) were proposed [143] for the former series and seemed to be supported by unit cell measurements [143]. However, the

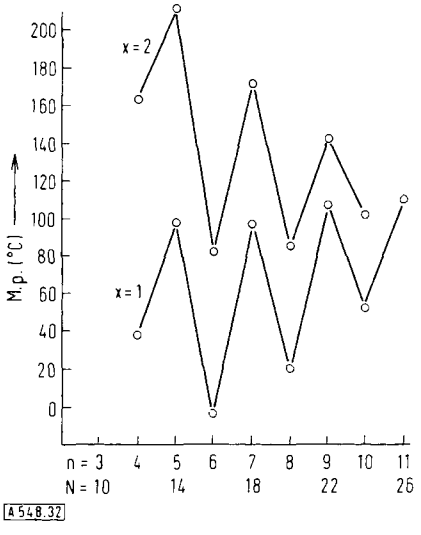



Fig. 32. Melting points [143] of cycloalkadiynes ($x = 1$) and cycloalkatetraynes ($x = 2$) of the type

$$\text{-}(CH_2)_n\text{-}(C{\equiv}C)_x\text{-}(CH_2)_n\text{-}(C{\equiv}C)_x\text{-}$$

Abscissa: Upper row, number of $CH_2$ groups between the acetylene groups, $n$; lower row, total number of ring members, $N$, for $x = 1$.

complete structure determination of cyclotetradeca-1,8-diyne has revealed [103] that the conformation *(19)* (Fig. 33), with two unfavorable *gauche* bonds, is preferred in the crystalline state. Perhaps this conformation packs better; type *(18)* may still be preponderant in

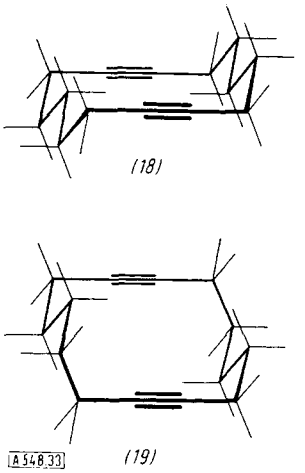



Fig. 33. Conformations of cyclotetradeca-1,8-diyne as proposed *(18)* [143] and as found in the crystal *(19)* [103].

solution. Recently, it has been shown [190] that with strong bases in dimethyl sulfoxide at 40 °C the triple bonds migrate (through intermediate allenes), and the equilibrium composition (Table 4), approached from

Table 4. Isomerization of cycloalkadiynes

$$\text{-}(CH_2)_m\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}C{\equiv}C\text{-}$$

with potassium t-butoxide in dimethyl sulfoxide at 40 °C [190].

| Ring atoms ($m + n + 4$) | Distribution of positional isomers at "equilibrium" | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 | $m + n$ | | 4 + 5 | | 3 + 6 | | 2 + 7 | | | |
| | % | | 91 | | 9 | | 0 | | | |
| 14 | $m + n$ | 5 + 5 [a] | | 4 + 6 | | 3 + 7 | | 2 + 8 | | |
| | % | 91 | | 9 | | 0 | | 0 | | |
| 15 | $m + n$ | | 5 + 6 | | 4 + 7 | | 3 + 8 | | | |
| | % | | 80 | | 16 | | 4 | | | |
| 16 | $m + n$ | 6 + 6 [a] | | 5 + 7 | | 4 + 8 | | 3 + 9 | | |
| | % | 9 | | 46 | | 38 | | 8 | | |
| 18 | $m + n$ | 7 + 7 [a] | | 6 + 8 | | 5 + 9 | | 4 + 10 | 3 + 11 | |
| | % | 49 | | 29 | | 11 | | 7 | 4 | |
| 20 | $m + n$ | 8 + 8 [a] | | 7 + 9 | | 6 + 10 | | 5 + 11 | 4 + 12 | 3 + 13 |
| | % | 11 | | 37 | | 31 | | 12 | 6 | 3 |

[a] Statistical probability 1/2.

different pure isomers, confirms that the diametrical isomer is much preferred in 14- and 18-membered rings, but is a minor constituent in 16- and 20-membered

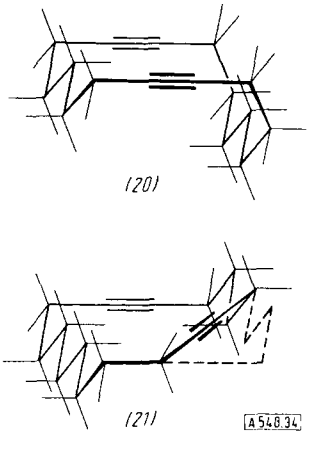



Fig. 34. Proposed conformations for the 1,8-isomer *(20)* and the 1,7-isomer *(21)* of cyclohexadecadiyne [190].

[188] *A. T. Blomquist* and *L. H. Liu*, J. Amer. chem. Soc. *75*, 2153 (1953).

[189] *G. Wittig et al.*, Chem. Ber. *94*, 3260, 3276 (1961); *96*, 329, 342 (1963).

[190] *A. J. Hubert* and *J. Dale*, J.chem.Soc. (London) *1965*, 3118.

rings; the odd-numbered rings ($C_{13}$ and $C_{15}$) resemble the 14-membered ring. For the isomers expected for 16- and 20-membered rings, the conformation *(20)* was *a priori* a good candidate since a strain-free skeleton is possible, although it is not very compact and has two extra *gauche* bonds; the unexpected preference for a still less symmetrical isomer can be explained by assuming it to have the conformation *(21)* (Fig. 34) which, although a little strained, is more compact and has only one extra *gauche* bond [190].

Table 5. Synthetic yield, melting point, and equilibrium distribution of cycloalkadiyne isomers [190].

$\text{-}(CH_2)_m\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}C{\equiv}C\text{-}$

| | | | | |
|---|---|---|---|---|
| $C_{14}$, $m + n$ | 5 + 5 | 4 + 6 | 3 + 7 | 2 + 8 |
| Yield in synthesis (%) | 57 | 18 | 1 | 7 |
| M.p. (°C) | 98 | 30 | liq. | 12 |
| % in equilibrium | 90 | 10 | *ca.* 1 | 0 |
| $C_{16}$, $m + n$ | 6 + 6 | 5 + 7 | 4 + 8 | 3 + 9 |
| Yield in synthesis (%) | 23 | 10 | 13 | |
| M.p. (°C) | −3 | 28 | 30 | |
| % in equilibrium | 10 | 44 | 38 | 9 |

Table 5 shows that there is a parallel between a high melting point and preponderance of cycloalkadiynes in the isomer equilibrium [190]. The synthetic yield is seen to deviate somewhat from this pattern, because it also is dependent on the conformation of the open chain immediately before cyclization.

Among the numerous known polyacetylenic cyclic compounds containing diacetylenic groupings [143, 173] the conformation of only one series has been investigated, namely, the symmetrical cycloalkatetraynes

$\text{-}(CH_2)_n\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}(CH_2)_n\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}$.

Alternations in yield, stability, and melting point [143] (Fig. 32) led to the proposal of conformations analogous to those for the corresponding cycloalkadiynes, although these might have excessive interior holes. For the lowest member $n = 3$, X-ray data [191] indeed indicate a chair-like shape *(22)* (Fig. 35), later [192] also deduced for 1,6-dioxacyclodeca-3,8-diyne, *(23)*; the too short transannular distance between the diacetylenic groups

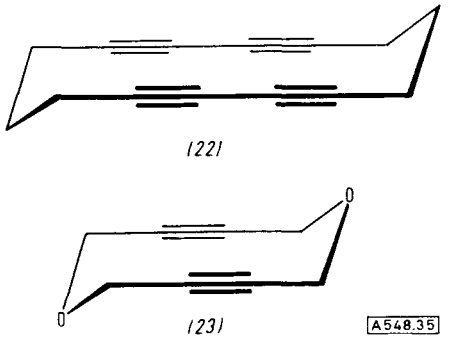



Fig. 35. Crystal structure of cyclotetradeca-1,3,8,10-tetrayne *(22)* [191] and of 1,6-dioxacyclodeca-3,8-diyne *(23)* [192].

[191] *F. Sondheimer, Y. Amiel,* and *R. Wolovsky,* J. Amer. chem. Soc. *79,* 6263 (1957).

[192] *F. Sondheimer, Y. Gaoni,* and *J. Bregman,* Tetrahedron Letters *1960,* No. 26, p. 25.

explains the instability and the anomalous ultraviolet spectrum [191].

The stereochemistry of the fully conjugated ethylenic-acetylenic rings, the dehydroannulenes, has been elucidated by NMR methods [173, 186] and in a few cases confirmed by X-ray methods; thus both 5,11,17-tridehydro[18]annulene [193] and 1,8-didehydro[14]annulene [194] have the planar structures *(24)* and *(25)* (Fig. 36, 37).

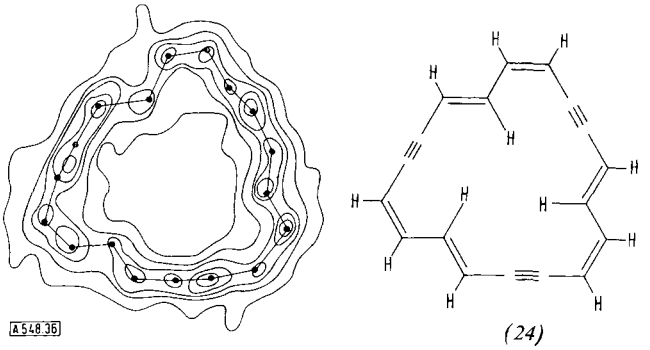



Fig. 36. Crystal structure of 5,11,17-tridehydro[18]annulene [193].

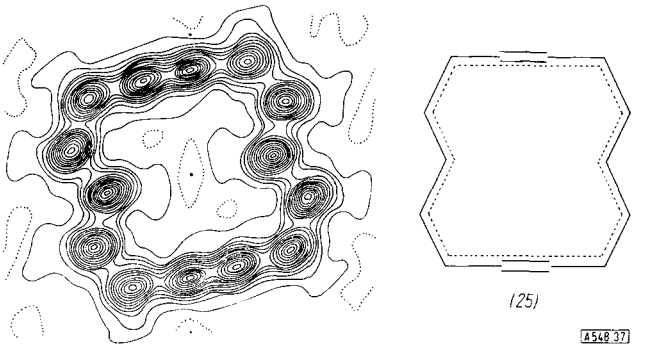



Fig. 37. Crystal structure of 1,8-didehydro[14]annulene [194].

## Rings Containing Phenylene Groups

An *ortho*-phenylene group in a ring compound should have essentially the same conformational consequence as a *cis* double bond, although the absence of a rotational barrier in the adjacent single bonds and the bulk of the aromatic ring may have some effect. Accordingly, most known benzocycloalkenes are liquid [10] or relatively low-melting [143]. Too few diametrical dibenzocycloalkadienes are known to permit general conclusions; in the case of dibenzocycloocta-1,5-diene the crystallo-

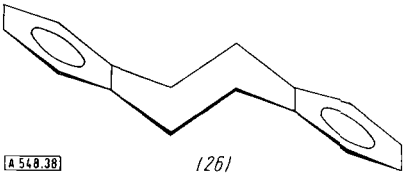



Fig. 38. Crystal structure of dibenzocycloocta-1,5-diene [195].

[193] *N. A. Bailey* and *R. Mason,* Proc. chem. Soc. (London) *1964,* 356.

[194] *N. A. Bailey* and *R. Mason,* Proc. chem. Soc. (London) *1963,* 180.

graphic data require a center of symmetry [195] as in the conformation *(26)* (Fig. 38). The crown conformation proposed [196] for cyclotriveratrylene, a derivative of tribenzocyclonona-1,4,7-triene, is analogous to that found [160] for all-*cis*-cyclonona-1,4,7-triene itself *(11)*. Crown conformations, with the benzene rings alternately above and below a plane, have been found to be the only ones possible with molecular models for even-membered oligo-*ortho*-phenylenes [197]; with tetraphenylene such a conformation is directly derivable from that of cyclooctatetraene, *(15)* [175].

*m*-Phenylene groups should be able to replace without strain three successive $CH_2$ groups in the middle of a straight chain of five or more $CH_2$ groups, such as can only occur in 14-membered and higher cycloalkanes. Too few examples are known with one or two such groups in a macrocyclic ring; only for [2,2]metacyclophane [198] has the conformation been established by X-ray methods and shown to have the centrosymmetrical *anti*-structure *(27)* (Fig. 39) and not *syn*; however,

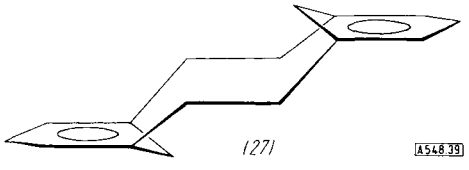



Fig. 39. Crystal structure of [2,2]metacyclophane [198].

this 10-membered ring is too rigidly strained (deformed benzene rings) to illustrate any general principle. The closest transannular distance between aromatic carbon atoms is only 2.69 Å, compared with 3.4 Å for graphite. Similar centrosymmetric conformations have been found for the 4,12-dimethyl derivative [199] and the analogous diaza derivative, di(pyridine-2,6-dimethylene) [200].

The *p*-phenylene group is linked linearly like the acetylene and diacetylene groups. Again, the known rings containing one such group, the [*n*]paracyclophanes, are liquids as are the cycloalkynes [10]. The smallest member known, the [8]paracyclophane [201], has its benzene ring bent from the planar configuration, as evidenced by the abnormal ultraviolet spectrum. The [9]paracyclophane [202] and higher homologues [203] have more normal spectra; nevertheless, even [10]- and [12]paracyclophane have slightly bent benzene rings [204]. The short saturated chain in these lower members stretches over and is in close contact with one face of the aromatic ring, as shown by the shift of the NMR signals of the $CH_2$-groups by the ring current in [9]- and [10]-paracyclophanes [205,206] and, less, in [12]paracyclophane [205], and by transannular reactions on solvolysis of [9]paracyclophane tosylates [206]. The rigidity of these structures is also demonstrated by the resolution [207] of an aromatic carboxylic acid derivative of [10]paracyclophane into the optical antipodes.

With two *p*-phenylene groups placed diametrically, the [*n*,*n*]paracyclophanes, an expected conformational stability for odd *n*, and instability for even *n*, is borne out by the observed [208] melting point alternation for $n > 3$ (Fig. 40) in complete analogy with the diametrical

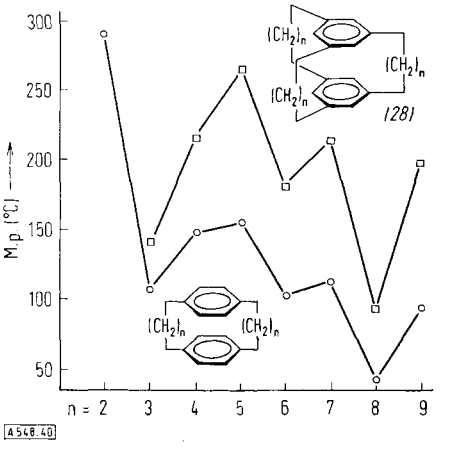



Fig. 40. Melting points of [*n*,*n*]paracyclophanes (lower curve) and of cage compounds of the type *(28)*, in which two benzene rings are symmetrically linked *via* three methylene bridges (upper curve) [208]. Abscissa: Number of $CH_2$ groups between the benzene rings.

cycloalka-diynes and -tetraynes (Fig. 32). Although the polymethylene chains do not need to have the maximal number of *anti*-bonds (cf. the acetylenic counterparts already discussed), this is nevertheless indicated to be the case by the similarity with the melting point curve of the multimacrocyclic cage analogues *(28)* (Fig. 40) [208], which have three equivalent polymethylene bridges linking two benzene rings in 1,3,5-position, since here no alternative strain-free conformation for even *n* with extra *gauche* bonds is possible. Further, in NMR spectra only the $\gamma$ and $\delta$ $CH_2$ groups show an abnormal chemical shift; when the chains are straight, these are the only ones that can direct their protons in between the two benzene rings. The crystal structure is known only for the two lowest members of the [*n*,*n*]-paracyclophanes ($n = 2$ and 3), but these are severely strained, as evidenced by the anomalous ultraviolet and infrared spectra [203,209]; the two aromatic rings avoid

[195] *W. Baker, R. Banks, D. R. Lyon,* and *F. G. Mann,* J. chem. Soc. (London) *1945*, 27.

[196] *A. S. Lindsey,* Chem. and Ind. *1963*, 823; *H. Erdtman, F. Haglid,* and *R. Ryhage,* Acta chem. scand. *18*, 1249 (1964).

[197] *G. Wittig* and *G. Lehmann,* Chem. Ber. *90*, 875 (1957).

[198] *C. J. Brown,* J. chem. Soc. (London) *1953*, 3278.

[199] *A. W. Hanson,* Acta crystallogr. *15*, 956 (1962).

[200] *W. Baker, K. M. Buggle, J. F. W. McOmie,* and *D. A. M. Watkins,* J. chem. Soc. (London) *1958*, 3594.

[201] *D. J. Cram* and *G. R. Knox,* J. Amer. chem. Soc. *83*, 2204 (1961).

[202] *D. J. Cram* and *M. F. Antar,* J. Amer. chem. Soc. *80*, 3109 (1958).

[203] *D. J. Cram, N. L. Allinger,* and *H. Steinberg,* J. Amer. chem. Soc. *76*, 6132 (1954).

[204] *N. L. Allinger, L. A. Freiberg, R. B. Hermann,* and *M. A. Miller,* J. Amer. Chem. Soc. *85*, 1171 (1963).

[205] *J. S. Waugh* and *R. W. Fessenden,* J. Amer. chem. Soc. *79*, 846 (1957).

[206] *D. J. Cram* and *M. Goldstein,* J. Amer. chem. Soc. *85*, 1063 (1963).

[207] *A. T. Blomquist* and *B. H. Smith,* J. Amer. chem. Soc. *82*, 2073 (1960).

[208] *A. J. Hubert* and *J. Dale,* J. chem. Soc. (London) *1965*, 3160, and unpublished work.

[209] *D. J. Cram* and *H. Steinberg,* J. Amer. chem. Soc. *73*, 5691 (1951).

coming too close by bending into a boat shape. In the case of [2,2]paracyclophane the molecule has really no freedom to choose, and the crystal structure, *(29)* (Fig. 41)[210], is as expected; it demonstrates, however,

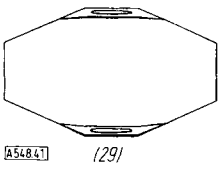



Fig. 41. Crystal structure of [2,2]paracyclophane [210].

that the strain is well distributed over the whole molecule and that the distance between the two aromatic planes, which is normally 3.4 Å (graphite), is here 3.09 Å in the middle and only 2.83 Å between linked atoms. The [3,3]paracyclophane has somewhat more freedom, and the strong $\pi$-electron repulsion causes the aromatic rings not only to bend but also to be displaced from a centered position, *(30)* (Fig. 42)[211]. When the

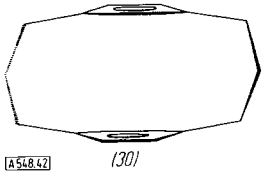



Fig. 42. Crystal structure of [3,3]paracyclophane [211].

repulsion is diminished by complex formation on one side[212], the structure presumably falls back into the centered position whereby bond angle strain is released; this is assumed[212] to be the driving force for the exceptionally strong tendency of *(30)* for complex formation with tetracyanoethylene.

A large number of other (unsymmetrical) paracyclophanes have been prepared by *Cram et al.*, and their physical properties studied, but information of conformational interest is limited to the distance between the two benzene rings. In the case of [1,*n*]paracyclophanes the synthetically available member[213] with the shortest polymethylene chain linking the 4- and 4'-positions of the diphenylmethane group is the one with $n = 7$, but spectral anomalies[213] appear also for $n = 8$ and 9 and are noticeable even for $n = 12$, indicating that the saturated chain draws the two benzene rings closer together and even deforms them. The limiting ring size for restricted rotation of the phenylene group in paracyclophanes is indicated by the resolution[214] of an aromatic carboxylic acid derivative of [3,4]paracyclophane and the failure to resolve[214] the corresponding derivative of [4,4]paracyclophane.

[210] *C. J. Brown*, J. chem. Soc. (London) *1953*, 3265.

[211] *P. K. Gantzel* and *K. N. Trueblood*, Acta crystallogr. *18*, 958 (1965).

[212] *L. A. Singer* and *D. J. Cram*, J. Amer. chem. Soc. *85*, 1080 (1963).

[213] *D. J. Cram* and *M. F. Antar*, J. Amer. chem. Soc. *80*, 3103 (1958).

[214] *D. J. Cram, W. J. Wechter*, and *R. W. Kierstead*, J. Amer. chem. Soc. *80*, 3126 (1958).

Ring systems composed of several different chemical groups (aromatic nuclei, multiple bonds, carbonyl groups, heteroatoms, *etc.*) have been extensively studied. However, such chemical and spectroscopic studies have been concerned mainly with the stereochemistry of *parts* of the ring, for example the question of planarity of chromophoric conjugated groups, or with transannular interactions of two such groups, or with the dependence of synthetic yield and resolvability on ring size, and no conclusions about the shape of the whole ring as such have been drawn.

Some X-ray results of such compounds merit mention; thus, the crystal structure of 1,2;7,8-dibenzocyclododeca-1,7-diene-3,5,9,11-tetrayne[215] reveals clearly curved diacetylene groups and well distributed angle strain, and the diolefin of [2,2]paracyclophane has a structure[216] strikingly similar to that of the parent compound *(29)*[210]. Of particular interest is the crystal structure of rifamycin B[217,218], in which an aliphatic bridge containing a diene conjugated with an amide group, an enol, and various substituents, spans over a naphthalenic system. Here again, abnormal chemical shifts of the NMR signals of two $CH-CH_3$ groups indicate that these are influenced by an aromatic ring current. The crystal structure[217] also reveals planar *anti*-amide groups, a correct stereochemistry next to double bonds, and a planar *transoid cis,trans*-diene. The latter feature seems to be general with such rings; thus, conjugated diene systems formed in the isomerization of macrocyclic hydrocarbons containing a phenylene group and two triple bonds prefer the *cis, trans*-configuration and the *anti*-conformation[219].

Several porphins have been examined by X-ray methods; perhaps unexpectedly, almost all of them show deviations from planarity attributable to steric hindrance. It has also been concluded[220] that these ring systems must be quite flexible, since the triclinic[220] and tetragonal[221] crystal forms of tetraphenylporphin have different conformations; the copper salt also is non-planar[222]. Similarly, nickel etioporphyrin I is non-planar[223], while nickeletioporphyrin II is flat[224]. The related phthalocyanines are planar[225].

The crystal structure of cyclotetramethylene tetranitramine[226] shows this molecule to contain an 8-membered puckered centrosymmetric ring, but this structure is too unusual to justify further discussion.

[215] *W. K. Grant* and *J. C. Speakman*, Proc. chem. Soc. (London) *1959*, 231.

[216] *C. L. Coulter* and *K. N. Trueblood*, Acta crystallogr. *16*, 667 (1963).

[217] *M. Brufani, W. Fedeli, G. Giacomello*, and *A. Vaciago*, Experientia *20*, 339 (1964).

[218] *W. Oppolzer, V. Prelog*, and *P. Sensi*, Experientia *20*, 336 (1964).

[219] *J. Dale* and *A. J. Hubert*, J.chem.Soc. (London) *1963*, 5475

[220] *S. Silvers* and *A. Tulinsky*, J.Amer.chem.Soc. *86*, 927 (1964).

[221] *J. L. Hoard, M. J. Hamor*, and *T. A. Hamor*, J. Amer. chem. Soc. *85*, 2334 (1963).

[222] *E. B. Fleischer*, J. Amer. chem. Soc. *85*, 1353 (1963).

[223] *E. B. Fleischer*, J. Amer. chem. Soc. *85*, 146 (1963).

[224] *M. B. Crute*, Acta crystallogr. *12*, 24 (1959).

[225] *J. M. Robertson*, J. chem. Soc. (London) *1936*, 1195.

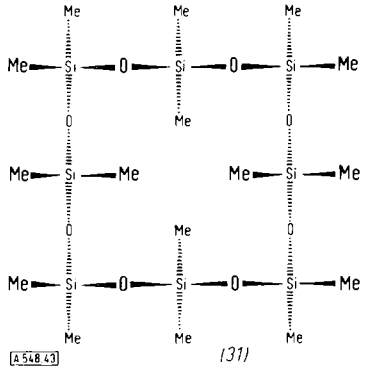
[226] *P. F. Eiland* and *R. Pepinsky*, Z. Kristallogr., Kristallgeometr., Kristallphysik, Kristallchem. *106*, 273 (1955).

The term "inorganic ring" is limited here to compounds whose molecular entity is preserved in solution and which do not contain carbon as a ring member but may contain organic groups as substituents. A wide variety of such compounds is known [227]; interestingly, there is a natural tendency not only for the formation of 6-membered rings, but also a preference for 8-membered rings not paralleled in organic ring systems. Both planar and chair-shaped 6-membered inorganic rings are known [227], and even chair-shaped isocyclic hexamers of sulfur [24] and of diphenyltin [228] have been described.

Among the 8-membered rings, the crystal structure of orthorhombic sulfur, $S_8$ [229], as well as of the aza-derivatives heptasulfurimide $S_7NH$ [230], hexasulfurdiimide$(S_3NH)_2$ [230] and tetrasulfurtetraimide $(SNH)_4$ [231] reveal closely similar crown conformations with dihedral angles of 99 °, much wider than in open chains [28]. On the other hand, when the nitrogen atoms carry no hydrogen, as in sulfur nitride, $(SN)_4$ [232], the ring "chooses" a saddle conformation with the nitrogen atoms at the "corners" and dihedral angles close to 60 °, but the valence description of this structure poses problems [232]. With a fluorine substituent on each sulfur atom, as in tetrathiazyl fluoride, $(NSF)_4$ [233], the ring assumes again a saddle conformation, but this time with the sulfur atoms at the corners, and the SN bonds are alternately long and short. With only tetrahedrally linked ring atoms, as in cyclic oligomers of dimethyl(phosphino)borine, the situation is less confusing; thus the trimer [234] is a chair-shaped 6-membered ring and the tetramer [235] a saddle-shaped 8-membered ring with phosphorus at the corners, suggesting normal staggered single BP bonds.

Eight-membered rings containing alternating silicon and oxygen (cyclosiloxanes), silicon and nitrogen (cyclosilazanes), or phosphorus and nitrogen (cyclophosphonitriles) as ring atoms, do not seem to prefer definite conformations, in keeping with the extreme flexibility [236] of such chains. Thus, the crystal structure of octamethyl cyclotetrasiloxane [237] reveals a centrosymmetric 8-membered chair, while the analogous crystalline octamethyl cyclotetrasilazane [238] is a mixture of two conformations, one being identical with the above chair, the other something between a saddle and a boat. Octamethylcyclotetraphosphonitrile [239] approaches a perfect saddle with the phosphorus atoms at the corners, as does the analogous octakis(dimethylamino)cyclotetraphosphonitrile [240] [*], while the tetrameric phosphonitrilic chloride [241] has a more flattened ring intermediate between a boat and the above type of saddle. The corresponding fluoride [242] finally is planar or close to planar; in this latter case another crystalline form exists at low temperature [242].

Since the above data suggest a certain tendency for these ring bonds to be "staggered" and for bulky substituents to prefer corner positions, it is of interest to examine whether the conformations of larger rings can also be derived from the diamond lattice [10]. It turns out that three-atom bridges are required, not only in order to have the substituted atoms (Si, P) at corner positions, but also because the "hole" is needed to accommodate substituents from those Si or P atoms which are not at the corners. This type of conformation becomes first possible for 16-membered rings (octamers), and it is gratifying to find that this is exactly the conformation




(31)

Fig. 43. Crystal structure of hexadecamethylcyclooctasiloxane [243].

established by X-ray methods [243] for hexadecamethylcyclooctasiloxane *(31)* (Fig. 43). Analogous conformations are possible for 20-, 24-, *etc.* membered rings, but not for 14-, 18-, 22-, *etc.* membered ones, so that a melting point alternation would be expected. In the series of cyclic phosphonitrile fluorides [236] (Fig. 44) such an alternation is observed, but the alternation continues also to the lower members both in this series and for the cyclic phosphonitrilic chlorides [244] and the cyclic

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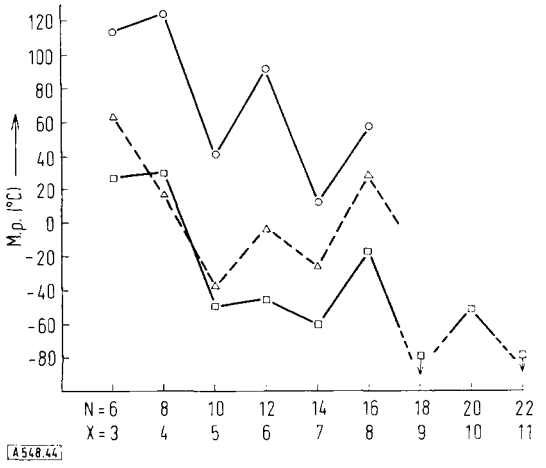


Fig. 44. Melting points of (o) cyclic phosphonitrile chlorides [244], of (□) cyclic phosphonitrile fluorides [236], and of (Δ) cyclic dimethylsiloxanes [245].

Abscissa: Upper row, total number of ring members, $N$; lower row, number of monomer units, $X$.

dimethylsiloxanes[245] (Fig. 44)[*]. This is somewhat surprising, since an analogous conformation for the 12-membered ring would have a severe transannular interaction. The striking similarity between the melting point curves in Fig. 44 may be a suggestion of isoelectronic structures, that is, tetrahedral positively charged phosphorus and "tetrahedral" negatively charged nitrogen. The additional ionic bonding might explain the shortening of the otherwise identical P–N bonds without hindrance to the almost "free" rotation which is suggested by the extreme flexibility[236,246] of these compounds. The bonding in cyclic phosphonitrile halides has for a long time remained controversial; the suggestion of electron delocalization and aromatic character[247] has been vigorously contested[248,249], one of the main counter-arguments being constancy[236,244,249] of the far-ultraviolet absorption along each of these series.

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# Inorganic, Organometallic, and Organic Analogues of Carbenes

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*This review deals with inorganic, organometallic, and organic compounds, as well as with elements, that on the basis of their electronic structure and their reactions can be regarded formally as analogues of carbenes. These "carbene analogues" include in particular the compounds of monovalent boron, aluminum, nitrogen, and phosphorus; those of divalent silicon, germanium, tin, and lead; atomic oxygen; atomic sulfur; and atomic selenium. The preparation and chemical properties of the carbenes and their analogues are compared.*

## 1. Introduction

The chemistry of carbenes has undergone a remarkable development in recent years[1–6]. The unusual reactions of these compounds are attributable to the fact that they contain a carbon atom with a sextet of electrons, two of which do not participate in the bonding. Depending on the preparation of the carbenes, these electrons may be in the unpaired (triplet) or paired (singlet) state. Owing to the unsaturation, most carbenes are electrophilic[7]. By addition of two electrons to complete the octet, the carbene carbon atom reverts to the tetravalent state, with formation of one ($sp^2$) or two ($sp^3$) new bonds.

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Many other elements have an electronic structure similar to that of carbene carbon atoms. *Volpin et al.* [8] characterized the "electronic analogue" of the carbenes by the following criteria:

1. At least one lone pair of s or p electrons (or two unpaired electrons) on the central atom;

2. at least one unoccupied p orbital (or two electrons in two p orbitals);

3. no unoccupied d level with a quantum number lower than that of the valence p electrons.

These features are found in the elements of Groups II and VI of the periodic system, as well as in compounds of the monovalent elements of Groups III and V, the bivalent elements of Group IV, and a few cations (*e.g.* $R_2N^+$, $RO^+$, $RS^+$, $Cl^+$, $Br^+$. However, many of the molecules and atoms mentioned react quite differently from the carbenes, whose characteristic property is the formation of one ($sp^2$) or two ($sp^3$) new covalent bonds. This chemical property will be regarded as a fourth criterion for carbene analogues.

For example, all cations of the types $R_2N^+$, $RO^+$, $Cl^+$ simply form a single ($sp^3$) covalent bond by accepting a pair of electrons from another atom or ion. These cations cannot be regarded as carbene analogues. The metals of Group II again satisfy only the first three conditions. They react with acids and halogens to form ionic salts. The metal M loses the valence electrons to form the cation $M^{2+}$, a reaction not observed with carbenes. Though Mg, Ba, and Ca react with aryl and alkyl halides to form compounds RMHal, corresponding to the insertion of carbenes into the C–Hal bond, the similarity is purely formal.

Thus of the numerous electronic analogues of carbenes, practically only a few compounds of elements of Groups III to V and the elements of Group VI in the atomic state remain as "chemical" analogues of carbenes. The present review deals with the preparation and properties of these compounds, and reactions that could proceed *via* such carbene analogues are also discussed.

## 2. Carbene Analogues with Elements of Group III

### a) Boron Compounds

Carbene analogues of the type :BR (R = halogen or H) are formed when energy is supplied to compounds of trivalent boron. For example, the action of a high-voltage or high-frequency electric discharge on $BCl_3$ vapor, without [9,10] or with added inert gas (argon, helium) [11], liberates :BCl, which was identified by its absorption and emission spectra. :BCl is formed also by UV discharge in $BCl_3$ [12,12a] and during flash photolysis of chlorides of trivalent boron, such as $BCl_3$, $B_2Cl_4$, or $(BCl)_4$ [13].

$$BCl_3 \xrightarrow{h\nu} :BCl + Cl_2$$

$$BCl_3 \xrightarrow[Hg]{h\nu} :BCl + HgCl_2$$

The :BCl liberated in this way has a life of about 0.01 sec [12], and can undergo insertion into the B–Cl bond as well as cyclopolymerization [13] and oxidation [12a].

$$BCl_3 + :BCl \underset{}{\overset{h\nu}{\rightleftharpoons}} B_2Cl_4$$

$$n{:}BCl \underset{}{\overset{h\nu}{\rightleftharpoons}} (BCl)_n$$

$$2{:}BCl + O_2 \longrightarrow 2\,BOCl \longrightarrow {}^2/_3\,(BOCl)_3$$

In the spontaneous dismutation of $B_2Cl_4$, which probably also proceeds *via* :BCl, *Urry et al.* [14] obtained not only the cyclotetramer $(BCl)_4$, but also stable free radicals of the composition $(B_{1.0}Cl_{0.9-1.1})_n$ and with a molecular weight of 650–750. These radicals are probably present as chains $\dot{Cl}B{-}(BCl)_{n-2}{-}\dot{B}Cl$.

By analogy with the formation of :BCl, it may be assumed that the polymers $(BH)_n$ formed by an electric discharge in diborane/hydrogen at a pressure of 10–15 mm Hg [15] result from the polymerization of borene, :BH.

$$B_2H_6 \longrightarrow [:BH] \longrightarrow 1/n\,(BH)_n$$

This assumption is supported by the formation of the analogous methylene ($:CH_2$) from hydrocarbons in an electric discharge [1].

The reaction of organoboron dichlorides $RBCl_2$ with alkali metals probably also proceeds *via* carbene analogues :BR. For example, when $C_6H_5BCl_2$ is heated with sodium, potassium, or a potassium-sodium alloy in toluene or xylene, the polymer $(BC_6H_5)_n$ ($n = 9$–12) is obtained [16], evidently from the initially formed monomeric phenylborene, $:BC_6H_5$.

$$C_6H_5BCl_2 \longrightarrow [:BC_6H_5] \longrightarrow 1/n\,(BC_6H_5)_n$$

The possibility of such a mechanism is suggested in particular by the formation of carbenes by the action of alkali metals on di-, tri-, and tetra-halogenomethanes [17].

### b) Aluminum Compounds

The monohalides of aluminum, :AlHal, are formed in the same way as :BCl when a UV discharge in a hydrogen discharge tube is passed through $AlBr_3$ vapor [12], or by a high-frequency discharge in $AlCl_3$, $AlBr_3$, or $AlI_3$ vapors [10]. The lifetime of :AlBr is approximately 0.01 sec [12].

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## 3. Carbene Analogues with Elements of Group IV

### a) Silicon Compounds

The compounds of bivalent silicon and germanium are of great interest from the point of view of carbene chemistry. In contrast to halogenocarbenes, which are readily formed by the action of strong bases (ROM or RLi) on halogenomethanes[4], :SiHHal and :$SiHal_2$ cannot be prepared from $H_2SiHal_2$, $HSiHal_3$, or $SiHal_4$. These compounds give products formed by nucleophilic substitution of the halogen and even of the H atoms by the group RO or R of the reagent used, probably due partly to the fact that the Si–H and C–H bonds are polarized in different directions (*e.g.* $\overset{\delta\ominus}{H}-\overset{\delta\oplus}{SiCl_3}$ and $\overset{\delta\oplus}{H}-\overset{\delta\ominus}{CCl_3}$) and partly to the stronger ionic character of the Si–Hal bond[18].

Whereas $CH_4$ and $CCl_4$ decompose into carbon and hydrogen or chlorine at 800–900 °C, $SiCl_4$ at 900 °C gives a gas mixture with an intense absorption maximum at 3150 Å. Similar spectra are given by $SnCl_2$ and $PbCl_2$ ($\lambda_{max}$ = 3100 Å). From these observations and from thermodynamic calculations, it was concluded[19] that $SiCl_4$ decomposes to :$SiCl_2$ and chlorine. Similarly, :$SiCl_2$ is formed from $SiCl_4$ and silicon at high temperatures[19]; it reacts further with silicon to SiCl.

$$SiCl_4 + Si \xrightarrow[800\,^\circ C]{} 2:SiCl_2 \xrightarrow[1150\,^\circ C]{2\,Si} 4\,SiCl$$

The formation of a mixture of lower silicon chlorides, *e.g.* of average composition $SiCl_{2.61}$, when silicon and tetrachlorosilane are heated together to about 1000 °C was observed by other authors[20]. *Schäfer* and *Nickl*[21] showed by kinetic and thermodynamic studies that the reaction of $SiCl_4$ with Si begins at 800 °C and is reversible. The heat and entropy of formation of gaseous :$SiCl_2$ are 29.9 kcal/mole and 71.1 cal $mole^{-1}\,deg^{-1}$, respectively, at 298 °K[21]. The intermediate formation of :$SiCl_2$ is the basis of most high-temperature methods for the preparation of chlorosilanes and organochlorosilanes from silicon or its alloys[22–24]. Under the conditions used, the silicon dichloride readily undergoes insertion into chemical bonds, such as H–Cl, C–Cl, or Si–Cl bonds to give compounds of tetravalent silicon.

For example, the high-temperature process for the preparation of chlorosilanes from carborundum (SiC) and $SiCl_4$ vapor diluted with a carrier gas such as $H_2$ or $N_2$ is based on the reactions[22]:

$$SiCl_4 + H_2 \rightleftharpoons :SiCl_2 + 2\,HCl$$
$$SiCl_4 + SiC \rightleftharpoons 2:SiCl_2 + C$$
$$HCl + :SiCl_2 \longrightarrow HSiCl_3$$
$$H_2 + :SiCl_2 \longrightarrow H_2SiCl_2$$
$$SiCl_4 + (n-1):SiCl_2 \longrightarrow Si_nCl_{2n+2}$$

For the preparation of higher chlorosilanes $Si_nCl_{2n+2}$, the reaction mixture must be quenched, since :$SiCl_2$ disproportionates on slow cooling to Si and $SiCl_4$[21].

The "direct" synthesis of trichlorosilane and organochlorosilanes from silicon and hydrogen chloride or organic chlorides also proceeds *via* :$SiCl_2$[23,24]. On the basis of the rate of formation of $HSiCl_3$ from Si and HCl and of the influence of the addition of HCl on the "direct" synthesis of methylchlorosilanes, *Joklik* and *Bažant*[24] proposed the following reaction scheme:

$$2\,HCl + Si \longrightarrow :SiCl_2 + H_2$$
$$HCl + :SiCl_2 \longrightarrow HSiCl_3$$
$$CH_3Cl + :SiCl_2 \longrightarrow CH_3\text{–}SiCl_3$$

Better yields of dialkyldichlorosilanes and alkyltrichlorosilanes are obtained in the "direct" synthesis when copper is added to the silicon[23]. This catalytic action is attributed[23] to the formation of cuprous chloride in the reaction zone; this reacts with silicon to form :$SiCl_2$, which is then converted into the organochlorosilanes:

$$CH_3Cl + Cu \longrightarrow CH_3Cl{\cdot}Cu$$
$$2\,CH_3Cl{\cdot}Cu \longrightarrow 2\,CuCl + CH_4 + C + H_2$$
$$Si + 2\,CuCl \longrightarrow :SiCl_2 + 2\,Cu$$
$$CH_3Cl{\cdot}Cu + :SiCl_2 \longrightarrow CH_3\dot{S}iCl_2 + CuCl$$
$$CH_3Cl{\cdot}Cu + CH_3\dot{S}iCl_2 \longrightarrow (CH_3)_2SiCl_2 + CuCl$$
$$CH_3Cl{\cdot}Cu + :SiCl_2 \longrightarrow CH_3SiCl_3 + Cu$$

The above scheme is confirmed by the increase in yield of $(C_2H_5)_2SiCl_2$ from $C_2H_5Cl$ and silicon when small quantities (*ca.* 2%) of CuCl are added to the silicon, and by the increase in yield of $C_2H_5SiCl_3$ when larger quantities ($\gg$2%) of CuCl are added[24].

The feasibility of the formation of :$SiCl_2$ under the conditions of the "direct" synthesis (300–400 °C) was confirmed by thermodynamic calculations[23,25]. :$SiCl_2$ has been detected by mass spectrometry in the gaseous products of the reaction of Si with CuCl at 180–200 °C[25].

According to thermodynamic calculations and kinetic measurements, :$SiCl_2$ also occurs as an intermediate in the preparation of Si by reduction of tri- and tetrachlorosilanes with hydrogen at 1000–2000 °K[26].

Whereas carbenes readily form dimers, no dimerization has been observed in the case of :$SiCl_2$, which telomerizes or polymerizes in the absence of electron acceptors. For example, $Si_{10}Cl_{22}$, $Si_{20}Cl_{42}$, and $Si_{25}Cl_{52}$ were obtained[27] by the decomposition of $SiCl_4$ in an atmosphere of nitrogen or hydrogen at 1000–1250 °C.

$$n\,SiCl_4 \longrightarrow n\,[:SiCl_2] \xrightarrow{SiCl_4} Cl_3Si\text{–}(SiCl_2)_n\text{–}Cl$$

In addition to $SiCl_4$, $H_2$ can also act as a telogen in this reaction, as is shown by the formation of $Si_{10}Cl_{20}H_2$

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and $Si_5Cl_{10}H_2$ from $SiCl_4$ in an atmosphere of hydrogen at 1150 to 1250 °C [27,28].

Similar polychlorosilanes having the composition $SiCl_{2.05-2.30}$, which may also be regarded as telomerization products of $:SiCl_2$ and $SiCl_4$ or $Si_2Cl_6$, are formed from hexachlorodisilane in the presence of trimethylamine or trimethylammonium halides at 80 to 100 °C [29] or in the presence of 2% of triethylamine in vacuum at room temperature [30].

$$n\,Si_2Cl_6 \xrightarrow[R_3N,\ R_3N\cdot HHal]{} Cl_3Si{-}(SiCl_2)_n{-}Cl + (n{-}1)SiCl_4$$

The thermal decomposition of $C_2H_5{-}SiCl_2{-}SiCl_3$ in the presence of $(CH_3)_3N{\cdot}HCl$ leads similarly to $(SiCl_2)_n$ and $C_2H_5{-}SiCl_3$ [29]; $(SiCl_{1.8})_n$ is formed when $Si_2Cl_6$ is heated with traces of $(C_2H_5)_3N$ [30]. The occurrence of $:SiCl_2$ as an intermediate in the decomposition of compounds of the type $RSiCl_2{-}SiCl_3$ (R = Cl or alkyl) is suggested not only by the composition of the resulting polymers, but also by the formation of dichlorocarbene when compounds of the type $RCCl_2{-}SiCl_3$ are heated [31].

The thermal reaction of $SiCl_4$ with Si has been used for the preparation of polymeric $(SiCl_2)_n$ ($n$ = 12–17) in the form of transparent, colorless or slightly yellow resins, which are readily soluble in organic solvents [32,33]. The probably cyclic $(SiCl_2)_n$ is formed above 900 °C, the yield and molecular weight increasing with rising temperature ($n$ increases from 12 at 900 °C to 16 at 1200 °C) [33]. The polymers prepared reduce $AgNO_3$ and $SbCl_3$ to the metals, and decompose to low molecular weight fragments $[(SiCl_2)_{n-a}$ to $:SiCl_2]$.

Similarly, when silicon tetrabromide is passed over silicon at 1200 °C in a high vacuum, the two substances form silicon dibromide $:SiBr_2$, which has been isolated in the polymeric form [34]. Reduction of the polymeric $(SiBr_2)_n$ with $LiAlH_4$ led to polymeric silylene $(SiH_2)_n$; alkylation with alkylmagnesium bromides gave polydialkylsilylenes $(SiR_2)_n$ (R=$CH_3$, $C_2H_5$, n-$C_3H_7$, or n-$C_4H_9$); and hydrolysis gave a polymeric acid of average composition $Si(OH)_{2.2}$.

Silicon difluoride can be prepared similarly to $:SiCl_2$ and $:SiBr_2$. $SiF_4$ vapor is led through a quartz tube packed with silicon powder at 1150–1200 °C in a high vacuum (residual pressure 0.04–0.2 mm Hg) [35,36]. $:SiF_2$ can also be prepared from carborundum (SiC) or calcium silicide ($CaSi_2$). Silicon difluoride exists as the monomer at −196 °C. Above −80 °C it gives a plastic polymer $(SiF_2)_n$, where $n \leq 16$. The "half-life" of gaseous $:SiF_2$ at room temperature is *ca.* 150 sec., *i.e.* at least 100 times greater than that of most carbenes [36].

According to *Schmeisser* and *Ehlers* [37], however, silicon difluoride prepared in this way, both in the monomeric and polymeric states, contains appreciable quantities of oxygen (≈ 0.3 atoms per atom of Si) derived from the quartz. $:SiF_2$ that is completely free from oxygen is formed on pyrolysis (700 °C) of hexafluorodisilane in a high vacuum [37].

$$Si_2F_6 \longrightarrow :SiF_2 + SiF_4$$

Polymeric $(SiF_2)_n$ is also obtained by the action of magnesium on dibromodifluorosilane in ether [38]. Probably, free $:SiF_2$ is involved as an intermediate by analogy with similar reactions of $CF_2Br_2$ and $CF_3Br$ [39]. The $(SiF_2)_n$ polymer generates on heating in vacuum to 200–400 °C all perfluorosilanes from $SiF_4$ to $Si_{14}F_{30}$ and a $(SiF)_x$ polymer or silicon. With 20% aqueous hydrofluoric acid $(SiF_2)_n$ forms silanes from $SiH_4$ to at least $Si_6H_{14}$ plus much hydrogen [36].

$:SiF_2$ reacts with $BF_3$ or $BCl_3$ at liquid nitrogen temperatures to form insertion products of type $Hal_2B(SiF_2)_nHal$, where $n$ = 2–4 and Hal = F or Cl [39a]. Under the same conditions $:SiF_2$ inserts readily into C–F bonds of trifluoroethylene [39b] and of perfluorobenzene [39c].

$$F_2C{=}CHF + :SiF_2 \longrightarrow$$

$$F_2C{=}CHSiF_3 + \begin{matrix} F_3Si & H \\ & C{=}C \\ F & F \end{matrix} + \begin{matrix} F_3Si & F \\ & C{=}C \\ F & H \end{matrix}$$

$$2\,C_6F_6 + 3\,:SiF_2 \longrightarrow C_6F_5SiF_3 + C_6F_4(SiF_3)_2$$

Addition of $:SiF_2$ to ethylene, acrylonitrile, 2,3-dimethyl-1,3-butadiene, and tetrafluoroethylene has been effected at −196 °C, the reaction with the last of these compounds leading to a solid polymer containing $SiF_2{-}SiF_2{-}CF_2{-}CF_2$ groups [35,39b].

Reaction of silicon difluoride with ethylene gives, among other products, cyclic adducts and some $C_2H_4SiF_2$ [39b].

$$H_2C{=}CH_2 + :SiF_2 \longrightarrow$$

$$\begin{matrix} H_2C{-}SiF_2 \\ | \quad\ | \\ H_2C{-}SiF_2 \end{matrix} + \begin{matrix} & H_2 & \\ H_2C & C & SiF_2 \\ | & & | \\ H_2C & & SiF_2 \\ & C & \\ & H_2 & \end{matrix} + C_2H_4SiF_2$$

Benzene and toluene give with $:SiF_2$ compounds of type $ArH(SiF_2)_n$, where $n$ = 2 to 8, in particular bicycles with $(SiF_2)_3$ bridges [39c].

[28] *R. Schwarz* and *R. Thiel*, Z. anorg. allg. Chem. *235*, 247 (1938); *R. Schwarz* and *A. Köster*, *ibid. 270*, 2 (1952).

[29] *C. J. Wilkins*, J. chem. Soc. (London) *1953*, 3409.

[30] *A. Kaczmarczyk* and *G. Urry*, J. Amer. chem. Soc. *82*, 751 (1960); also literature cited there.

[31] *W. I. Bevan*, *R. N. Haszeldine*, and *J. C. Young*, Chem. and Ind. *1961*, 789.

[32] *M. Schmeisser* and *P. Voss*, Z. anorg. allg. Chem. *334*, 50 (1964); see there for further literature.

[33] *P. W. Schenk* and *H. Bloching*, Z. anorg. allg. Chem. *334*, 57 (1964); see there for further literature.

[34] *M. Schmeisser* and *M. Schwarzmann*, Z. Naturforsch. *11b*, 278 (1956).

[35] *D. C. Pease*, US-Pat. 2840588 (24 June, 1958), Chem. Abstr. *52*, 19245 (1958).

[36] *P. L. Timms et al.*, J. Amer. chem. Soc. *87*, 2824 (1965).

[37] *M. Schmeisser* and *K.-P. Ehlers*, Angew. Chem. *76*, 781 (1964); Angew. Chem. internat. Edit. *3*, 700 (1964).

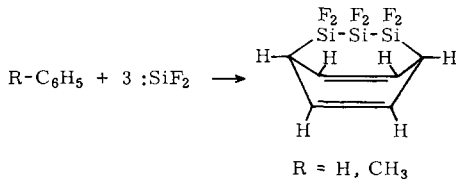
[38] *M. Schmeisser*, Angew. Chem. *66*, 713 (1954).

[39] *V. Franzen* and *L. Fikentscher*, Chem. Ber. *95*, 1958 (1962); *V. Franzen*, *ibid. 95*, 1964 (1962).

[39a] *P. L. Timms et al.*, J. Amer. chem. Soc. *87*, 3819 (1965).

[39b] *J. C. Thompson*, *J. L. Margrave*, and *P. L. Timms*, Chem. Commun. *1966*, 566.

[39c] *P. L. Timms*, *D. D. Stump*, *R. A. Kent*, and *J. L. Margrave*, J. Amer. chem. Soc. *88*, 940 (1966).



R = H, $CH_3$

Infrared studies of silicon difluoride and its reactions with $BF_3$, $O_2$, CO, NO, and other molecules in low-temperature matrices at 20–50 °K indicates the occurrence of a reactive species, probably $(SiF_2)_2$ [39d].

Polymeric silicon diiodide, $(SiI_2)_n$, a solid, amorphous, orange substance, was obtained [40] when $SiI_4$ was passed over silicon in a high vacuum at 800–900 °C (yield *ca.* 1%). A similar polymer, $(SiI_{2.2})_n$, which is insoluble in the common organic solvents was obtained in a yield of 60 to 70% when a glow discharge was passed through $SiI_4$ vapor in a high vacuum [40].

$$n\,SiI_4 \longrightarrow (SiI_{2.2})_n + 0.9\,n\,I_2$$

In a high vacuum at 220–230 °C, $(SiI_{2.2})_n$ changes into $(SiI_2)_n$, from which polymeric silicon mixed dihalides can be prepared by treatment with chlorine or bromine in benzene at −30 to +25 °C [40]:

$$(SiI_{2.2})_n \longrightarrow (SiI_2)_n + SiI_4 + Si_2I_6$$
$$(SiI_2)_n + Cl_2 \longrightarrow (SiClI)_n$$
$$(SiI_2)_n + Br_2 \longrightarrow (SiBrI)_n$$

The benzene-soluble polymer $(SiI_2)_n$ probably is also formed in the pyrolysis of $SiI_4$ in high vacuum at 800 to 900 °C [40].

High-temperature reactions of silicon tetrahalides with silicon and the pyrolytic decomposition of hexahalogenodisilanes $Si_2Hal_6$ or tetrahalogenosilanes $SiHal_4$ are general methods for the preparation of silicon dihalides, $:SiHal_2$. In contrast to $:SiHal_2$, dichlorocarbene cannot be prepared from $CCl_4$ and activated charcoal at 1200–1300 °C [41]. Kinetic investigation of this reaction with the aid of mass spectrometry shows that $:CCl_2$ does not occur as intermediate [42].

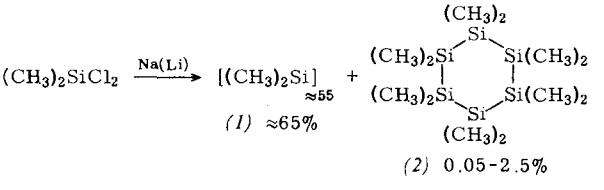
Silicon(II) dihalides are formed from halogen compounds of tetravalent silicon not only on heating, but also by the action of other sources of energy. For example, the telomers $Si_5Cl_{12}$ and $Si_6Cl_{14}$ have been prepared with the aid of a glow discharge in a mixture of gaseous $HSiCl_3$ and $H_2$ [43]. Passage of a mixture of $SiCl_4$ and $H_2$ through a glow discharge between Al electrodes (10000 V) in vacuum results in solid polymers of $(SiCl_2)_n$ and $(SiH_2)_n$ [43a]. On flash photolysis of $H_3SiCl$ or $H_3SiBr$, the fragments $:SiHCl$ or $:SiHBr$ occur in the absorption and fluorescence spectra in the region 4100 to 6000 Å [44].

Organic compounds of bivalent silicon and polymers thereof are obtained, unlike the halogen compounds, by reaction with metals. *Kipping et al.* [45] obtained polymers $[(C_6H_5)_2Si]_n$ from diphenyldichlorosilane and liquid sodium in the absence of solvents or in boiling toluene or xylene. *Gilman et al.* [46] later found that these products, which are also formed in the reaction of $(C_6H_5)_2SiCl_2$ with sodium, lithium, or magnesium in tetrahydrofuran, are essentially mixtures of the cyclopolymers $[(C_6H_5)_2Si]_n$ having $n = 4$ [47], 5, 6, and much greater than 6.

In our opinion the formation of these products may be attributed to cyclopolymerization of the intermediate diphenylsilylene which, unlike diphenylcarbene (formed *e.g.* from $(C_6H_5)_2CCl_2$ and lithium [17]), cannot dimerize. However, recent attempts [48] to identify $(C_6H_5)_2Si:$, which may be formed from $(C_6H_5)_2SiCl_2$ and lithium, by addition to cyclohexene were unsuccessful. [49].

Other diaryldichlorosilanes, *e.g.* $(p\text{-}CH_3\text{–}C_6H_4)_2SiCl_2$ [50], as well as phenoxydiphenylchlorosilane [51] react with sodium in the same way as $(C_6H_5)_2SiCl_2$.

Dialkyldichlorosilanes also react with alkali metals. Thus the reaction of $(CH_3)_2SiCl_2$ both with liquid sodium in benzene at 115–200 °C and *ca.* 16 atm [52] and with lithium in tetrahydrofuran at 250 °C and 50 atm [53] leads to a mixture of the polymer $[(CH_3)_2Si]_n$ *(1)*, where $n \approx 55$, with dodecamethylcyclohexasilane *(2)* [54].



*(1)* ≈65%

*(2)* 0.05–2.5%

The polydimethylsilylene $[(CH_3)_2Si]_n$ *(1)*, which is insoluble in organic solvents, and the cyclohexasilane *(2)* [54] were obtained in a total yield of 90–97% by the

[39d] *J. M. Bassler, P. L. Timms,* and *J. L. Margrave,* Inorganic Chem. *5*, 729 (1966).

[40] *M. Schmeisser* and *K. Friederich,* Angew. Chem. *76*, 782 (1964); Angew. Chem. internat. Edit. *3*, 699 (1964).

[41] *M. Schmeisser, H. Schröter,* and *H. Schilder,* Chem. Ber. *95*, 1648 (1962).

[42] *D. R. Bidinosti* and *R. F. Porter,* J. Amer. chem. Soc. *83*, 3737 (1961).

[43] *A. Besson* and *L. Fournier,* C. R. hebd. Séances Acad. Sci. *251*, 2987 (1960); cf. also *ibid. 150*, 1118 (1910) and [1].

[43a] *R. Schwarz* and *G. Pietsch,* Z. anorg. allg. Chem. *232*, 249 (1937).

[44] *G. Herzberg* and *R. D. Verma* in: Symposium on Molecular Structure and Spectroscopy, Columbus, Ohio, 1963, p. 49; cf. also [1,12,13].

[45] *F. S. Kipping* and *J. E. Sands,* J. chem. Soc. (London) *119*, 830, 848 (1921); *F. S. Kipping, ibid. 123*, 2590, 2598 (1923); *125*, 2291 (1924); *1927*, 2719; *F. S. Kipping* and *H. E. Murray, ibid. 1929*, 360.

[46] *H. Gilman* and *G. L. Schwebke,* Advances organometal. Chem. *1*, 89 (1964); and literature cited there.

[47] The primary product of this reaction is probably octaphenylcyclotetrasilane (see [39]). According to *E. Hengge, H. Reuter,* and *R. Petzold* [Z. Naturforsch. *18b*, 425 (1963)] this compound exists in two stereoisomeric forms.

[48] *H. Gilman* and *D. J. Peterson,* J. Amer. chem. Soc. *87*, 2389 (1965).

[49] Monoaryl- and particularly diarylcarbenes also have very low activities in electrophilic additions to double bonds; see *e.g.* [5,17]. Diphenylcarbene (from $(C_6H_5)_2CCl_2$ and Li in tetrahydrofuran) cannot even add to cyclohexene at −10 to 30 °C [*O. M. Nefedov* and *V. I. Shiryaev,* Ž. obšč. Chim., in press].

[50] *A. R. Steele* and *F. S. Kipping,* J. chem. Soc. (London) *1929*, 2545; and literature cited there.

[51] *F. S. Kipping,* J. chem. Soc. (London) *1927*, 2728.

[52] *C. A. Burkhard,* J. Amer. chem. Soc. *71*, 963 (1949).

[53] *E. Hengge* and *H. Reuter,* Naturwissenschaften *49*, 514 (1962).

[54] According to [53,60] the crystal form of *(2)* changes at 74 °C, and the compound sublimes above 120 °C, m.p. ≈140 °C. However, the publications [57,58] give m.p. 228–231 °C (with slight sublimation) and 248–250 °C (with preliminary heating of the block to 240 °C), respectively, in agreement with the data reported by *H. Gilman* and *R. A. Tomasi* [J. org. Chemistry *28*, 1651 (1963)].

reaction of $(CH_3)_2SiCl_2$ with lithium or sodium in tetrahydrofuran at atmospheric pressure between −60 and +70 °C[55–59]. This reaction yields linear and cyclic polymers in the ratio of from 9:1 to 1:3, depending on the conditions[57,58]. The reaction of dimethyldichlorosilane with an Na/K alloy in boiling tetrahydrofuran proceeds similarly (yield of *(1)* 13%, of *(2)* 81%[60].

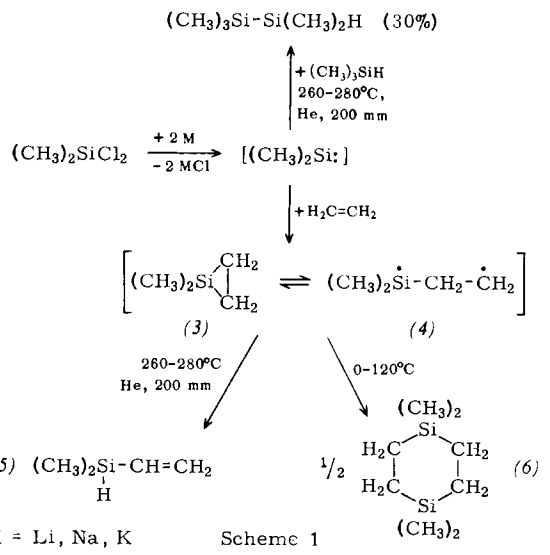
Similar products, *i.e.* the polymer $[(C_2H_5)_2Si]_n$, which is insoluble in organic solvents, and a crystalline cyclopolymer probably having the composition $[(C_2H_5)_2Si]_6$ or greasy or liquid polymers of the general formula $[(C_2H_5)_2Si]_n$, are formed in the reaction of $(C_2H_5)_2SiCl_2$ with lithium in tetrahydrofuran[56,58,59] or with sodium in boiling xylene[61] or toluene with added ethyl acetate[62].

By analogy with the reactions of halogenomethanes with lithium or lithium alkyls, in which carbenes are formed[63], $R_2Si$: is assumed to occur as intermediate in the reaction of dialkyldichlorosilanes with lithium or sodium[55,56,58,59].

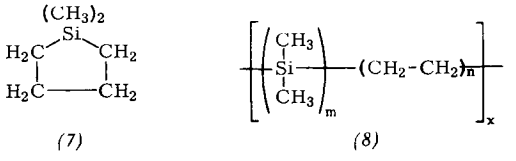
$$R_2SiCl_2 \xrightarrow[-LiCl]{2\ Li} R_2Si(Li)Cl \xrightarrow[-LiCl]{} [R_2Si:] \longrightarrow 1/n(R_2Si)_n$$

Scheme 1 shows a number of reactions that offer evidence of the intermediate formation of dimethylsilylene, $(CH_3)_2Si$:. These include the reaction of lithium with excess of dimethyldichlorosilane[64] and the addition of dimethylsilylene to trimethylsilane[65], to ethylene, and to a number of other olefins (isobutylene, 1-heptene, cyclohexene)[56,58,59,65,66].

The unstable primary products *(3)* and *(4)* can not only be stabilized by isomerization to form dimethylvinylsilane *(5)* or by dimerization to form the heterocycle *(6)*, but also by further reactions of *(4)* with ethylene

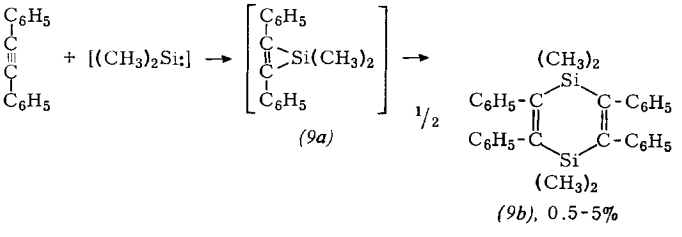



and dimethylsilylene to form 1,1-dimethyl-1-silacyclopentane *(7)* and a copolymer *(8)*, respectively.




The dimethylsilylene prepared in this way, which is probably in the singlet state, is characterized by low reactivity in electrophilic additions (*e.g.* the yields of *(6)*, *(7)*, and similar adducts are generally 2 to 10%). This can be attributed to the stabilizing influence of the unoccupied d orbitals of the silicon atom. In contrast to the alkylcarbenes, which very readily undergo the carbene-olefin or carbene-cyclopropane isomerization[5,61][*], dimethyl- and other dialkylsilylenes isomerize only to a maximum extent of 5% or not at all[57–59,65].

Dimethylsilylene is also assumed to be involved in the formation of the unsaturated heterocycle *(9b)*[67] from tolan, $(CH_3)_2SiCl_2$, and sodium in boiling xylene[8,68,69].




[*] The carbene-olefin and carbene-cyclopropane isomerizations may be illustrated by the equation

$$RR^1CH\text{-}CHR^2\text{-}\ddot{C}R^3 \longrightarrow RR^1CH\text{-}CR^2{=}CHR^3 + \begin{matrix} RR^1C\text{-}CHR^2 \\ \quad\ \diagdown C \diagup \\ \quad\ H \quad R^3 \end{matrix}$$

[55] *O. M. Nefedov, M. N. Manakov,* and *A. D. Petrov,* Izvest. Akad. Nauk SSSR, Otdel. chim. Nauk *1961*, 1717; *1962*, 1228.

[56] *O. M. Nefedov, M. N. Manakov,* and *A. D. Petrov,* Plaste u. Kautschuk *10*, 721 (1963).

[57] *O. M. Nefedov, G. Garzó, T. Székely,* and *W. I. Schiryaev,* Doklady Akad. Nauk SSSR *164*, 822 (1965).

[58] *O. M. Nefedov, W. I. Schiryaev, M. N. Manakov, et al.,* Ž. obšč. Chim., in press; *M. N. Manakov,* Dissertation, Moscow 1963.

[59] *O. M. Nefedov, T. Székely, et al.* in: Internat. Symposium on Organosilicon Chemistry, Sci. Commun. Prague 1965, p. 65.

[60] *U. Graf zu Stolberg,* Angew. Chem. *75*, 206, 347 (1963); Angew. Chem. internat. Edit. *2*, 150 (1963).

[61] Brit. Pat. 671774 (7 May 1952); Chem. Abstr. *46*, 8895 (1952).

[62] *A. D. Petrov, W. F. Mironov,* and *W. G. Gluchovzev,* Ž. obšč. Chim. *27*, 1535 (1957).

[63] See [5,17] and particularly [39], as well as *O. M. Nefedov* and *R. N. Shafran,* Izvest. Akad. Nauk. SSSR, Ser. chim. *1965*, 538. As was recently shown [*G. Köbrich, K. Flory,* and *W. Drischel,* Angew. Chem. *76*, 536 (1964); Angew. Chem. internat. Edit. *3*, 513 (1964); *W. T. Miller* and *D. M. Whalen,* J. Amer. chem. Soc. *86*, 2089 (1964)], compounds of carbon similar to $R_2(Li)SiCl$, *e.g.* $LiCHCl_2$ and $LiCCl_3$, are stable only at low temperatures (below −60 °C, generally from −110 to −115 °C).

[64] With a two- to threefold excess of $(CH_3)_2SiCl_2$, as with an excess of lithium, an extremely insoluble polymer *(1)* (yield 80%) and the cyclohexamer *(2)* (yield *ca.* 10%) are formed together with a very small quantity of linear α,ω-dichlorodi- and trisilanes (1–1.5%); see [58]; cf. *S. M. Shivukhin et al.,* Ž. obšč. Chim. *33*, 3274 (1963).

[65] *P. S. Skell* and *E. J. Goldstein,* J. Amer. chem. Soc. *86*, 1442 (1964).

[66] *O. M. Nefedov* and *M. N. Manakov,* Angew. Chem. *76*, 270 (1964); Angew. Chem. internat. Edit. *3*, 226 (1964).

[67] It was originally assumed that *(9a)* is formed from $(CH_3)_2Si$: and tolan, whereas its dimer *(9b)* is actually formed. See [68,69], and *N. G. Bokii,* Ž. strukturnoy Chim. *6*, 476, 571 (1965).

[68] *R. West* and *R. E. Bailey,* J. Amer. chem. Soc. *85*, 2871 (1963).

[69] *F. Johnson, R. S. Gohlke,* and *W. A. Nasutavicus,* J. organometal. Chem. *3*, 233 (1965).

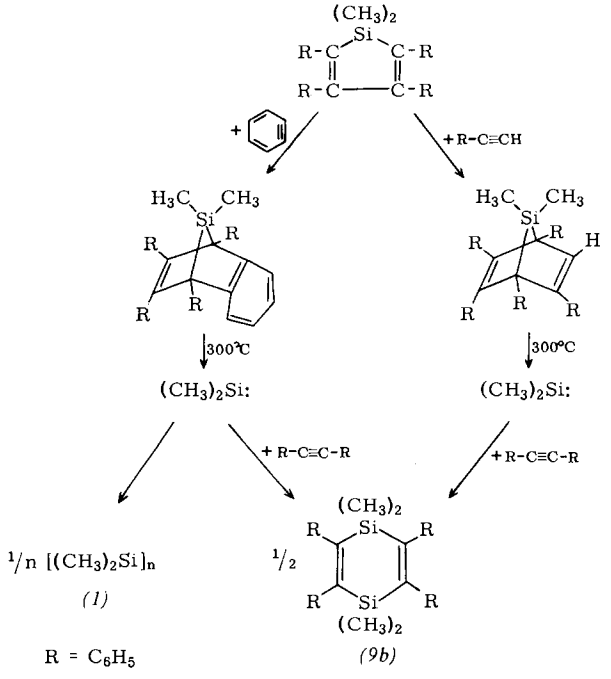
Monomeric and polymeric compounds of bivalent silicon can be obtained by the action of Grignard compounds having bulky substituents on bromosilanes [70].

$$2\,RMgBr + 2\,BrSiR'_3 \xrightarrow[-2MgBr_2]{} 2\,RSiR'_3 \xrightarrow[-R_2]{} R'_3Si{-}SiR'_3$$

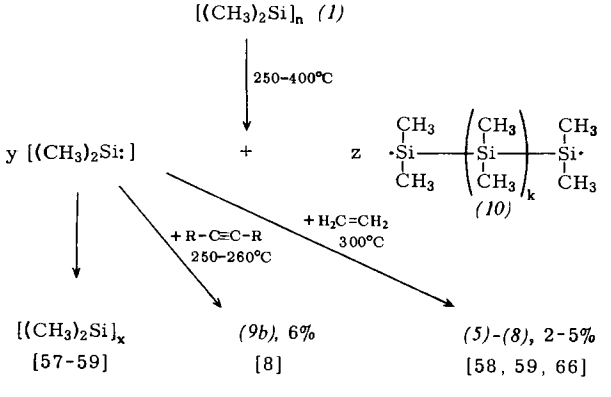
$$\xrightarrow[-R'_3SiR]{RMgBr} R'_3SiMgBr \xrightarrow[-R'MgBr]{} [:SiR'_2] \longrightarrow 1/n(SiR'_2)_n$$

R = sec-$C_4H_9$, tert-$C_4H_9$; R' = Br or R.

Dimethylsilylene was obtained [71] by thermolysis of adducts of 1,1-dimethyl-2,3,4,5-tetraphenyl-1-silacyclopentadiene with alkynes, *e.g.* benzyne or phenylacetylene.




The dimethylsilylene prepared in this way also adds to ethylene and other olefins to form heterocycles and linear hetero compounds of the type *(5)* to *(8)* [59]. Dimethylsilylene polymerizes to give, in the absence of acceptors, the polymer *(1)* [71]. Similarly diphenylsilylene was prepared from the adduct of 1,1,2,3,4,5-hexaphenyl-1-sila-2,4-cyclopentadiene with benzyne, and its polymerization and addition to tolan was achieved [71a].




R=$C_6H_5$

$0 \leqslant k < n$; $4 \leqslant x < n$

Dimethylsilylene probably is also formed, together with dimeric and polymeric biradicals *(10)*, in the pyrolysis of polymeric dimethylsilicon *(1)* in an inert atmosphere [8,57–59,66]. In the presence of acceptors (ethylene, tolan), adducts are formed; in the absence of acceptors, the biradicals recombine to give cyclic and linear polymer $[(CH_3)_2Si]_x$.

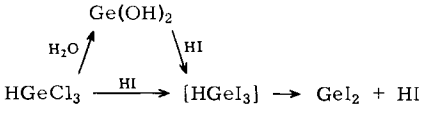
### b) Germanium Compounds

Germanium difluoride and particularly germanium diiodide, unlike the corresponding carbon and silicon dihalides, are stable even in the monomeric state. "Monomeric" here refers to the gaseous state; $GeI_2$ crystallizes in the brucite lattice, m.p. 48.5 °C. Solid $GeF_2$ is orthorhombic, m.p. 111 °C.

The classic preparation of germanium diiodide is the partial reduction of germanium tetraiodide with hypophosphorous acid [72] (75% yield):

$$GeI_4 + H_3PO_2 + H_2O \longrightarrow GeI_2 + H_3PO_3 + 2\,HI$$

$GeI_2$ is also formed [73] by the spontaneous decomposition of the unstable triiodogermane, which is prepared by exchange reactions from $HGeCl_3$ or its ether adducts [74].




Despite its stability, $GeI_2$ undergoes many reactions characteristic of carbenes and their analogues, though under more vigorous conditions. In particular, it inserts into C–I bonds [75–77]. This reaction is carried out in a sealed tube or in an autoclave.

$$Co_2(CO)_8 + GeI_2 \xrightarrow[THF]{\approx 20\,°;\ 10\ min} I_2Ge[Co(CO)_4]_2$$

$$RCH_2I + GeI_2 \xrightarrow[80–140\,°C]{} RCH_2GeI_3 \quad [75,76]$$

80–90%

$$C_6H_5I + GeI_2 \xrightarrow[160\,°C]{} C_6H_5GeI_3 \quad [76]$$

$$CF_3I + GeI_2 \xrightarrow[135\,°C]{} CF_3GeI_3 + (CF_3)_2GeI_2 \quad [77]$$

43% traces

R = H, $CH_3C_3H_7$, $CH_3O$, $C_2H_5OCO$, I

[70] *G. Schott* and *J. Meyer*, Z. anorg. allg. Chem. *313*, 107 (1961).

[71] *H. Gilman, S. G. Cottis*, and *W. H. Atwell*, J. Amer. chem. Soc. *86*, 1596 (1964).

[71a] *H. Gilman, S. G. Cottis*, and *W. H. Atwell*, J. Amer. chem. Soc. *86*, 5584 (1964).

[72] *E. A. Flood, L. S. Foster*, and *E. W. Pietrusza*, Inorg. Syntheses *2*, 106 (1946); *3*, 63 (1950).

[73] *T. K. Gar* and *W. F. Mironow*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 855; also literature there cited.

[74] *O. M. Nefedov, S. P. Kolesnikov*, and *W. I. Shevychenko*, Angew. Chem. *76*, 498 (1964); Angew. Chem. internat. Edit. *3*, 508 (1964); Doklady Akad. Nauk SSSR *162*, 589 (1965).

[75] *E. A. Flood*, J. Amer. chem. Soc. *55*, 4935 (1933); *E. A. Flood, L. S. Foster*, and *K. L. Godfrey*, Inorg. Syntheses 3, 64 (1950.)

[76] *M. Lesbre, P. Mazerolles*, and *G. Manuel*, C. R. hebd. Séances Acad. Sci. *257*, 2303 (1963).

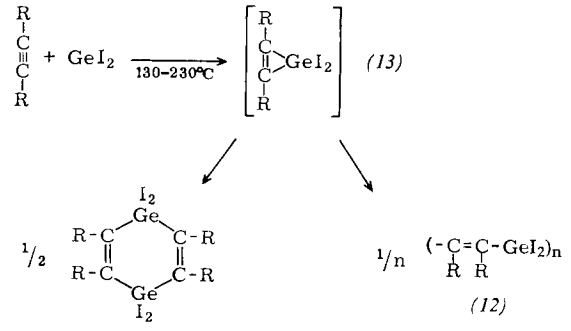
[77] *H. C. Clark* and *C. J. Willis*, J. Amer. chem. Soc. *84*, 898 (1962).

:$SiCl_2$ [78] and the carbenes, particularly methylene [79, 80], react similarly with organic halides. Germanium diiodide readily reacts with octacarbonyldicobalt [80a]:

$GeI_2$ also reacts with trialkyl- and triarylphosphines at about 130 °C to form adducts *(11)* that are formally analogous to phosphoranes [82].

$$R_3P + GeI_2 \longrightarrow R_3P{\cdot}GeI_2 \quad [81]$$
*(11)* R = alkyl, aryl

Like the dihalogenocarbenes [5,83], $GeI_2$ can add to CC triple bonds [8]. Like their silicon analogues [67] the germacyclopropenes *(13)* probably formed first are unstable and are converted into stable heterocycles *(14)* or polymers *(12)* [69,84].




R = H, $C_6H_5$

Nascent ethylene (liberated from 1,2-diiodoethane at 150 °C in a sealed tube) adds to $GeI_2$ to form a polymer $(CH_2{-}CH_2{-}GeI_2)_n$ [76].

$GeI_2$ can be added to isoprene and 2,3-dimethyl-1,3-butadiene in 1,4-position to form the corresponding heterocycles [84a]. This reaction with isoprene requires 3 hr at 60 °C, that with dimethylbutadiene is exothermic.

The stable monomeric germanium difluoride is obtained when germanium powder is heated with hydrogen fluoride (225 °C, 16 hours, 93% yield) [85].

$$Ge + 2HF \longrightarrow GeF_2 + H_2$$

$GeF_2$, like the silicon dihalides, also can be prepared from germanium and tetrafluorogermane at or above 100 °C [86].

$GeF_2$ readily forms the $GeF_3^{\ominus}$ ion and its salts, *e.g.* $CsGeF_3$ [85]. This formally corresponds to the equilibrium between dihalogenocarbenes and trihalogenomethyl anions [4,5]:

$$CHal_3^{\ominus} \rightleftharpoons :CHal_2 + Hal^{\ominus}$$

It is assumed [73] that germanium dibromide also exists as the monomer in solution. It is obtained in 56 to 65% yield by vacuum distillation of a solution of $HGeBr_3$ in aqueous hydrobromic acid or of a mixture with ether.

$GeBr_2$ can insert into polarized C-halogen bonds, and can add to CC triple bonds [73]:

$$H_2C{=}CH{-}CH_2Br + GeBr_2 \longrightarrow \underset{65\%}{H_2C{=}CH{-}CH_2{-}GeBr_3}$$

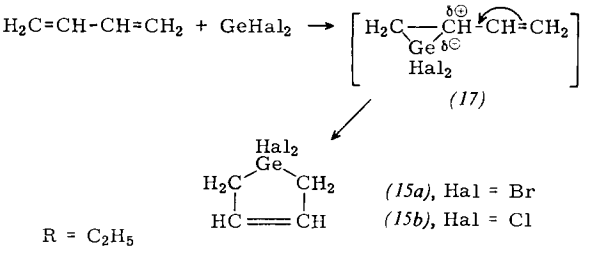
$$HC{\equiv}CH + GeBr_2 \longrightarrow 1/n(HC{=}CH{-}GeBr_2)_n$$

$GeBr_2$ reacts with butadiene at room temperature to give in 28% yield 1,1-dibromo-1-germa-3-cyclopentene *(15a)*, which is formally a 1,4-adduct [87]. Compound *(15a)* [73] or the dichloro derivative *(15b)* [74,88,89] is also formed when butadiene is passed through the ether adducts of tribromo- or trichlorogermane *(16)* [74]. The dichloro derivative *(15b)* is also formed, together with 2-butenyltrichlorogermane, by the reaction of butadiene with trichlorogermane [88,90]. The formation of germanium dihalides from trihalogenogermanes and particularly from their ether adducts *(16)* is attributable to the strong polarization of these compounds [74,89,91]. In addition to isomerization to the stable *(15)*, the unstable intermediate heterocycle *(17)* forms oligomers

$$HGeHal_3 \rightleftharpoons H^{\oplus} + GeHal_3^{\ominus}$$

$$[R_2O{\rightarrow}H{\cdots}OR_2]^{\oplus}GeHal_3^{\ominus} \rightleftharpoons [2\,R_2O{\cdot}H]^{\oplus} + GeHal_3^{\ominus}$$
*(16)*

$$GeHal_3^{\ominus} \rightleftharpoons GeHal_2 + Hal^{\ominus}$$




R = $C_2H_5$

[78] See Section 3a, particularly [23,25].

[79] *V. Franzen*, Liebigs Ann. Chem. *627*, 22 (1959).

[80] *M. Hudlický* and *V. König*, Collect. czechoslov. chem. Commun. *28*, 2824 (1963).

[80a] *D. J. Patmore* and *W. A. G. Graham*, Inorganic Chem. *5*, 1405 (1966).

[81] *R. B. King*, Inorganic Chem. *2*, 199 (1963).

[82] See [5], particularly p. 184.

[83] *R. R. Kostikov* and *I. A. Dyakonov*, Ž. obšč. Chim. *34*, 3845 (1964); *E. V. Dehmlov*, Tetrahedron Letters *1965*, 2317.

[84] *M. E. Volpin et al.*, Izvest. Akad. Nauk SSSR, Ser. chim. *1963*, 2067; further literature cited there; *L. W. Vilkov et al.*, Ž. fiz. Chim. *38*, 2674 (1964).

[84a] *P. Mazerolles* and *G. Manuel*, Bull. Soc. chim. France *1966*, 327; cf. [73, 87, 89].

[85] *E. L. Muetterties*, Inorganic Chem. *1*, 342 (1962).

[86] *L. M. Dennis* and *A. W. Laubengayer*, Z. physik. Chem. *130*, 530 (1927); *N. Bartlett* and *K. C. Yu*, Canad. J. Chem. *39*, 80 (1961). Cf. [21,32–34], particularly [35,36].

[87] Products of the formal 1,4-addition to 1,3-butadiene are also formed in reactions with other carbene analogues, *e.g.* :NH [*R. Appel* and *O. Büchner*, Angew. Chem. *74*, 430 (1962); Angew. Chem. internat. Edit. *1*, 332 (1962)] and carbenes, *e.g.* :$CH_2$ and :$CCl_2$ [*V. Franzen*, Chem. Ber. *95*, 571 (1962); *B. Grzybowska, J. H. Knox, et al.*, J. chem. Soc. (London) *1962*, 3826; *M. Orchin* and *E. C. Herrick*, J. org. Chemistry *24*, 139 (1959)].

[88] *O. M. Nefedov, S. P. Kolesnikov, A. S. Khatschaturov*, and *A. D. Petrov*, Doklady Akad. Nauk SSSR *154*, 1389 (1964).

[89] *O. M. Nefedov* and *S. P. Kolesnikov*, Izvest. Akad. Nauk SSSR, Ser. chim. *1966*, 201, and literature cited there.

[90] *W. F. Mironov* and *T. K. Gar*, Doklady Akad. Nauk SSSR *152*, 1111 (1963).

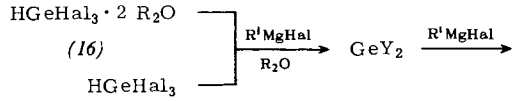
[91] Cf. method for the preparation of :$CHal_2$ by alkaline hydrolysis of $HCHal_3$ [4–6].

and polymers containing $CH_2-CH=CH-CH_2-GeHal_2$ units [88,89,92].

Trihalogenogermanes and their ether adducts react with other conjugated dienes to form similar compounds [90,92].

The ether adducts *(16)* have been found useful in many other reactions as sources of carbene-like compounds [74,89,90]. In particular, hydrolysis of *(16)* (and of $HGeHal_3$) leads to GeO or $Ge(OH)_2$. Organomagnesium and organolithium compounds cause the telomerization of germanium dihalides or their alkylation (arylation) products that is characteristic of carbenes and their analogues.

For example, the adducts *(16)* react with Grignard compounds to the polymers *(18)*.




$$R'-(GeY_2)_k-MgHal \xrightarrow[(R'Hal)]{R'MgHal} R'-(GeR'_2)_n-R' \quad [74,89]$$

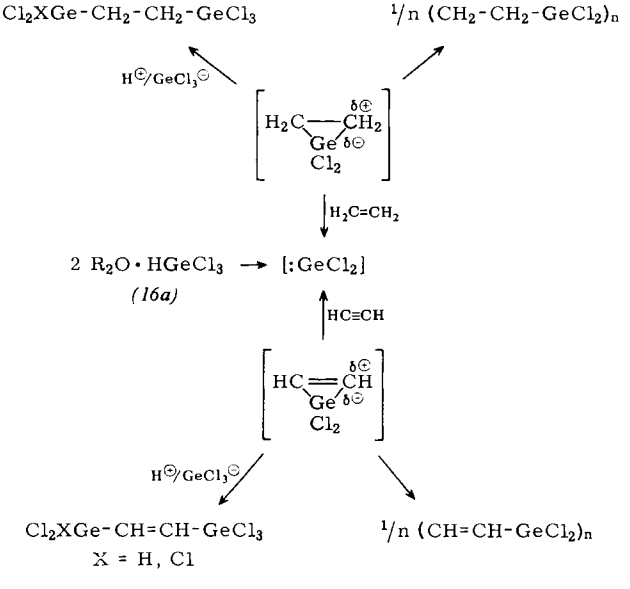
$R=C_2H_5$; $R'$ = Alkyl or Aryl; Hal = Cl, Br; Y = Cl, Br, Alkyl, or Aryl

The telomers *(18)* are formed also from $GeI_2$ and R'MgHal or R'Li [74,89].

The "carbene-like" character of the trihalogenogermanes, and in particular of their ether adducts *(16)*, is shown by their strong reducing action towards inorganic oxide salts and aromatic nitro compounds [74,93].

$GeCl_2$ is assumed to occur as an intermediate also in the reactions of trichlorogermane ether adducts *(16a)* with ethylene and acetylene [74,89,92]. Polymers containing $GeCl_2$ groups in the main chain are obtained also by the reaction of other olefins with $HGeCl_3$ in ether [92].

Corresponding to the preparation of $GeBr_2$ and $GeI_2$, germanium dichloride can be obtained from $HGeCl_3$ [94]




or its ether adduct [74,89], but only in the polymeric form. $(GeCl_2)_n$ is a solid which decomposes at about 140 °C. $(GeCl_2)_n$ and the monomeric germanium dihalides and their ether adducts dissolve readily in hydrochloric acid to form the trihalogenogermanes [74,89,95]. Germanium dichloride, probably also in the polymeric form, is formed when $GeCl_4$ vapor is passed over germanium powder at 350–430 °C [95].

Monomeric $GeCl_2$ in the form of its complex with dioxane, $C_4H_8O_2 \cdot GeCl_2$ is formed when trichlorogermane is mixed with dioxane [95a]. This complex reacts with 1,3-dienes, alkynes, benzyl chloride and other compounds similarly to the stable germanium dihalides and the ether complexes of trihalogermanes. $GeF_2$ forms the similar complex $(C_4H_8O_2)_x \cdot GeF_2$ ($x = 0.92–0.95$) with dioxane [85].

Chlorination of $(GeCl_2)_n$ leads to $GeCl_4$, hydrolysis to GeO, and the action of $H_2S$ to GeS. Heating yields subchlorides $(Ge_2Cl_3)_n$ and $(GeCl)_n$, or even Ge and $GeCl_4$ [74,95].

Unlike $GeF_2$, $GeBr_2$, and $GeI_2$, compounds of bivalent germanium with hydrogen or organic substituents are unstable in the monomeric state. $:GeH_2$ and $:GeR_2$ generally are liberated thermally or *via* organometallic compounds. For example, pyrolysis of the germanium hydrides $Ge_4H_{10}$ and $Ge_5H_{12}$ above 100 °C leads to germylene $:GeH_2$, which then polymerizes [96]. $:GeH_2$ and $(GeH_2)_n$ can be prepared also by reaction of bromobenzene with $NaGeH_3$ in benzene below −33 °C [97]. $NaGeH_3$ is obtained from $GeH_4$ and sodium in liquid ammonia.

$$NaGeH_3 + C_6H_5Br \longrightarrow [:GeH_2] \longrightarrow 1/n(GeH_2)_n$$

$$3(GeH_2)_n \xrightarrow[> 33\,^\circ C]{} n\,GeH_4 + 2(GeH)_n;$$

$$(GeH)_n \xrightarrow[180-300\,^\circ C]{} n\,Ge + n/2\,H_2$$

$(GeH_2)_n$, which is stable at room temperature, has also been prepared by reduction of tetrachlorogermane with $LiAlH_4$ in ether [98].

Dialkyl- and diarylgermanium dihalides $R_2GeHal_2$ react with alkali metals in the same way as $R_2SiHal_2$ to form linear and cyclic polymers $(R_2Ge)_n$. For example, $(C_6H_5)_2GeCl_2$ and sodium in boiling xylene give a cyclotetramer (35% yield) and a higher polymer (65% yield) [99].

The reaction proceeds probably *via* diphenylgermanium.

Diphenylgermanium may occur as an intermediate in the reaction of diphenyldichlorogermane with naphthalene-sodium in dimethoxyethane [99].

[92] *O. M. Nefedov* and *S. P. Kolesnikov*, Vysokomol. Soedin. *7*, 1857 (1965).

[93] *O. M. Nefedov, S. P. Kolesnikov*, and *N. N. Machova*, Izvest. Akad. Nauk SSSR, Ser. chim. *1964*, 2224; and literature cited there.

[94] *C. W. Moulton* and *J. G. Miller*, J. Amer. chem. Soc. *78*, 2702 (1956).

[95] *L. M. Dennis* and *H. L. Hunter*, J. Amer. chem. Soc. *51*, 1151 (1929).

[95a] *S. P. Kolesnikow, W. I. Schirjaew*, and *O. M. Nefedov*, Izvest. Akad. Nauk SSSR, Ser. chim. *1966*, 584.

[96] *E. Amberger*, Angew. Chem. *71*, 372 (1959); cf. [1,5,15].

[97] *S. N. Glarum* and *C. A. Kraus*, J. Amer. chem. Soc. *72*, 5398 (1950).

[98] *E. D. Macklen*, J. chem. Soc. (London) *1959*, 1984; the yield of $GeH_4$ in this case was only 30%, whereas almost quantitative yields of $CH_4$ and $SiH_4$ are obtained under the same conditions from $CCl_4$ and $SiCl_4$, respectively.

[99] *W. P. Neumann* and *K. Kühlein*, Liebigs Ann. Chem. *683*, 1 (1965); further literature cited there.

$$(C_6H_5)_2GeCl_2 \longrightarrow [(C_6H_5)_2Ge:] \longrightarrow [(C_6H_5)_2Ge]_5 + [(C_6H_5)_2Ge]_6 + [(C_6H_5)_2Ge]_n$$
37% 17%

Dialkyldichlorogermanes react similarly with alkali metals. Thus reduction of $(CH_3)_2GeCl_2$ with lithium in tetrahydrofuran leads to dodecamethylcyclohexagermane *(19)* and a polymer *(20)* that is insoluble in the usual solvents [56–59, 100].

$$(CH_3)_2GeCl_2 \longrightarrow (CH_3)_2Ge(Li)Cl \longrightarrow [(CH_3)_2Ge:] \longrightarrow [(CH_3)_2Ge]_6 + [(CH_3)_2Ge]_n$$
*(19)* *(20)*

Under optimal conditions, the yields of *(19)* and *(20)* were as high as 70–80%. Monomeric dimethylgermanium was detected by the almost complete absence of low molecular weight polygermanes when lithium was added to a large excess of $(CH_3)_2GeCl_2$ [58] and by the addition of $(CH_3)_2Ge:$ to ethylene [56, 58, 59, 66].

Diethylgermanium $(C_2H_5)_2Ge:$ probably occurs as intermediate in the reaction of $(C_2H_5)_2GeCl_2$ with lithium in tetrahydrofuran, which leads mainly to insoluble polydiethylgermanium $[(C_2H_5)_2Ge]_n$ [58, 59]. Phenylgermanium chloride $C_6H_5(Cl)Ge:$ may be involved as intermediate in the reactions of $C_6H_5GeCl_3$ with alkali metals [101].

Polymers of bivalent germanium can be prepared by thermal or photochemical decomposition of polymeric germanium-mercury compounds [99].

$$(C_6H_5)_2GeH_2 + (C_2H_5)_2Hg \xrightarrow[-2\,C_2H_6]{} {}^1/_m \left( \begin{matrix} C_6H_5 \\ | \\ -Ge- \\ | \\ C_6H_5 \end{matrix} -Hg- \right)_m$$

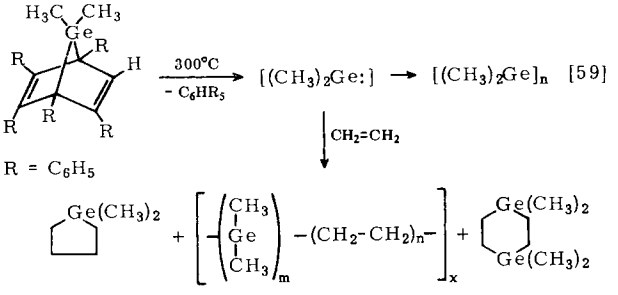
$$\xrightarrow[-Hg]{\Delta,\ h\nu} [(C_6H_5)_2Ge:] \longrightarrow [(C_6H_5)_2Ge]_4 + [(C_6H_5)_2Ge]_n$$
34% 66%

Neither $(C_6H_5)_2Ge:$ nor the polymers $[(C_6H_5)_2Ge]_n$ can be prepared by the action of $C_6H_5Li$, $C_6H_5MgBr$, or $(C_6H_5)_3Al$ on $GeI_2$. It must nevertheless be assumed that $(C_6H_5)_2Ge:$ is formed initially. Its formation is indicated in particular by the production of small quantities of triphenylgermane in the hydrolysis of $(C_6H_5)_3GeLi$, which was probably formed from $(C_6H_5)_2Ge:$ and $C_6H_5Li$ [102].

$$GeI_2 + 2\,C_6H_5Li \xrightarrow[-2\,LiI]{} [(C_6H_5)_2Ge:]$$
$$\downarrow C_6H_5Li$$
$$(C_6H_5)_3GeLi$$
$$\swarrow H_2O \qquad \searrow [(C_6H_5)_2Ge:]$$
$(C_6H_5)_3GeH$ Telomers

Diethyl- and di-n-butylgermanium is formed by the action of mercury dialkyls $R_2Hg$ on $GeI_2$ in ether [103]. However, these compounds immediately change into stable telomers.

Finally, $R_2Ge:$ can be obtained by thermal depolymerization of $(R_2Ge)_n$ [57–59, 66] and by pyrolysis of the phenylacetylene-germacyclopentadiene adduct [59].




### c) Tin Compounds

The halogen compounds of bivalent tin are obtained when tin is dissolved in halohydric acids [104]. They are stable in air.

$$Sn + 2\,HHal \longrightarrow SnHal_2 + H_2$$
Hal = Cl, Br, I

The difluoride is formed by the action of anhydrous hydrogen fluoride on tin [85] (8 hours at 200 °C). Tin diiodide can also be prepared from $SnCl_2$ and KI [104].

The unsaturated (carbene-like) character of the tin dihalides is shown in many addition reactions that are also characteristic of dihalogenocarbenes and their other analogues.

$$SnHal_2 + 1/2O_2 \longrightarrow OSnHal_2 \quad [105]$$

$$SnHal_2 + Hal_2 \longrightarrow SnHal_4 \quad [105]$$

$$SnI_2 + CH_3I \xrightarrow[4\ hr]{160\,^\circ C} CH_3SnI_3 \quad [106]$$
25%

$$2\,SnCl_2 + 2{:}CH_2 \longrightarrow 2\,[Cl_2Sn{=}CH_2] \xrightarrow{SnCl_2} 1/n(SnCl_2CH_2SnCl_2CH_2SnCl_2) \quad [105a]$$

$$\pi\text{-}C_5H_5Fe(CO)_2Cl + SnCl_2 \longrightarrow \pi\text{-}C_5H_5Fe(CO)_2SnCl_3 \quad [106a]$$

$$[\pi\text{-}C_5H_5Fe(CO)_2]_2 + SnHal_2 \longrightarrow [\pi\text{-}C_5H_5Fe(CO)_2]_2SnHal_2 \quad [106a, 106b]$$

$$[\pi\text{-}C_5H_5NiCO]_2 + SnCl_2 \xrightarrow[2hr,THF]{\approx 80°C} Cl_2Sn[\pi\text{-}C_5H_5NiCO]_2 \quad [106b]$$

$$[(C_6H_5)_3PCo(CO)_3]_2 + SnCl_2 \xrightarrow[THF]{\approx 80°C;\ 3\,hr} Cl_2Sn[(C_6H_5)_3PCo(CO)_3]_2 \quad [106b]$$

$$Co_2(CO)_8 + SnHal_2 \xrightarrow[THF]{\approx 20°C;\ 15\,min} Hal_2Sn[Co(CO)_4)_2 \quad [106b]$$

[100] *O. M. Nefedov, M. N. Manakov,* and *A. D. Petrov,* Doklady Akad. Nauk SSSR *147,* 1376 (1962).

[101] *W. Metlesics* and *H. Zeiss,* J. Amer. chem. Soc. *82,* 3321 (1960); further literature cited there.

[102] *F. Glockling* and *K. A. Hooton,* J. chem. Soc. (London) *1963,* 1849; cf. the reaction of the ether adducts *(16)* with organometallic compounds [74, 89].

[103] *G. Jacobs,* C. R. hebd. Séances Acad. Sci. *238,* 1825 (1954).

[104] *G. Brauer:* Handbuch der Präparativen Anorganischen Chemie. Enke, Stuttgart 1954.

[105] *P. Pfeiffer,* Ber. dtsch. chem. Ges. *44,* 1269 (1911).

[105a] *A. Ya. Yakubovich et al.,* Doklady Akad. Nauk SSSR *72,* 69 (1950).

[106] *P. Pfeiffer* and *I. Heller,* Ber. dtsch. chem. Ges. *37,* 4618 (1904).

[106a] *F. Bonati* and *G. Wilkinson,* J. chem. Soc. (London) *1964,* 179.

[106b] *D. J. Patmore* and *W. A. G. Graham,* Inorganic Chem. *5,* 1405 (1966).

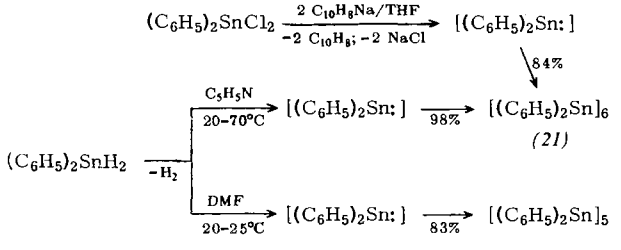
$SnCl_2$ and $SnBr_2$ can displace mercury from its dialkyl and in particular from its diaryl derivatives[107]:

$$R_2Hg + SnHal_2 \longrightarrow R_2SnHal_2 + Hg$$

$SnCl_2$ and its solutions in hydrochloric acid, as well as $SnCl_2$-ether adducts, have a strong reducing action towards inorganic salts, aromatic nitro compounds, and azides[93,107,108].

Preparation and properties of organic derivatives of bivalent tin have been reported by *Ingham et al.*[109] and by *Neumann*[110]. Dialkyl- and diaryltin, like their silicon and germanium analogues, are stable only in the polymeric form[110], although monomeric tin dialkyls and in particular monomeric diphenyltin were formerly thought to be fairly stable[111]. The polymeric nature of dibutyltin and diphenyltin has been deduced from the Mössbauer spectra[112].

The best methods for the preparation of cyclopolymers of diphenyltin $[(C_6H_5)_2Sn]_n$ are the catalytic decomposition of diphenyltin hydride in the presence of amines or amides[110, 113] and the action of naphthalenesodium on diphenyldichlorostannane[113].




Cyclohexamers of di-*p*-tolyl-, di-*p*-ethoxyphenyl-, di-*p*-biphenylyltin, and di-α- and di-β-naphthyltin have been obtained in high yields by catalytic decomposition of the corresponding diaryltin dihydrides[114].

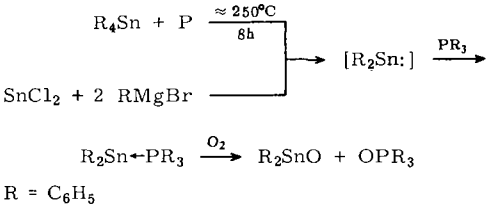
The cyclohexamer *(21)* is formed also by the action of alkali metals, zinc, or magnesium on $(C_6H_5)_2SnCl_2$ in tetrahydrofuran (yield 5–25%)[113]. However, the reaction of $C_6H_5MgBr$ with $SnCl_2$ in tetrahydrofuran leads to polymers *(22)* with $n = 13–14$, which are probably also cyclic[113]. The polymer *(22)* is formed also during the thermal dehydrobromination of diphenylbromostannane[115].

$$(C_6H_5)_2SnHBr \longrightarrow [(C_6H_5)_2Sn:] \longrightarrow 1/n[(C_6H_5)_2Sn]_n \quad (22)$$

Probably the cyclopolymers *(22)* readily undergo complete depolymerization. Their chemical properties show them to be typical carbene analogues. In particular, they are readily oxidized by atmospheric oxygen or hydrogen peroxide to $(C_6H_5)_2SnO$. They add sulfur and halogens to form $(C_6H_5)_2SnS$ and $(C_6H_5)_2SnHal_2$, respectively, and reduce $AgNO_3$ and $HgCl_2$ to the metals[109,113,116]. A particularly characteristic property of diphenyltin is its ability to undergo insertion into the S–S bond of dibenzyl disulfide[116]:

$$C_6H_5{-}CH_2{-}S{-}S{-}CH_2{-}C_6H_5 + 1/n[(C_6H_5)_2Sn]_n \longrightarrow (C_6H_5)_2Sn(S{-}CH_2{-}C_6H_5)_2$$

Like carbenes and other carbene analogues diphenyltin forms an easily oxidized complex $(C_6H_5)_2Sn{\cdot}P(C_6H_5)_3$ with triphenylphosphine[116a]:




Diphenyltin adds to compounds containing CC double bonds, *e.g.* tetrafluoroethylene[117].

$$x\,F_2C{=}CF_2 + x/n[(C_6H_5)_2Sn] \xrightarrow{h\nu} [(C_6H_5)_2Sn{-}CF_2{-}CF_2]_x$$

Diphenyltin, like carbene, can insert into C–Li bonds[109,118]:

$$SnCl_2 + 2\,C_6H_5Li \longrightarrow [(C_6H_5)_2Sn:] \xrightarrow{C_6H_5Li} (C_6H_5)_3SnLi$$

The tendency of polymeric diphenyltin to depolymerize and the biradical character of $(C_6H_5)_2Sn:$ are confirmed by the addition of free radicals[116,119].

$$(C_6H_5COO)_2 \xrightarrow{\Delta} 2\,C_6H_5COO\cdot \xrightarrow{2\,[(C_6H_5)_2Sn:]} \begin{matrix}(C_6H_5)_2Sn\text{-}Sn(C_6H_5)_2\\ C_6H_5COO\quad OCOC_6H_5\end{matrix} \quad [116]$$

$$(C_6H_5)_3C{-}N{=}N{-}C_6H_5 \xrightarrow{\Delta} C_6H_5\cdot \xrightarrow{[(C_6H_5)_2Sn:]} (C_6H_5)_3Sn\cdot \longrightarrow 1/2\,(C_6H_5)_3Sn{-}Sn(C_6H_5)_3 \quad [119]$$

$$C_6H_5{-}\underset{\underset{O}{\downarrow}}{\overset{\overset{\downarrow}{N}}{N}}{-}COCH_3 \xrightarrow{\Delta} C_6H_5\cdot + CH_3COO\cdot \xrightarrow{[(C_6H_5)_2Sn:]} 1/2\,(C_6H_5)_4Sn + 1/2\,(C_6H_5)_2Sn(OCOCH_3)_2 \quad [119]$$

[107] *A. N. Nesmejanow* and *K. A. Kozeschkow*, Ber. dtsch. chem. Ges. *63*, 2496 (1930).

[108] *O. Dimroth et al.*, Ber. dtsch. chem. Ges. *40*, 2376 (1907); *43*, 2757 (1910); *50*, 1534 (1917).

[109] *R. K. Ingham*, *S. D. Rosenberg*, and *H. Gilman*, Chem. Reviews *60*, 459 (1960).

[110] *W. P. Neumann*, Angew. Chem. *75*, 225 (1963); Angew. Chem. internat. Edit. *2*, 165 (1963).

[111] See, *e.g.*, *E. Krause* and *R. Becker*, Ber. dtsch. chem. Ges. *53*, 173 (1920); *R. F. Chambers* and *P. C. Scherer*, J. Amer. chem. Soc. *48*, 1054 (1926).

[112] *W. I. Goldansky*, *W. Ya. Rochev*, and *W. W. Khrapov*, Doklady Akad. Nauk SSSR *156*, 909 (1964).

[113] *W. P. Neumann* and *K. König*, Liebigs Ann. Chem. *677*, 1 (1964); further literature cited there.

[114] *W. P. Neumann* and *K. König*, Liebigs Ann. Chem. *677*, 12 (1964).

[115] *G. Fritz* and *H. Scherer*, Z. anorg. allg. Chem. *338*, 1 (1965).

[116] *H. G. Kuivila* and *E. R. Jakusik*, J. org. Chemistry *26*, 1430 (1961).

[116a] *H. Schumann*, *H. Köpf*, and *M. Schmidt*, Z. Naturforsch. *19b*, 168 (1964); cf. [81,82].

[117] *A. A. A. Beg* and *H. C. Clark*, Chem. and Ind. *1962*, 140.

[118] *G. Wittig*, *F. I. Meyer*, and *G. Lange*, Liebigs Ann. Chem. *571*, 167 (1951).

Dialkyltin polymers are prepared like polymeric diaryltin, *e.g.* by reaction of alkylmagnesium halides or alkyl-lithium with tin dihalides[109,110,120] or with the ether adducts $2R_2O{\cdot}HSnCl_3$[89], by reaction of dialkyltin dihalides with alkali metals or organic bases[116]. Moreover, the formation of the cyclotetramer *(23)* has been observed during the reaction of excess of t-butylmagnesium chloride on t-butyltin chloride in boiling tetrahydrofuran[121].

$$(t\text{-}C_4H_9)_2SnCl_2 \longrightarrow \underset{(23)}{1/4[(t\text{-}C_4H_9)_2Sn]_4} \quad 56\%$$

The most suitable method for the preparation of dialkyltins is the catalytic or thermal dehydrogenation of the dialkyltin dihydrides; the degree of polymerization of the final product $(R_2Sn)_n$ in this case is mainly determined by the catalyst[110,120].

$$(C_2H_5)_2SnH_2 \xrightarrow[-H_2]{(C_2H_5)_2SnCl_2{\cdot}2\,C_5H_5N} [(C_2H_5)_2Sn:] \longrightarrow \underset{94\,\%}{1/9[(C_2H_5)_2Sn]_9} \quad [120]$$

$$(n\text{-}C_4H_9)_2SnH_2 \xrightarrow[-(CH_3)_2CHOH]{(CH_3)_2CO} (\text{or } \xrightarrow[-H_2]{100\,^\circ C}) \; [(n\text{-}C_4H_9)_2Sn:] \longrightarrow 1/n[(n\text{-}C_4H_9)_2Sn]_n \quad [122]$$

The preparation and decomposition of the dialkyltin dihydrides (and diaryltin dihydrides) can be carried out in a single process:

$$R_2SnCl_2 + 2(C_2H_5)_3SnH \xrightarrow[4-7\ hr]{100-120\,^\circ C} 1/n(R_2Sn)_n + 2(C_2H_5)_3SnCl + H_2 \quad [123]$$

R = $C_2H_5$, n-$C_4H_9$, $C_6H_5$.

Ethyltin bromide can be prepared similarly from $C_2H_5SnH_2Br$, the product again being polymeric[115].

The chemical properties of the tin dialkyls closely resemble those of the polymeric tin diaryls.

$$(R_2Sn)_n + n/2\,O_2 \longrightarrow n\,R_2SnO \quad [109]$$

$$[(C_2H_5)_2Sn]_9 + 9\,Cl_2 \xrightarrow[-70\,^\circ C]{} 9(C_2H_5)_2SnCl_2 \quad [120]$$

$$[(C_2H_5)_2Sn]_n + n\,HgCl_2 \longrightarrow n(C_2H_5)_2SnCl_2 + n\,Hg \quad [124]$$

$$[(C_2H_5)_2Sn]_n + n(C_6H_5)_2Hg \longrightarrow n(C_2H_5)_2Sn(C_6H_5)_2 + n\,Hg \quad [124]$$

$$[(C_2H_5)_2Sn]_n + n(C_6H_5COO)_2 \xrightarrow{\Delta} n(C_2H_5)_2Sn(OCOC_6H_5)_2 \quad [123]$$

R = Alkyl

Dialkyltin also readily inserts into C–Hal, Sn–Na, Sn–H, and apparently also Sn–Cl bonds.

$$[(C_2H_5)_2Sn]_n + nC_2H_5I \longrightarrow n(C_2H_5)_3SnI \quad [105]$$

$$[(n\text{-}C_4H_9)_2Sn]_n + n\,RHal \longrightarrow n\,(n\text{-}C_4H_9)_2Sn(Hal)R \quad [125]$$

R = n-$C_4H_9$, $C_6H_5$, $CH_2{=}CH{-}CH_2$, $C_6H_5{-}CH_2$; Hal = Br, Cl

$$[(CH_3)_2Sn]_n + n\,Na_2Sn(CH_3)_2 \longrightarrow n(CH_3)_2Sn(Na){-}Sn(Na)(CH_3)_2 \quad [126]$$

$$[(C_4H_9)_2Sn]_n + n\,H_2Sn(C_4H_9)_2 \longrightarrow n(C_4H_9)_2SnH{-}SnH(C_4H_9)_2 \quad [122]$$

$$(R_2Sn)_n + n\,R_2SnCl_2 \longrightarrow R_2SnCl{-}SnClR_2 \quad [116]$$

R = Alkyl or Aryl

In addition to the tin dialkyls and diaryls, many other organic and inorganic derivatives of bivalent tin have been prepared, mostly from tin dihalides, *e.g.*:

$$2SnBr_2 + 4NaOCH_3 \longrightarrow 2Sn(OCH_3)_2 \xrightarrow[-2\,HB(OCH_3)_2]{3\,B_2H_6} 2Sn(BH_4)_2 \quad [127]$$

### d) Lead Compounds

Lead dihalides should also exhibit properties of carbenes, but these should be much less pronounced than those of tin dihalides. For example, whereas chlorine adds irreversibly to $SnCl_2$ with formation of $SnCl_4$, $PbCl_4$ prepared similarly explodes spontaneously[104].

Organic derivatives of bivalent lead probably are formed in the reaction of Pb(II) salts with organometallic compounds.

$$PbCl_2 + 2\,CH_2{=}CH{-}CH_2{-}MgBr \longrightarrow (CH_2{=}CH{-}CH_2)_2Pb + MgCl_2 + MgBr_2 \quad [128]$$

$$Pb(NO_3)_2 + 2\,C_5H_5Na \longrightarrow (C_5H_5)_2Pb + 2\,NaNO_3 \quad [129]$$

$$PbCl_2 + 2\,ArMgBr \longrightarrow Ar_2Pb + MgCl_2 + MgBr_2 \quad [130,131]$$

$$PbCl_2 + 2\,C_6H_5Li \longrightarrow (C_6H_5)_2Pb + 2\,LiCl \quad [131]$$

Ar = $C_6H_5$, $CH_3{-}C_6H_4$

The compounds $R_2Pb$ formed under these conditions cannot generally be isolated, even as polymers, since they readily react further.

$$3\,R_2Pb \longrightarrow 2\,R_3Pb + Pb \; \textit{etc.}$$

$$2\,R_2Pb \longrightarrow R_4Pb + Pb \quad [128,131,132]$$

[119] *G. A. Rasuvaev* and *E. I. Fedotova*, Ž. obšč. Chim. *21*, 1118 (1951).

[120] *W. P. Neumann* and *J. Pedain*, Liebigs Ann. Chem. *672*, 34 (1964); further literature cited there.

[121] *W. V. Farrar* and *H. A. Skinner*, J. organometal. Chem. *1*, 434 (1964); cf. [70].

[122] *H. G. Kuivila et al.*, J. Amer. chem. Soc. *83*, 1246 (1961); *85*, 1010 (1963).

[123] *N. S. Vyasankin*, *G. A. Rasuvaev*, and *S. P. Korneva*, Ž. obšč. Chim. *34*, 2787 (1964).

[124] *A. N. Nesmeyanov*, *K. A. Kocheshkov*, and *W. P. Puzireva*, Ž. obšč. Chim. *7*, 118 (1937).

[125] *W. T. Bischkov* and *N. S. Vyasankin*, Ž. obšč. Chim. *35*, 687 (1965).

[126] *C. A. Kraus* and *W. N. Greer*, J. Amer. chem. Soc. *47*, 2568 (1925).

[127] *E. Amberger* and *M.-R. Kula*, Chem. Ber. *96*, 2556, 2562, (1963); further literature cited there.

[128] *K. V. Vijayarahavan*, J. Indian chem. Soc. *22*, 227 (1945).

[129] *E. O. Fischer* and *H. Grubert*, Z. anorg. allg. Chem. *286*, 237 (1956).

[130] *E. Krause* and *G. G. Reissaus*, Ber. dtsch. chem. Ges. *55*, 888 (1922).

[131] *E. Bindschadler* and *H. Gilman*, Proc. Iowa Acad. Sci. *48*, 273 (1941); Chem. Abstr. *36*, 1595 (1942).

[132] *L. C. Willemsens* and *G. J. M. van der Kerk*, J. organometal. Chem. *2*, 271 (1964); further literature cited there.

Reactions of $PbCl_2$ with organometallic compounds are used to prepare organic derivatives of quadrivalent lead [133], *e.g.*:

$$4\,C_6H_5Li + 2\,PbCl_2 \longrightarrow 2(C_6H_5)_2Pb \xrightarrow{2\,C_6H_5Li} 2\,(C_6H_5)PbLi$$

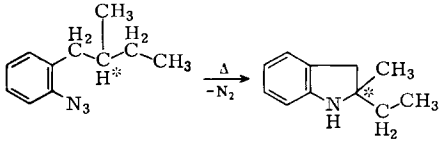
$$\xrightarrow{PbCl_2} [(C_6H_5)_3Pb]_2Pb \longrightarrow 1/2\,[(C_6H_5)_3Pb]_4Pb + 1/2\,Pb$$

## 4. Carbene Analogues with Elements of Group V

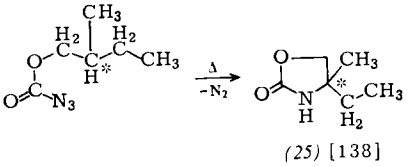
### a) Nitrogen Compounds

The compounds of univalent nitrogen, :NR or ·NR, which are known as imenes, nitrenes, or azenes, have been studied more fully than any other carbene analogues [134, 135]. Imenes and carbenes, which are prepared from azides and diazo compounds, respectively, were compared by *Kirmse* [136].

Of the more recent publications that were not mentioned in the reviews [134–136], we shall select only a few. Studies on intermolecular and intramolecular insertions of imenes into aliphatic C–H bonds were concerned with the direction and selectivities of these reactions, the relative reactivities of various imenes, and the optical activity of the resulting heterocyclic compounds, *e.g. (24)* and *(25)* [137, 138].

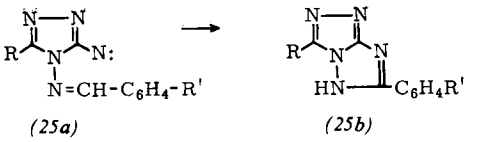


*(24)*



*(25)* [138]

The intramolecular cyclization of imene *(25a)*, formed by thermal decomposition of 3-azido-4-benzylideneamino-s-triazoles, gives triazolotriazoles *(25b)* [138a]:

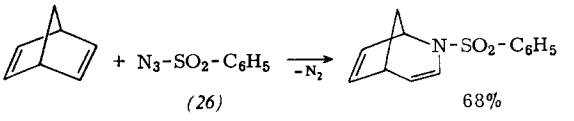


*(25a)* *(25b)*

R = H, $CH_3$, $C_2H_5$, $C_6H_5$; R′ = H, *p*-$CH_3$, *p*-$CH_3O$, *p*-Cl, *o*- and *p*-$NO_2$, *o*-$N_3$.

*Lwowski et al.* [138b] examined the stereospecificity of the addition of ethoxycarbonylimene to olefins.

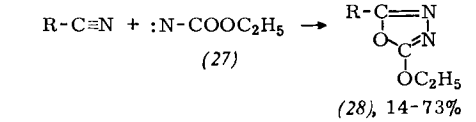
Phenylimene can insert into the Al–C bond [139]. Like the alkoxycarbonylimenes, it has a dehydrogenating and decarbonylating action on alcohols and aldehydes [140, 141]. An unusual reaction is that of the azide *(26)* with norbornadiene, which formally is an insertion of the phenylsulfonylimene into a C–C bond [142].



*(26)* 68%

The photolysis of phenyl azide in diethylamine leads to ring enlargement with the formation of 2-diethylamino-3*H*-azepine [142a].

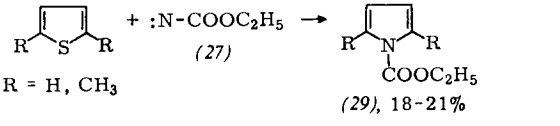
Another interesting reaction is that of ethoxycarbonylimene *(27)* with aliphatic nitriles, which leads to substituted 1,3,4-oxadiazoles *(28)* [143].



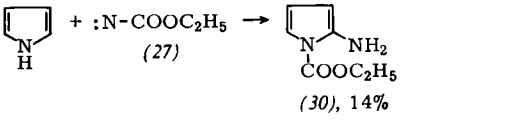
*(28)*, 14–73%

R = $CH_3$, iso-$C_3H_7$, $C_2H_5O$–$CH_2$–$CH_2$, $CH_2$=CH

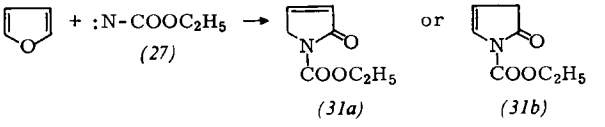
The reaction of ethoxycarbonylimene *(27)* with thiophene, pyrrole, and furan [144] leads to the heterocycles *(29)* to *(31)*.



R = H, $CH_3$ *(29)*, 18–21%



*(30)*, 14%



*(31a)* *(31b)*

[133] *L. C. Willemsens* and *G. J. M. van der Kerk*, J. organometal. Chem. *2*, 260 (1964); see also [128, 130–132]; *E. C. Juenge* and *S. E. Cook*, J. Amer. chem. Soc. *81*, 3578 (1959).

[134] *L. Horner* and *A. Christmann*, Angew. Chem. *75*, 707 (1963); Angew. Chem. internat. Edit. *2*, 599 (1963).

[135] *R. A. Abramovitch* and *B. A. Davis*, Chem. Reviews *64*, 149 (1964).

[136] *W. Kirmse*, Angew. Chem. *71*, 537 (1959).

[137] *M. F. Sloan, T. J. Prosser, N. R. Newburg*, and *D. S. Breslow*, Tetrahedron Letters *1964*, 2945; *T. J. Prosser et al., ibid. 1964*, 2483; *J. H. Hall, J. W. Hill*, and *Hu-chu Tsai, ibid. 1965*, 2211; *W. Lwowski* and *T. J. Maricich*, J. Amer. chem. Soc. *86*, 3164 (1964).

[138] *G. Smolinsky* and *B. I. Feuer*, J. Amer. chem. Soc. *86*, 3085 (1964).

[138a] *H. H. Takimoto, G. C. Denault*, and *S. Hotta*, J. heterocyclic Chem. *3*, 119 (1966).

[138b] *W. Lwowski et al.*, J. Amer.chem. Soc. *87*, 5490, 5491 (1965).

[139] *K. Hoegerle* and *P. E. Butler*, Chem. and Ind. *1964*, 933.

[140] *R. Puttner* and *K. Hafner*, Tetrahedron Letters *1964*, 3119.

[141] *T. J. Prosser, A. F. Marcantonio*, and *D. S. Breslow*, Tetrahedron Letters *1964*, 2479.

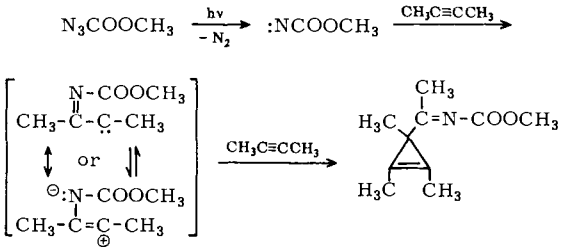
[142] *J. E. Franz* and *C. Osuch*, Chem. and Ind. *1964*, 2058.

[142a] *W. von E. Doering* and *R. A. Odum*, Tetrahedron *22*, 81 (1966).

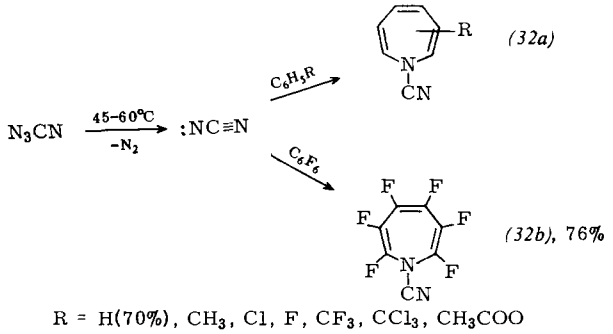
[143] *W. Lwowski et al.*, Tetrahedron Letters *1964*, 2497.

[144] *K. Hafner* and *W. Kaiser*, Tetrahedron Letters *1964*, 2185.

The 1,3-dipolar cycloaddition of alkoxycarbonylimenes to C≡C triple bonds leads usually to the corresponding oxazoles [144a]. However, formation of a cyclopropene derivative was recently observed [144b].

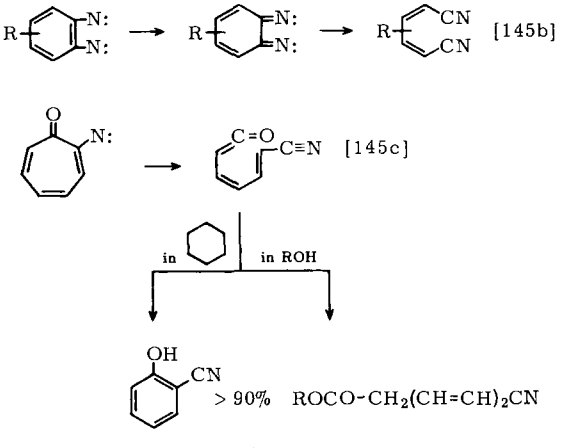


Reference should also be made to the synthesis of *N*-cyanoazepines *(32)* from cyanoimene and aromatic compounds [145].



R = H(70%), $CH_3$, Cl, F, $CF_3$, $CCl_3$, $CH_3COO$

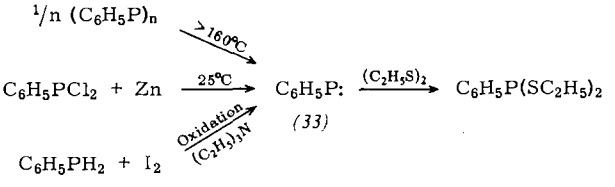
Combination reactions of the imene :NH, generated in the flash photolysis of isocyanic acid (HNCO), were discussed by *Back* [145a]. Aromatic imenes formed from azides isomerize intramolecularly to nitriles [145b, c].



The electron spin resonance spectra of various imenes have been studied [146–146b] and the bond energies, the lifetimes, and the electronic states of the alkoxycarbonylimenes, which were prepared by photolysis of the alkyl azidoformates in the gas phase, have been determined [147].

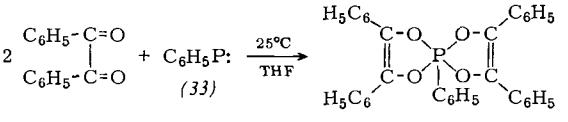
### b) Phosphorus Compounds

The most intensively studied of the compounds of univalent phosphorus is phenylphosphorus *(33)*, which can be prepared by dechlorination of phenyldichlorophosphine, by dehydrogenation of phenylphosphine, or by cleavage of the corresponding cyclopolymer, and which can be readily detected as the disulfide adduct [148].

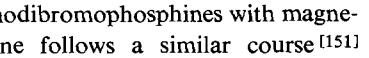


Disulfides react similarly with diphenyltin [116] and methylene [149].

Phenylphosphorus *(33)* prepared from $C_6H_5PCl_2$ and zinc also adds to benzil [148].



Organic derivatives of univalent phosphorus, RP:, are assumed to occur as intermediates in the reactions of aryl- or alkyldichlorophosphines with magnesium or lithium in tetrahydrofuran, which lead to cyclic or linear polymers *(34)* [150]:



R = Alkyl or Aryl; $n = 4$ or 5

The reaction of organodibromophosphines with magnesium in ether/benzene follows a similar course [151] (R = $CH_3$, $C_2H_5$, $C_6H_5$; $n = 5$ or 6).

[144a] *R. Huisgen* and *H. Blaschke*, Chem. Ber. *98*, 2985 (1965); further literature cited there. On the mechanism of 1,3-dipolar cycloaddition see *R. Huisgen, R. Sustmann*, and *K. Bunge*, Tetrahedron Letters *1966*, 3603; further literature cited there.

[144b] *J. Meinwald* and *D. H. Aue*, J. Amer. chem. Soc. *88*, 2849 (1966).

[145] *F. D. Marsh* and *H. E. Simons*, J. Amer. chem. Soc. *87*, 3529 (1965); cf. the analogous reaction of the imene *(27)* [*K. Hafner* and *C. König*, Angew. Chem. *75*, 89 (1963); Angew. Chem. internat. Edit. *2*, 96 (1963)].

[145a] *R. A. Back*, J. chem. Physics *40*, 3493 (1964).

[145b] *K. Nakagawa* and *H. Onoue*, Chem. Commun. *1965*, 396, and literature cited there.

[145c] *J. D. Hobson* and *J. R. Malpass*, Chem. Commun. *1966*, 141.

[146] *E. Wassermann, G. Smolinsky*, and *W. A. Yager*, J. Amer. chem. Soc. *86*, 3166 (1964).

[146a] *R. M. Moriarty, M. Rahman*, and *G. J. King*, J. Amer. chem. Soc. *88*, 842 (1966).

[146b] *J. A. R. Coope et al.*, J. chem. Phys. *42*, 54 (1965).

[147] *D. W. Cornell, R. S. Berry*, and *W. Lwowski*, J. Amer. chem. Soc. *87*, 3626 (1965).

[148] *U. Schmidt* and *Ch. Osterroht*, Angew. Chem. *77*, 455 (1965); Angew. Chem. internat. Edit. *4*, 437 (1965).

[149] *A. Schönberg, O. Schütz*, and *J. Peter*, Ber. dtsch. chem. Ges. *62*, 440 (1929).

[150] *W. A. Henderson, M. Epstein*, and *F. S. Seichter*, J. Amer. chem. Soc. *85*, 2462 (1963); and literature cited there. Cf. [63,65, 66,98]. For preparation, properties, reactions, and structures of cyclopolyphosphines see also *A. H. Cowley*, Chem. Reviews *65*, 617 (1965).

[151] *W. Kuchen* and *W. Grünewald*, Chem. Ber. *98*, 480 (1965). Concerning the ring sizes of cyclopolyphosphines formed in these ways see *A. H. Cowley* and *R. P. Pinnell*, Inorganic Chem. *5*, 1459 (1966), and literature cited there.

RP: may occur as intermediate in other reactions used for the preparation of polymers.

$$RPH_2 \xrightarrow{H_2O_2} RP(O)H_2 \xrightarrow[-H_2O]{\Delta} [RP:] \longrightarrow 1/n(RP)_n \quad [150]$$

$$RPH_2 + RPCl_2 \xrightarrow[-2\,HCl]{\Delta} 2/n(RP)_n \quad [150]$$

$$C_6H_5PCl_2 \xrightarrow{LiAlH_4} [C_6H_5P:] \longrightarrow \underset{58\,\%}{1/n(C_6H_5P)_n} \quad [150]$$
*(33)*

$$4\,C_6H_5P(CO{-}NH{-}C_6H_5)_2 \xrightarrow[2\ hr]{180\,^\circ C} (C_6H_5P)_4 + 4(C_6H_5NH)_2CO + 4CO \quad [152]$$

$$CF_3{-}PI_2 + Hg \xrightarrow{20\,^\circ C} 1/n(CF_3P)_n + HgI_2 \quad [153]$$

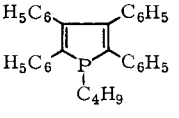
$n = 4$, 5, or 6

Derivatives of univalent phosphorus are formed in the pyrolytic or catalytic cleavage of some phosphines or diphosphines [153].

$$\left.\begin{array}{l}(CF_3)_2P{-}P(CF_3)_2 \xrightarrow[-(CF_3)_3P]{350\,^\circ C} \\ (CF_3)_2PH \xrightarrow[-HCF_3]{350\,^\circ C}\end{array}\right\} \longrightarrow [CF_3P:] \longrightarrow {}^1/_n\,(CF_3P)_n$$

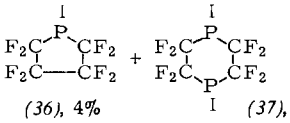
The polymers $(CF_3P)_n$, like the other polymeric carbene analogues, readily add halogenes to form $CF_3{-}PHal_2$; they are oxidized by oxygen to $(CF_3{-}PO_2)_x$ [153]. The organodifluorophosphines $RPF_2$ lose a molecule of fluorine at 20–40 °C to form the carbene analogues, which are then converted into the cyclopolymers [154]. Butylphosphorus *(35)*, which can add to alkynes, is formed by the catalytic cleavage of tributylphosphine [69]:

$$(C_4H_9)_3P \xrightarrow[I_2]{\Delta} \underset{(35)}{[C_4H_9P:]} \xrightarrow{2\,C_6H_5C{\equiv}CC_6H_5}$$



Finally, :PI could occur as intermediate in the formation of the heterocycles *(36)* and *(37)* from tetrafluoroethylene, red phosphorus, and iodine [155].

$$F_2C{=}CF_2 + P + I_2 \xrightarrow{300\,^\circ C}$$



*(36)*, 4% *(37)*, 27%

### c) Arsenic, Antimony, and Bismuth Compounds

The compounds of univalent arsenic, antimony, and bismuth and their polymers have been studied even less than the analogous phosphorus compounds. The unstable arylarsenes ArAs: are probably formed in the reduction of the arylarsonic acids, and are subsequently stabilized by cyclopolymerization [156].

$$ArAsO_3H_2 \xrightarrow{H_3PO_2} \underset{50-80\,\%}{[ArAs:]} \longrightarrow 1/6\,(ArAs)_6$$

$Ar = C_6H_5$, *p*- and *m*-$CH_3{-}C_6H_4$

Like the diorganotin dihydrides, phenylstibine, which is prepared at −196 ° to −60 °C, decomposes with evolution of hydrogen, giving first monomeric and then polymeric phenylantimony *(38)* [157]:

$$C_6H_5SbCl_2 \xrightarrow[{}^1/_2LiBH_4]{{}^1/_2LiAlH_4} C_6H_5SbH_2 \xrightarrow[-H_2]{\approx 20\,^\circ C} [C_6H_5Sb:] \longrightarrow \underset{(38)}{1/n(C_6H_5Sb)_n}$$

Similarly, polymeric $(C_6H_5Bi)_n$ *(39)* is formed *via* $C_6H_5Bi$: from $C_6H_5BiH_2$, which is prepared at −110 to −70 °C [157].

Oxidation of the polymer *(38)* by atmospheric oxygen leads to a polymer containing $-(C_6H_5)Sb(=O)-$ units. Unlike *(38)*, polymeric phenylbismuth *(39)* behaves towards oxygen and halogens in the same way as the other carbene analogues and their polymers:

$$\underset{(39)}{(C_6H_5Bi)_n} + n/2\,O_2 \longrightarrow n\,C_6H_5BiO$$

$$\underset{(39)}{(C_6H_5Bi)_n} + n\,Br_2 \longrightarrow n\,C_6H_5BiBr_2$$

## 5. Elements of Group VI as Carbene Analogues

Oxygen, sulfur, selenium, and tellurium atoms are carbene analogues on the basis of their electronic structure and their chemical properties. They undergo many carbene reactions, such as dimerization and polymerization, addition to double and triple bonds, and insertion into single bonds. The addition of atoms of group VI elements in the singlet state to the C=C double bond is strictly electrophilic, as in the case of singlet carbenes (Table 1). The reaction leads stereospecifically to three-membered rings.

Table 1. Reaction of carbenes and carbene analogues with olefins. The data are the relative rates ($k_1/k_2$) of addition of various reagents to olefins.

| Olefin | :$CCl_2$ [158] | :$CBr_2$ [159] | :O [160] | :S [161] | :Se [162] |
|---|---|---|---|---|---|
| $H_2C{=}CH_2$ | — | — | 1.00 | 1.00 | 1.00 |
| $CH_3{-}CH{=}CH_2$ | — | — | 5.8 | 3.6 | 2.6 |
| $C_4H_9{-}CH{=}CH_2$ | 0.023 | 0.07 | — | — | — |
| $C_2H_5{-}CH{=}CH_2$ | — | — | 5.8 | 3.6 | 7.1 |
| $(CH_3)_2C{=}CH_2$ | 1.00 | 1.00 | 25.0 | — | 44.7 |
| *trans*-$CH_3{-}CH{=}CH{-}CH_3$ | — | — | 28.3 | — | 56.0 |
| $(CH_3)_2C{=}CH{-}CH_3$ | 2.90 | 3.20 | 79.3 | — | — |
| $(CH_3)_2C{=}C(CH_3)_2$ | 6.60 | 3.50 | 101.8 | — | — |
| $CH_2{=}CHCl$ | — | $\ll$0.1 | — | — | 1.3 |

[152] *H. Fritzsche, U. Hasserodt,* and *F. Korte,* Angew. Chem. *75*, 1205 (1963); Angew. Chem. internat. Edit. *3*, 64 (1964).

[153] *W. Mahler* and *A. B. Burg,* J. Amer. chem. Soc. *80*, 6161 (1958).

[154] *W. N. Kulakova, Yu. M. Zinovyev,* and *L. Z. Soborovsky,* Ž. obšč. Chim. *29*, 3957 (1959).

[155] *C. G. Krespan* and *C. M. Langkammerer,* J. org. Chemistry *27*, 3584 (1962).

[156] *G. M. Badger, R. J. Drewer,* and *G. E. Lewis,* Austral. J. Chem. *16*, 285 (1963); further literature cited there.

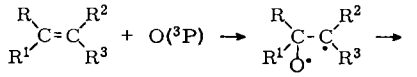
[157] *E. Wiberg* and *K. Mödritzer,* Z. Naturforsch. *12b*, 128, 131 (1957).

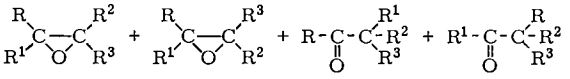
[158] *W. von E. Doering* and *W. A. Henderson,* J. Amer. chem. Soc. *80*, 5274 (1958).

However, most of the reactions of molecular oxygen, sulfur, and selenium in which individual atoms could formally participate are not associated with preliminary dissociation or depolymerization of the molecules. Therefore most of these reactions will not be discussed.

### a) Oxygen

Atomic oxygen is usually produced by the passage of a high-voltage discharge through water vapor or molecular oxygen or by photolysis of nitrous oxide or nitrogen dioxide [160, 163]. Atomic oxygen, which is formed on UV irradiation ($\lambda$ = 2450–3700 Å) of $N_2O$ and $NO_2$, and which is in the ground triplet state ($^3P$), reacts as a triplet carbene with olefins and dienes, forming epoxides, aldehydes, or ketones [164, 165].





R, $R^1$, $R^2$ and $R^3$ = H, Alkyl, or Alkenyl

However, when nitrogen dioxide is irradiated with light of wavelength 2288 Å, an excited oxygen atom ($^1D$) is obtained, which can add to olefins in one step like a singlet carbene. This is seen from the greatly increased yield of epoxide [165].

Like that of the singlet carbenes the addition of excited oxygen $O(^1D)$ to olefins is stereospecific. However, the stereospecificity is somewhat relaxed by the transition $O(^1D) \rightarrow O(^3P)$ [165]. The reaction of atomic oxygen with lower olefins generally leads to an aldehyde and a carbene.

$H_2C{=}CH_2 + O \longrightarrow CH_2O + :CH_2$ [166]

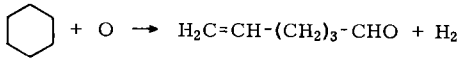
$CH_3{-}CH{=}CH_2 + O \longrightarrow CH_3{-}CHO + :CH_2$ [166]

$F_2C{=}CF_2 + O(^3P) \longrightarrow CF_2O + :CF_2$ (triplet) [167]

Atomic oxygen can also attack aliphatic and aromatic C–H and even C–C single bonds [166, 168]. The formation of small amounts of acetaldehyde alongside formaldehyde as main product is explained by the insertion of atomic oxygen in C-H bonds during its reaction with ethylene [166].

$$CH_4 + O \longrightarrow CH_3OH$$

$$H_2C{=}CH_2 + O \longrightarrow H_2C{=}CHOH \longrightarrow CH_3{-}CHO$$



The reactions of oxygen and of sulfur with phosphines, carbenes, other carbene analogues, borontrialkyls *etc.* are very similar to the corresponding reactions of carbenes. However, the participation of atomic oxygen or sulfur in these reactions is very doubtful.

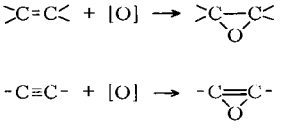
$R_3P + [O] \longrightarrow R_3PO$ [169]

$R_2C: + [O] \longrightarrow R_2CO$ [5,6]

$R_2Sn: + [O] \longrightarrow R_2SnO$ [109]

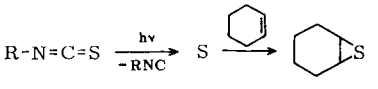
$R_3B + [O] \longrightarrow R_2BOR$ [170]

The Prileshayev reaction (oxidation of alkenes and alkynes by peracids or hydrogen peroxide [171]) formally resembles the reactions of carbenes.



### b) Sulfur

Atomic sulfur in solution occurs during the photochemical formation of isonitriles from isothiocyanates ($\lambda$ = 254 mμ), and can be detected like the carbenes by addition to cyclohexene [148].



Atomic sulfur is formed in the excited singlet state $S(^1D)$ in the gas phase occurs during the photolysis ($\lambda$ = 2290–2555 Å) of carbonyl sulfide at 25 °C [161, 172, 172a].

In the photolysis of COS in an inert gas at high pressures, the conversion of the initially formed $S(^1D)$ into the ground triplet state $S(^3P)$ is increased by collisions with the gas molecules [173]. The singlet sulfur can insert into C–H bonds of alkanes, cycloalkanes, and alkenes, whereas the triplet sulfur cannot; on the other hand, both types can add to C=C double bonds [161, 172–172b].

[159] *P. S. Skell* and *A. Y. Garner*, J. Amer. chem. Soc. *78*, 5430 (1956).

[160] *R. J. Cvetanović*, Adv. Photochem. *1*, 115 (1963); further literature cited there.

[161] *P. O. Strausz* and *H. E. Gunning*, J. Amer. chem. Soc. *84*, 4080 (1962).

[162] *A. B. Callear* and *W. J. R. Tyerman*, Proc. chem. Soc. (London) *1964*, 296.

[163] *F. Kaufman*, Progr. Reaction Kinetics *1*, 1 (1951); further literature cited there.

[164] *S. Sato* and *R. J. Cevetanović*, Canad. J. Chem. *36*, 279, 970 (1958); *R. J. Cvetanović, ibid. 36*, 623 (1958); *R. J. Cvetanović* and *L. C. Doyle, ibid. 38*, 2187 (1960).

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[166] *L. I. Avramenko* and *R. W. Kolesnikova*: The Problem of Chemical Kinetics, Catalysis, and Reactivity. Academy of Sciences, Moscow 1955, p. 7; further literature cited there; Advances in Photochemistry *2*, 25 (1964).

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[168] *L. I. Avramenko, R. W. Kolesnikova*, and *G. I. Savinova*, Izvest. Akad. Nauk SSSR, Ser. chim. *1965*, 28.

[169] *E. Müller*: Neuere Anschauungen der organischen Chemie. Springer, Berlin 1957.

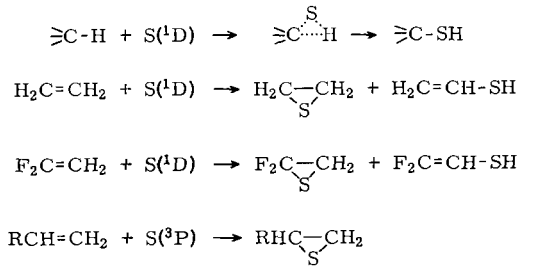
[170] *J. R. Johnson* and *M. G. van Campen*, J. Amer. chem. Soc. *60*, 121 (1938).

[171] See, *e.g.*, *N. Prileschajyev*, Ž. russ. fiziko-chim. Obščestva *42*, 1387 (1910); *H. H. Schlubach* and *V. Franzen*, Liebigs Ann. Chem. *577*, 60 (1952); *W. N. Sapunov* and *N. N. Lebedev*, Ž. organ. Chim. *2*, 225 (1966), and further literature cited there.

[172] *A. R. Knight, O. P. Strausz, et al.*, J. Amer. chem. Soc. *85*, 2349 (1963); *86*, 4243 (1964); *87*, 1443 (1965).

[172a] *K. S. Sidhu, E. M. Lown, O. P. Strausz*, and *H. E. Gunning*, J. Amer. chem. Soc. *88*, 254 (1966).

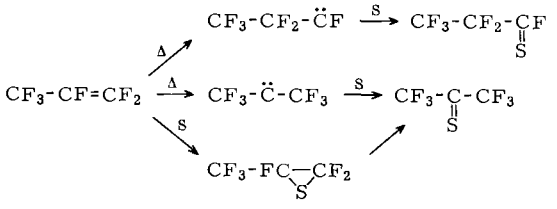
[172b] On reactions of sulfur atoms see also *H. E. Gunning*, Trans. Roy. Soc. Canada, Sec. 1–3, *2*, 293 (1964).

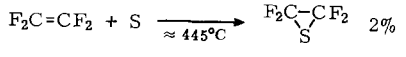


As was recently shown [172a] episulfides formed from *cis*- and *trans*-2-butene retain the geometry of the parent olefin (retention >87 and >98%, respectively) not only with singlet but with triplet-state sulfur as well.

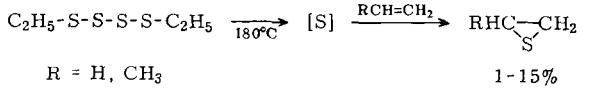
The addition of sulfur atoms to 1,3-butadiene gives at least 91% of vinylthiirane, with thiophene (≤9%) as second major product [172a].

Atomic sulfur is thought to be involved in the reactions of hexafluoropropylene and tetrafluoroethylene with sulfur vapor at 400–500 °C [174, 174a]:





Atomic sulfur probably is formed when diethyl tetrasulfide is heated [175].



Molecular (polymeric) sulfur can undergo insertion into the Sn–Li bond to form the group SnSLi [176]. At 130–650 °C, it adds to olefins, dienes, and alkynes to form hetero chains and heterocycles [177]. However, it is unlikely that atomic sulfur is involved in these reactions.

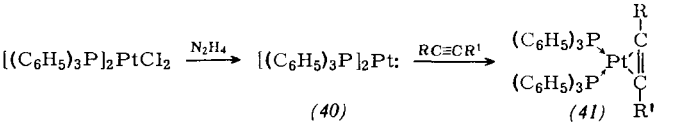
### c) Selenium and Tellurium

Atomic selenium in the excited state is formed during isothermal flash photolysis of carbon diselenide vapor, and adds electrophilically to olefins [162]. In the presence of an inert gas, *e.g.* nitrogen, the initially formed "hot" selenium atoms (lifetime *ca.* $10^{-4}$ sec) are deactivated and subsequently dimerize to form $Se_2$.

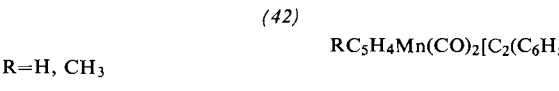
Like oxygen and sulfur, selenium and tellurium insert into the Sn–Li [178] and even Sn–C [179] bonds; however, the reaction probably does not involve preliminary depolymerization of the $Se_x$ and $Te_x$ molecules. $Se_x$ and $Te_x$ also react with tetrafluoroethylene [155], olefins, and acetylene [180].

## 6. Transition Metal Compounds with Carbene-like Properties

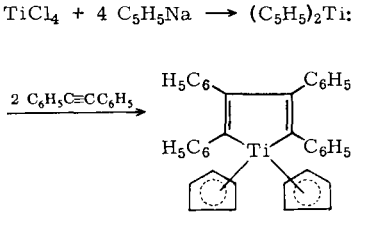
No carbene-like properties can be expected of free transition metals, in which the d levels with lower principal quantum numbers than those of the s and p valence electrons are not filled. However, some derivatives of these metals are formed by filling of the d levels to form complexes or "sandwich" structures. Such complexes could formally be expected to include carbene analogues. For example, the platinum complex $[(C_6H_5)_3P]_2PtCl$ is converted by hydrazine or other reducing agents into a carbene analogue *(40)*, which can add to alkynes to form the compounds *(41)* [181]. Compound *(40)* also forms unstable adducts with olefins [181].



The photolysis of derivatives of cyclopentadienylmanganese tricarbonyl with subsequent addition of tolan can also be formulated as proceeding *via* a carbene analogue *(42)*, though it probably involves displacement of CO by tolan [182].



The formation of the titanocene derivative could also be formulated as involving a carbene analogue [183]:



[173] Cf. the singlet-triplet transition of methylene in the gas phase [5, 6].

[174] *K. V. Martin*, J. chem. Soc. (London) *1964*, 2944.

[174a] *W. R. Brasen et al.*, J. org. Chemistry *30*, 4188 (1965).

[175] *S. O. Jones* and *E. E. Reid*, J. Amer. chem. Soc. *60*, 2452 (1938).

[176] *H. Schumann, K. F. Thom*, and *M. Schmidt*, J. organometal. Chem. *2*, 97 (1964).

[177] *H. E. Westlake et al.*, J. Amer. chem. Soc. *68*, 748 (1946); further literature cited there; *B. A. Arbuzov* and *E. G. Kataev*, Doklady Akad. Nauk SSSR *96*, 983 (1954); *J. B. Peel* and *P. L. Robinson*, J. chem. Soc. (London) *1928*, 2068.

[178] *H. Schumann, K. F. Thom*, and *M. Schmidt*, J. organometal. Chem. *2*, 361 (1964).

[179] *M. Schmidt* and *H. Schumann*, Chem. Ber. *96*, 780 (1963).

[180] *W. E. Garwood, F. M. Seger*, and *A. N. Sachanen*, US-Pat. 2500164 and 2500167 (14 March, 1950); Chem. Abstr. *44*, 4670 (1950).

[181] *J. Chatt, G. A. Rowe*, and *A. A. Williams*, Proc. chem. Soc. (London) *1957*, 208.

[182] *W. Strohmeier, H. Laporte*, and *D. von Hobe*, Chem. Ber. *95*, 455 (1962).

[183] *M. E. Volpin, W. A. Dubovizky, O. W. Nogina*, and *D. N. Kursanov*, Doklady Akad. Nauk SSSR *151*, 1100 (1963).

### 7. Carbene-like Properties of other Compounds

Some elements of the third and subsequent periods (phosphorus, antimony, sulfur, selenium, and others) can form five covalent bonds, *i.e.* can possess a stable decet of electrons.

Accordingly, many compounds of these elements exhibit carbene-like properties, even when the atom still possesses eight valence electrons. In particular, phosphoranes and phosphine oxides with covalent structures may be regarded as adducts of such carbene analogues with carbenes or oxygen [169].

$$R_3P + :CX_2 \longrightarrow R_3P{=}CX_2$$

$$R_3P + 1/2O_2 \longrightarrow R_3P{=}O$$

The reaction of phosphorus trihalides with compounds containing conjugated double bonds [184] appears to suggest carbene-like properties in the former:

$$H_2C{=}CH{-}CH{=}CH_2 + :PHal_3 \longrightarrow$$

Hal = Cl, Br

[184] *U. Hasserodt, K. Hunger,* and *F. Korte,* Tetrahedron *19,* 1563 (1963); *B. A. Arbuzov* and *A. O. Vizel,* Doklady Akad. Nauk SSSR *158,* 1105 (1964), and literature cited there. Cf. the 1,4-addition of other carbene analogues and carbenes to 1,3-dienes [73,74,87].

Sulfur and selenium dioxides form similar products with conjugated dienes [185]. $SO_2$ and $SeO_2$ add particularly readily to 2,3-di t-butyl-1,3-butadiene.

1,3-Dienes add easily not only $PHal_3$, but also alkyl- and aryldichlorophosphines $RPCl_2$. However, the adducts *(43)* are ionic and can be reduced smoothly with magnesium in THF to derivatives of three-covalent phosphorus *(44)* [186].

$$H_2C{=}CH{-}CH{=}CH_2 + RPCl_2 \longrightarrow$$

*(43)* $\xrightarrow[THF]{Mg}$ *(44)*

These results shows that compounds having carbene-like properties do not necessarily have the electronic arrangement of the carbenes. The central atoms of these compounds have no free p orbitals, but use vacant d orbitals to form the decet of electrons at the expense of pd hybridization.

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Translated by Express Translation Service, London

[185] *H. J. Backer* and *J. Strating,* Recueil Trav. chim. Pays-Bas *53,* 525, 1113 (1934); *54,* 170 (1935).

# COMMUNICATIONS

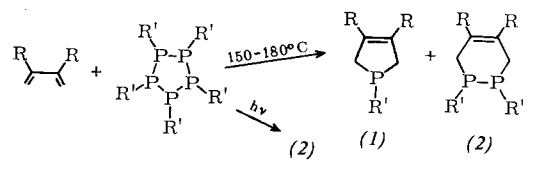
## Thermal and Photochemical Formation of Phospholenes and Tetrahydrophosphorins from Cyclophosphines and Dienes [1]

By Prof. Ulrich Schmidt and I. Boie

Chemisches Laboratorium, Universität Freiburg (Germany)

We have previously inferred the formation of phosphinidene (R–P:), on heating and irradiation of cyclophosphines $(R{-}P)_5$, from reactions leading to insertion into disulfide bonds [2], formation of 1,1'-spirobi(phosphadioxole) [2], and exchange of ring members of cyclopolyphosphines [3]. We have now observed addition of fragments formed thermally and photochemically from cyclophosphines to dienes.

Cyclophosphines were heated with dienes for 20 hr at 150 to 180 °C. On subsequent distillation a mixture of a phospholene *(1)* and a tetrahydro-1,2-diphosphorin *(2)* was obtained in a total yield of 40 to 60 %. These products were separated by fractional distillation. 1,2,3,6-Tetrahydro-1,2-diphosphorins *(2)* can be isolated in better yield and without simultaneous formation of phospholenes *(1)* by irradiation of the cyclophosphine-diene mixture with a high-pressure mercury vapor lamp.




The structures of the phospholenes and tetrahydro-1,2-diphosphorins (the latter are derivatives of a new ring system) follow from their compositions, molecular weights (determined mass-spectrometrically), and NMR spectra.

The tetrahydrophosphorins react rapidly with alkylating agents to give monophosphonium salts and with sulfur to give P,P'-bissulfides.

| R | R' | Method and yield (%) | B.p. (°C/mm) | NMR | M.p. (°C) of derivatives [a] |
|---|---|---|---|---|---|
| *Phospholenes (1)* | | | | | |
| H | $CH_3$ | Heat, 10 | 115/760 | | B, 189 |
| $CH_3$ | $CH_3$ | Heat, 23 | 55–57/12 | [b] | B; 183.5 |
| $CH_3$ | $C_6H_5$ | Heat, 23 | 65–67/0.05 | | B, 219–221 |
| *1,2,3,6-Tetrahydro-1,2-diphosphorins (2)* | | | | | |
| H | $CH_3$ | Heat, 22 | 82–83/11 | | D, 176–177 |
| H | $C_2H_5$ | hv, 19 | 114/9 | | D, 94 |
| $CH_3$ | $CH_3$ | Heat, 40 hv, 53 | 100/8 | [c] | D, 193 |
| $CH_3$ | $C_6H_5$ | Heat, 25 | 150/0.005 | | D, 178–179 |

[a] B = 1-Benzylphospholenium bromide; D = 1,2,3,6-Tetrahydro-1,2-diphosphorin 1,2-bissulfide.

[b] Doublet $\tau$ = 9.15 ppm (3 H); $J$ = 3.3 Hz; singlet $\tau$ = 8.30 ppm (6 H); multiplet $\tau$ = 7.12 — *ca.* 8.55 ppm (4 H).

[c] Triplet $\tau$ = 9.02 ppm (6 H); $J$ = 18.6 Hz; singlet $\tau$ = 8.20 ppm (6 H); multiplet $J$ = 7.37–8.47 ppm (4 H).

(Neat liquids, TMS as internal standard).

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[1] Part 3 of Phosphinidenes. — Part 2: ref. [3].

[2] *U. Schmidt* and *Ch. Osterroht,* Angew. Chem. *77,* 455 (1965); Angew. Chem. internat. Edit. *4,* 437 (1965).

[3] *U. Schmidt, R. Schröer,* and *H. Achenbach,* Angew. Chem. *78,* 307 (1966); Angew. Chem. internat. Edit. *5,* 316 (1966).

## A New Synthesis of the Oxepin System from Furan and Dimethyl Acetylenedicarboxylate

By Prof. H. Prinzbach, M. Arguëlles, and E. Druckrey

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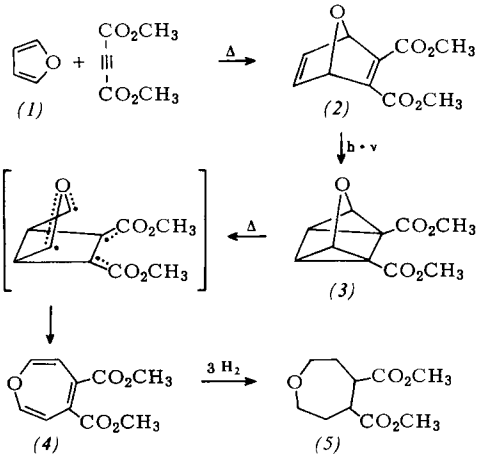
We have synthesized the 8 π-electron system *(4)* by the new reaction sequence represented as *(1)* → *(2)* → *(3)* → *(4)*.



On addition by portions of a total of 21 g (0.29 mole) of furan to a boiling etheral solution of 10 g (0.076 mole) of dimethyl acetylenedicarboxylate during 130 hr, the monoadduct *(2)* was obtained in 70 to 75 % yield[1]; it has $\lambda_{max}$ in ether at 288 mμ (ε = 1060) and a shoulder at 222 mμ (ε = 4260); its NMR spectrum in $CCl_4$ contains two signals at τ = 2.83 and τ = 4.43, showing some fine structure, as well as the $CH_3O$ singlet at τ = 6.24 (ratio 2:2:6); the fragments to be expected for the reverse change *(2)* → *(1)* were responsible for the main peaks (*m/e* = 210, 111, 68...) in the mass spectrum[2].

If the ester *(2)* in 0.06 M ethereal solution ($O_2$-free) is irradiated at −15 °C with light from a high-pressure mercury arc filtered through Vycor glass, it is isomerized to compound *(3)* in 55 to 60 % yield. This forms colorless crystals, m.p. 82–83 °C (from cyclohexane)[3],; its UV spectrum in ether shows only end absorption (ε 210 mμ = 2950); its NMR spectrum in $CDCl_3$ contains two doublets (J = 3.5 Hz) at τ = 5.12 and τ = 7.35 and a singlet at τ = 6.36 (ratio 2:2:6); reverse isomerization to *(2)* is only a minor reaction under electron impact[4], a base peak at *m/e* = 179 ($M-CH_3O$) being recorded alongside a very intense molecule ion ($M^+$=210).

Compound *(3)* is converted into the oxepin ester *(4)* from about 100 °C ($t_{½}$ = 48 min at 108 °C, 35 min at 113 °C, and 19 min at 118 °C; $E_a$ = 27.6 ± 2 kcal/mole; $k_0 = 7.9\times10^{13}$). For instance, 3.4 g of ester *(3)* was heated in 85 ml of xylene at 140 to 150 °C for 20 min, then about 10 % of a dimer was filtered off at room temperature and the product *(4)* was isolated by chromatography in benzene on $SiO_2$; it is an orange oil, yield 70–75 %, $\lambda_{max}$ (ethanol) = 304 mμ (shoulder, ε = 1400) and 269 mμ (ε = 2100); $\nu_{C=C}$ $(CH_2Cl)_2$ = 1635 and 1575 $cm^{-1}$. Its NMR spectrum is temperature dependent[5]: at 30 °C ($CCl_4$) it comprises two doublets (*J* = 5.0 Hz) at τ = 3.73 and τ = 4.94 and a $CH_3O$ singlet at τ = 6.28. There are strong peaks in the mass spectrum at *m/e* = 210 ($M^+$, base peak), 194 (M−O), 179 ($M-CH_3O$) and 163 ($M-O-CH_3O$). In the presence of prereduced $PtO_2$ the oxepin *(4)* rapidly absorbs 3 equivalents of $H_2$, giving a 75 % yield of product *(5)* whose structure is proved by elemental analysis and IR, NMR, and mass spectra. 1:1 Cycloadducts are formed by *(4)* with maleic anhydride or dimethyl acetylenedicarboxylate[5].

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[1] *G. Stork, E. E. van Tamelen, L. J. Friedman,* and *A. W. Burgstahler,* J. Amer. chem. Soc. *75*, 384 (1953).

[2] We thank Dr. *B. Willhalm,* Firmenich & Co., Geneva, for the mass-spectrometric measurements.

[3] *S. P. Mannsfeld,* Dissertation, Universität Göttingen, 1963.

[4] *Z. Dolejšek, V. Hanuš,* and *H. Prinzbach,* Angew. Chem. *74*, 902 (1962); Angew. Chem. internat. Edit. *1*, 598 (1962).

[5] Cf. *E. Vogel, W. A. Böll,* and *H. Günther,* Tetrahedron Letters *1965*, 609; *H. Günther, ibid. 1965*, 4085.

## Reactions of Benzonitrile Oxide with Alkylidenephosphoranes

By Prof. H. J. Bestmann and R. Kunstmann

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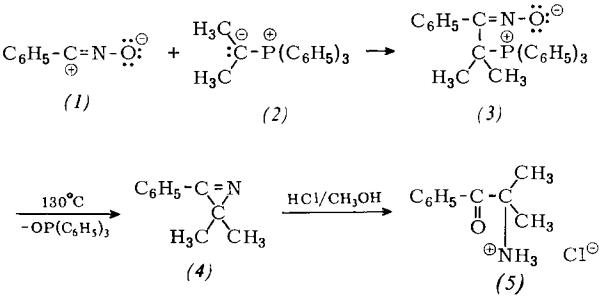
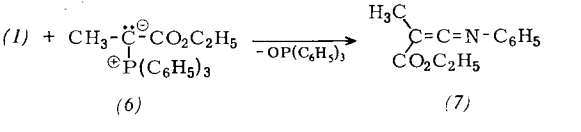
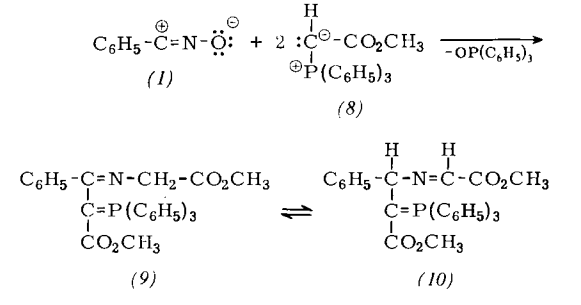
Benzonitrile oxide *(1)* adds (1-methylethylidene)triphenylphosphorane *(2)* in anhydrous benzene at room temperature, giving the betaine *(3)*, m.p. 122 °C, in 54 % yield. When heated in a rotating bulb-tube at 130 °C/0.05 mm, *(3)* eliminates triphenylphosphine oxide and gives the azirine *(4)* quantitatively as a distillate; *(4)* has a characteristic band at 5.7 μ in the IR spectrum and absorbs at 246 mμ in the UV[1] (NMR: singlet for the methyl protons at τ = 8.51, multiplet for the aromatic protons at τ = 2.3). Methanolic hydrochloric acid hydrolyses compound *(4)* to the amino ketone hydrochloride *(5)* (picrate, m.p. 174 °C; lit.[2] 175 °C).



Reaction of the nitrile oxide *(1)* with the phosphorane ethyl ester *(6)* in benzene affords the ketene imine derivative *(7)*, ethyl 3-phenylimino-2-methylacrylate, b.p. 140 °C/0.05 mm; characteristic IR band at 4.92 μ; yield 68 %. It cannot yet be decided at what stage in the reaction the phenyl group migrates, and so far no intermediate has been isolated. On alkaline hydrolysis, compound *(7)* yields methylmalonic acid and aniline.

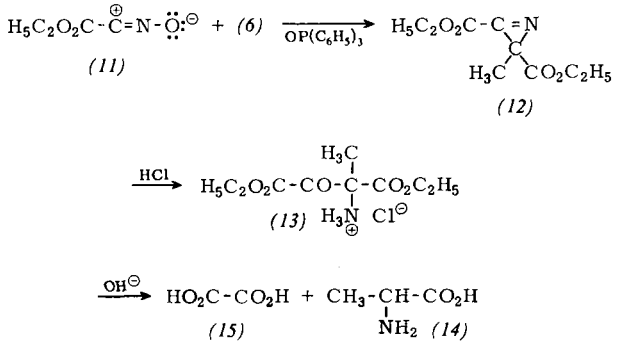


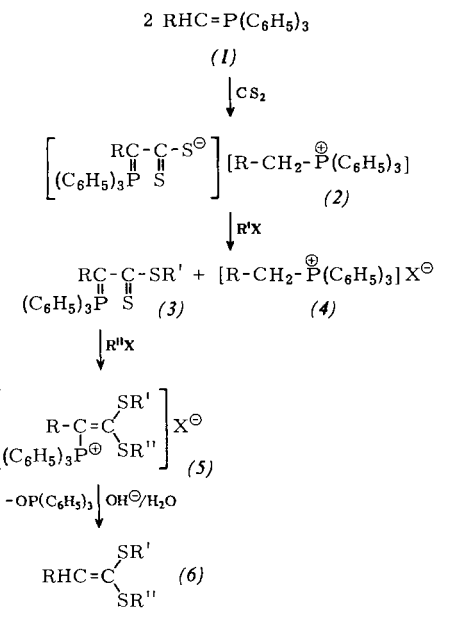
On treatment of benzonitrile oxide *(1)* with the phosphorane methyl ester *(8)*, two molecules of *(8)* react with one of *(1)*, affording to ylide *(9)*, m.p. 193 °C, in 67 % yield. The IR spectrum includes the ester-carbonyl band at 6.15 μ characteristically shifted as for phosphorus ylide esters[3]. NMR studies indicate that in solution this substance is in equilibrium with its tautomer *(10)*.



Elemental analysis of all the compounds prepared gave the expected C, H, and N values. The modes of reaction of alkylidenephosphoranes with nitrile oxides mentioned above are being studied in detail.

*Added in proof*: The azirine *(12)* has now been isolated from the products of the reaction of ethyl cyanoformate *N*-oxide *(11)* with *(6)* in boiling benzene (b.p. 80 °C/0.05 mm; yield 65 %; IR: broad bands with two shoulders at 5.7–5.8 μ; UV: $\lambda_{max}$ = 214, 267 mμ; $^1$H–NMR: singlet for methyl group attached to ring at τ = 8.33, 2 triplets for the ester methyl groups at τ = 8.54 and 8.72, 2 quartets for the ester methyl groups at τ = 5.51 and 5.82). A betaine analogous to *(3)* was not observed in this reaction.





benzene at 50 °C gives 2-(triphenylphosphoranylidene)dithiocarboxylic esters *(3)* and alkyltriphenylphosphonium salts *(4)*, the latter remaining undissolved whereas the compounds *(3)* pass into solution.

| R | *(2)* Yield (%) | *(3)* R′ | M.p. (°C) | Yield (%) | *(5)* R″X | M.p. (°C) | Yield (%) | *(6)* B.p. (°C/mm) | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$ | 95 | $CH_3$ | 244 | 93 | $CH_3I$ | 225 | 96 | 105–107/0.05 | 78 |
| | | $C_6H_5$–$CH_2$ | 216 | 94 | $C_6H_5$–$CH_2Cl$ | 187 | 90 | M.p. 49 °C | 82 |
| | | | | | $CH_3I$ | 191 | 95 | 154–156/0.2 | 90 |
| H | 96 | $C_2H_5$ | 196 | 96 | $C_2H_5I$ | 163 | 95 | 76–78/12 | 46 |
| $CH_3$ | 94 | $C_2H_5$ | 196 | 96 | $C_2H_5I$ | 186 | 80 | 87–89/11 | 70 |
| | | $C_6H_5$–$CH_2$ | 155 | 89 | | 179 | 85 | 128–130/0.2 | 71 |
| $C_6H_5$–$CH_2$–$CH_2$ | 85 | $C_2H_5$ | 196 | 76 | $C_2H_5I$ | 212 | 85 | 131–133/0.2 | 79 |
| c-$C_6H_{11}$ | 81 | $C_2H_5$ | 202 | 90 | $C_2H_5I$ | 220 | 78 | 90/0.2 | 46 |

On treatment of *(12)* with aqueous HCl, ring opening produced the hitherto unknown diethyl β-amino-β-methyl-α-oxosuccinate, which decomposes to aniline *(14)* and oxalic acid on alkaline saponification.

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[1] *G. Smolinsky*, J. org. Chemistry *27*, 3557 (1962), gives IR and UV absorption at 5.74 μ and 240 mμ, respectively, as typical of azirines.

[2] *S. Gabriel*, Ber. dtsch. chem. Ges. *44*, 57 (1911).

[3] *H. J. Bestmann* and *H. Schulz*, Liebigs Ann. Chem. *674*, 11 (1964).

## A New Synthesis of Ketene Mercaptals

By Prof. H. J. Bestmann, R. Engler, and Dr. H. Hartung

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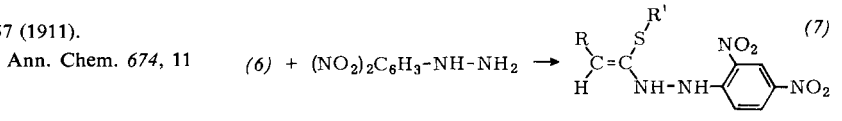
Reaction of the stable ylides diphenylmethylidene- and fluorenylidene-phosphorane with carbon disulfide gives polymeric or dimeric thioketenes [1].

If salt-free solutions of basic alkylidenephosphoranes *(1)* [2] in benzene are treated with carbon disulfide at room temperature (molar ratio 2:1), the yellow, stable phosphonium salts *(2)* (unsharp melting points) of 2-(triphenylphosphoranylidene)dithiocarboxylic acids are precipitated. Reaction of the salts *(2)* with an equimolar amount of alkyl halide in benzene at 50 °C gives 2-(triphenylphosphoranylidene)dithiocarboxylic esters *(3)* and alkyltriphenylphosphonium salts *(4)*, the latter remaining undissolved whereas the compounds *(3)* pass into solution.

The new ylides *(3)* are alkylated at the sulfur by alkyl halides to the phosphonium salts *(5)*, which afford the ketene mercaptals *(6)* on alkaline hydrolysis in boiling 20 % potassium hydroxide.

On treatment with aqueous $HgCl_2$ the ketene mercaptals *(6)* are converted into the carboxylic acids $RCH_2$–COOH; when R′ = R″they afford 2-[1-(alkylthio)-1-alkenyl]-1-(2,4-dinitrophenyl)hydrazines *(7)* [3] with 2,4-dinitrophenylhydrazine in phosphoric acid.



Elemental analysis gives the expected values for all the products. The IR and $^1$H–NMR data are evidence for structures *(3)*, *(5)*, *(6)*, and *(7)*.

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[1] *H. Staudinger*, *G. Rathsam*, and *F. Kjelsberg*, Helv. chim. Acta *3*, 853 (1920); *A. Schönberg*, *E. Frese*, and *K.-H. Brosowski*, Chem. Ber. *95*, 3077 (1962).

[2] Cf. *H. J. Bestmann*, Angew. Chem. *77*, 609 (1965); Angew. Chem. internat. Edit. *4*, 583 (1965).

[3] Exchange of an alkylthio group for a substituted amino group was first reported by *R. Gompper* and *W. Töpfl*, Chem. Ber. *95*, 2871 (1962).

## Existence of the $VO_2^+$, $TiO^{2+}$ and $ZrO^{2+}$ Cations

By Dr. K. Dehnicke and Dr. J. Weidlein

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der Technischen Hochschule Stuttgart (Germany)

*J. Selbin*[1] recently questioned the existence of the oxo-cations $VO_2^+$, $TiO^{2+}$, and $ZrO^{2+}$. However, their existence has been established recently.

The group $VO_2^+$ exists in the compound $VO_2Cl$, which according to its IR spectrum (300–1500 $cm^{-1}$) consists of discrete $VO_2Cl$ units (symmetry Cs)[2]. We have now recorded the IR spectrum of $VO_2Cl$ also between 33 and 300 $cm^{-1}$. It confirms the previously proposed structure[2]. The six fundamental vibrations to be expected for the point group $C_s$ can be observed (Table 1).

By fluorination of $VO_2Cl$ with $F_2$ at room temperature we obtained $VO_2F$ in practically 100 % yield. Its IR spectrum (Table 1) shows no evidence of a V–F stretching or deformation vibration. Number, positions, and intensities of the IR absorptions suggest discrete $VO_2^+$ (symmetry $C_{2v}$) and $F^-$ ions. $VO_2F$ reacts with an excess of $SbF_5$ at 200 °C quantitatively to give $VO_2^+ SbF_6^-$. The compound obtained exhibits the characteristic IR absorptions of the $SbF_6^-$ anion (symmetry $O_h$) of the class $F_{1u}$ and the three absorptions to be expected for the $VO_2^+$ cation, which show practically the same frequencies as in the spectrum of $VO_2^+F^-$ (Table 1). $VO_2F$ and $VO_2SbF_6$ are typical ionic compounds, stable up to 350 °C, very hygroscopic, and insoluble in nonpolar solvents.

Table 1. IR spectra of $VO_2Cl$ ($C_s$), $VO_2^+ F^-$ ($C_{2v}$), and $VO_2^+ SbF_6^-$ ($C_{2v}$, $O_h$).

| $VO_2Cl$ | | | | $VO_2^+ F^-$ | | | $VO_2^+ SbF_6^-$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Class | $\tilde{\nu}$ ($cm^{-1}$) | Int. | Assignment | Class | $\tilde{\nu}$ ($cm^{-1}$) | Int. | Class | $\tilde{\nu}$ ($cm^{-1}$) | Int. | Assignment |
| A'' | 997 | vs [a] | $\nu_{as}$ $VO_2$ | $B_1$ | 1024 | vs | $B_1$ | 1028 | s | $\nu_{as}$ $VO_2^+$ |
| A' | 857 | m–s | $\nu_s$ $VO_2$ | $A_1$ | 875 | m–s | $A_1$ | 885 | s | $\nu_s$ $VO_2^+$ |
| A' | 537 | Sh | $\delta$ $VO_2$ | $A_1$ | 558 | s | $A_1$ | 566 | m–s | $\delta$ $VO_2^+$ |
| A' | 503 | vs | $\nu$ VCl | | | | | | | |
| A' | 272 | w–m | $\delta$ VOCl | | | | $F_{1u}$ | 678 | vs | $\nu_{as}$ $SbF_6^-$ |
| A'' | 112 | w | $\delta$ VOCl | | | | $F_{1u}$ | 283 | m | $\delta_{as}$ $SbF_6^-$ |

[a] vs = very strong, s = strong, m = medium, w = weak, Sh = shoulder

$TiO^{2+}$ cations also occur in $Ti_2OF_6$[3] which, according to the IR spectrum, consists of $TiO^{2+}$ and $TiF_6^{2-}$ ions. For this a total of three IR-absorptions is expected, one for the cation (class $\Sigma^+$) and two for the anion (class $F_{1u}$). Table 2 shows that the number and the frequencies of the absorbtion bands are consistent with this[3]. When $TiOCl_2$ is treated with an excess of $SbF_5$ at 150 to 200 °C (3 hr), titanyl hexafluoroantimonate, $TiO^{2+}(SbF_6^-)_2$, is formed in nearly 100 % yield. This compound also shows the characteristic $TiO^{2+}$ frequency at 965 $cm^{-1}$ and the two absorptions of the complex anion (Table 2).

Table 2. IR-spectra of $TiO^{2+}TiF_6^{2-}$ and $TiO^{2+}(SbF_6^-)_2$.

| Class | $TiO^{2+}$ $TiF_6^{2-}$ | | $TiO^{2+}$ $(SbF_6^-)_2$ | | Assignment |
|---|---|---|---|---|---|
| | $\tilde{\nu}$ ($cm^{-1}$) | Int. | $\tilde{\nu}$ ($cm^{-1}$) | Int. | |
| $\Sigma^+$ | 964 | s | 965 | s | $\nu$ $TiO^{2+}$ |
| $F_{1u}$ | 541 | s | 675 | s | $\nu_{as}$ $MF_6$ |
| $F_{1u}$ | 333/311/291 | m | 285 | m | $\delta_{as}$ $MF_6$ |

The IR spectrum of $ZrOCl_2$[4], with a ZrO stretching vibration at 877 $cm^{-1}$, can be interpreted only by assuming a considerable double-bond character. Taking the rest of the spectrum the proposed model $\infty$ $ZrO^{2+}$ $(ZrOCl_4^{2-})\infty$ is the only reasonable one. The partial hydrolysis of $ZrCl_4$ in acetonitrile produces $ZrOCl_2$, which is probably an isomer having no ZrO bonds of higher order, as its highest absorption band is found at 675 $cm^{-1}$[5].

Received: August 15th, 1966 [Z 340 IE]
German version: Angew. Chem. 78, 1065 (1966)

[1] *J. Selbin*, Angew. Chem. *78*, 736 (1966); Angew. Chem. internat. Edit. *5*, 712 (1966).

[2] *K. Dehnicke*, Angew. Chem. *73*, 535 (1961); Chem. Ber. *97*, 3354 (1964).

[3] *G. Lange* and *K. Dehnicke*, Naturwissenschaften *53*, 38 (1966).

[4] *K. Dehnicke* and *K.-U. Meyer*, Z. anorg. allg. Chem. *331*, 121 (1964).

[5] *A. Feltz*, Z. anorg. allg. Chem. *335*, 304 (1965).

## Use of the *N*-(5,5-Dimethyl-3-oxo-1-cyclohexen-1-yl) Protective Group in Solid Phase Peptide Synthesis

By Dr. A. Deér[1]

Institute of Steroid Chemistry, Syntex Research, Palo Alto, California (U.S.A.)

In peptide synthesis by the Merrifield method on chloromethylated polystyrene resins[2], loss of the amine protecting group on detachment of the completed peptide chains was previously unavoidable. The free peptides formed must be separated from by-products with shorter chains by ion-exchange chromatography.

This difficult purification step can now be avoided by utilizing the high acid and base stability of the 5,5-dimethyl-3-oxo-1-cyclohexen-1-yl protecting group as well as the high degree of crystallinity of *N*-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl) peptides[3]. Thus, at the final stage of chain lengthening[4] an *N*-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl) amino acid is used.

Hydrolysis of the resin ester bond followed by filtration and acidification gives *N*-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl) peptides of high purity[5] by direct crystallization. The protecting group can be removed with bromine or nitrous acid[3,6].

| Peptide [a] | M.p. (°C) | $[\alpha]_D$ |
|---|---|---|
| Dim–Val–Ala–OH | 246 | –202 |
| Dim–Val–Leu–Ala–OH | 310–312 | –228 |
| Dim–Val–Val–Phe–Leu–Ala–OH | 280–282 | –154 |
| Dim–Val–Gly–Val–Phe–Leu–Ala–OH | 305–307 | –142 |
| Dim–Leu–Val–Ala–Phe–OH | 296–297 | –24 |

[a] Dim– denotes *N*-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl).

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German version: Angew. Chem. 78, 1064 (1966)

[1] Syntex Postdoctoral Fellow, 1965–1966. Present address, Squibb Institute for Medical Research, New Brunswick, N.J.

[2] *R. B. Merrifield*, Federat. Proc. *21*, 412 (1962); J. Amer. chem. Soc. *85*, 2149 (1963); *86*, 304 (1964); *R. B. Merrifield* and *J. M. Stewart*, Nature (London) *207*, 522 (1965).

[3] *B. Halpern* and *L. B. James*, Nature (London) *202*, 592 (1964); *B. Halpern*, Austral. J. Chem. *19*, 417 (1965).

[4] Condensations were carried out at 20 °C with dicyclohexylcarbodiimide in dimethylformamide and t-butyloxycarbonyl amino acids or *N*-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl amino acids.

[5] Satisfactory steric purity was demonstrated by gas-liquid chromatography: *B. Halpern* and *J. W. Westley*, Biochem. biophysic. Res. Commun. *19*, 361 (1965); Tetrahedron Letters *21*, 2283 (1966). Dr. *B. Halpern*'s aid in this determination is gratefully acknowledged.

[6] *B. Halpern* and *A. D. Cross*, Chem. and Ind. *1965*, 1183.

## 1,5-Cyclization of Vinyl-substituted Sulfur Diimides

By Prof. G. Kresze and Chr. Seyfried

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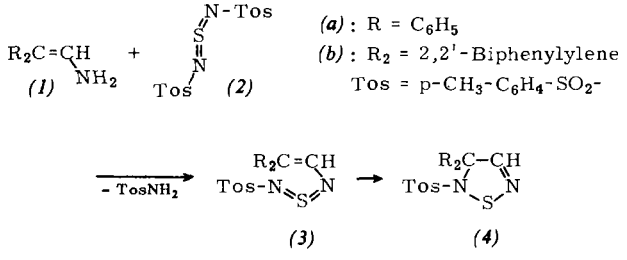
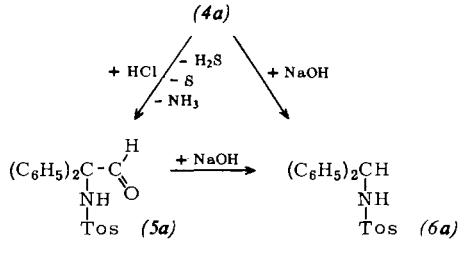
Technische Hochschule München (Germany)

*S*-Arylsulfonylimido-2*H*-1,2,4-benzothiadiazines[2] are obtained by 1,6-cyclization on reaction of *N*-arylamidines $ArN{=}CR(NH_2)$, [R = H, alkyl, or aryl], *N*-aryl-isoureas, -isothioureas and -guanidines with *N*-sulfinylsulfonamides $OS{=}N{-}SO_2R$, arylsulfonylimidosulfur dichlorides $ArSO_2{-}N{=}SCl_2$, or sulfur di(arylsulfonylimides)[1] such as *(2)*. However, enamines[3] *(1)* with primary amino groups react to yield $\Delta^2$-1,2,5-thiadiazolines *(4)* by 1,5-cyclization.




In this way 4,4-diphenyl-5-tosyl-$\Delta^2$-1,2,5-thiadiazoline *(4a)*, m.p. 169–171 °, is formed when 2,2-diphenylvinylamine *(1a)* and an equivalent amount of sulfur di-(*p*-toluenesulfonyl-diimide) *(2)* are kept in anhydrous benzene at room temperature for one day. When 9-(aminomethylene)fluorene *(1b)* is used, the intermediate *(3b)* [violet-black needles, m.p. 121–122 °C; 51 % yield; IR bands at 1010 and 965 $cm^{-1}$ (? ν(N=S=N))] can be isolated after ½ hr at not more than 30 °C with exclusion of moisture. This intermediate forms the product *(4b)*, m.p. 165–167 °C, only when boiled in benzene or, faster, when heated to 140 °C.

The structures of compounds *(3b)*, *(4a)*, and *(4b)* have been proved by degradation, as well as by IR and NMR spectra: with cold 20 % NaOH, *(3b)* yields *p*-toluenesulfonamide, *(1b)*, and $SO_2$; when boiled for 3 hr with 20 % aqueous-alcoholic hydrochloric acid, *(4a)* yields $H_2S$, sulfur, $NH_3$, and *N*-(formyldiphenylmethyl)-*p*-toluenesulfonamide *(5a)* [m.p. 164 °C; yield 93 %; IR bands at 1725 $cm^{-1}$ ($\nu_{CO}$) and 3295 $cm^{-1}$ ($\nu_{NH}$); aldehyde-proton NMR signal at 9.36 ppm (in $CDCl_3$; TMS as internal standard)]; cold 20 % NaOH readily decarbonylates *(5a)* to *N*-(diphenylmethyl)-*p*-toluenesulfonamide *(6a)*, m.p. 155–156 °C.




Compounds *(6a)* and *(6b)* are formed directly, in 80 to 90 % yield, on treatment of *(4a)* or *(4b)*, respectively, with cold 20 % NaOH, the products being identical (IR spectrum and mixed melting point) with those described previously[4].

A quasi-electrophilic aromatic substitution with participation of a positive sulfur atom can be envisaged for the 1,6-cyclization of the *N*-arylamidines, and nucleophilic behavior of the toluenesulfonamide-nitrogen atom of *(3)* can be considered for the 1,5-cyclization of enamines *(1)*. In both cases α,β-unsaturated sulfur diimides occur as intermediates. It seems remarkable that reduction of the sulfur is involved in the 1,5-cyclization.

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German version: Angew. Chem. *78*, 1061 (1966)

[1] *W. Wucherpfennig* and *G. Kresze*, Tetrahedron Letters *1966*, 1671.

[2] *G. Kresze*, *Chr. Seyfried*, and *A. Trede*, Tetrahedron Letters *1965*, 3933.

[3] *D. Y. Curtin*, *J. A. Kampmeier*, and *B. R. O'Connor*, J. Amer. chem. Soc. *87*, 863 (1965).

[4] *G. W. H. Cheeseman*, J. chem. Soc. (London) *1957*, 115; *A. Nickon* and *A. S. Hill*, J. Amer. chem. Soc. *86*, 1152 (1964).

## Substituted Pyrimidine-5-carbonitriles by Vilsmeier Reaction of Malonodinitrile

By Dr. Ch. Jutz and W. Müller

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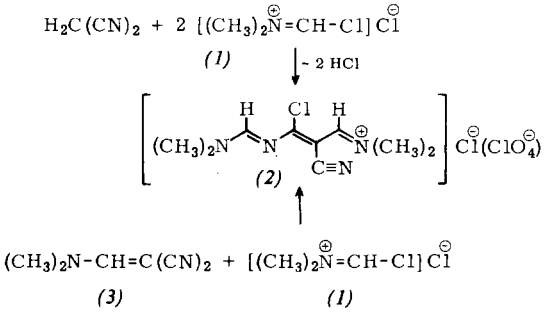
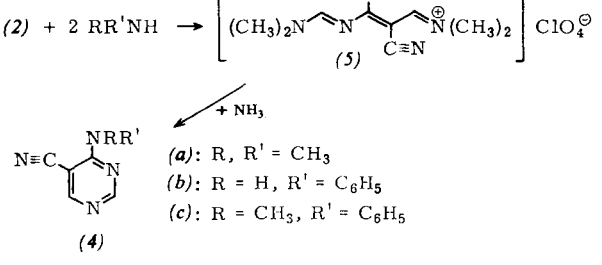
(Chloromethylene)dimethylammonium chloride *(1)* or dimethylformamide/$POCl_3$ (Vilsmeier reagent) readily react with malonodinitrile to give *N,N*-dimethyl-3-chloro-2-cyano-5-dimethylamino-4-aza-2,4-pentadienylideneammonium chloride *(2)*, which was isolated in 81 % yield as the corresponding perchlorate (yellow needles, m.p. 171 °C). Elemental analyses, UV ($\lambda_{max}$ = 382 mμ, log ε = 4.80 in $CH_3CN$), IR, and NMR spectra, and reactions confirm the structure *(2)*. In the $^1H$-NMR spectrum in trifluoroacetic acid with tetramethylsilane as internal standard there are four signals for the *N*-methyl groups (restricted rotation about the C–N bonds, anisotropy in the methine chain) at τ = 6.52 (3 H), τ = 6.45 (3 H), τ = 6.37 (3 H), and τ = 6.30 (3 H); the two methine protons appear as singlets at τ = 1.55 (1 H) and τ = 1.30 (1 H).




Since (dimethylaminomethylene)malonodinitrile *(3)*[1] also reacts smoothly with *(1)* to yield the salt *(2)*, the reaction with malonodinitrile probably occurs by way of *(3)*.

The chlorine atom of *(2)* can be replaced easily by bases, *e.g.* primary and secondary amines. When warmed with aqueous ammonium chloride or dilute ammonia solution, compound *(2)* undergoes ring closure and substitution to 4-dimethylaminopyrimidine-5-carbonitrile *(4a)* (white platelets, m.p. 114 °C in *ca.* 60 % yield). Reaction of *(2)* with an excess of aniline or *N*-methylaniline leads to azamethine salts *(5)*, which when warmed in dilute ammonia solution are cyclized to the pyrimidines *(4b)* and *(4c)*, respectively, in



total yields of 90 % [white needles, *(4b)*: m.p. 168 °C; *(4c)*: m.p. 92 °C].

*N,N-Dimethyl-3-chloro-2-cyano-5-dimethylamino-4-aza-2,4-pentadienylideneammonium perchlorate (2)*:

(a) 0.3 mole of compound *(1)* (prepared from 22 g of dimethylformamide and phosgene or 38 g of oxalyl chloride) and 0.1 mole of malonodinitrile in 60 ml of chloroform are heated on the water-bath; a vigorous reaction occurs and HCl is evolved. The chloroform is evaporated in vacuum, the residue is dissolved in a little ice-water, and $NaClO_4$ is added. The crystals are sucked dry, washed with water, dried, and recrystallized from acetonitrile/ether; yield 25.5 g (81 %) of *(2)*, yellow needles, m.p. 171 °C.

(b) 0.03 mole of compound *(1)* (from 2.2 g of DMF) and 0.02 mole of *(2)* are heated in 20 ml of chloroform for 1 hr. The product is isolated as in (a); yield 5.0 g (80 %) of *(2)*.

*4-Dimethylaminopyrimidine-5-carbonitrile (3a)*:

A solution of 0.02 mole of *(1)* in 50 ml of saturated aqueous $NH_4Cl$ is heated with 1 ml of conc. $NH_3$ solution for 10 min on a boiling water-bath. On cooling, needles of *(3a)* separate from the clear solution. These are extracted several times with chloroform, the united extracts are dried and evaporated, and the residue is recrystallized from 2-propanol or a little water; yield 1.70 g (58 %) of *(3a)*, white needles, m.p. 114 °C.

$^1$H–NMR spectrum in $CDCl_3$, TMS as internal standard: $\tau = 6.64$ (6 H) for $N$–$CH_3$, $\tau = 1.54$ (1 H), and $\tau = 1.40$ (1 H) for the ring protons.

*4-Methylanilinopyrimidine-5-carbonitrile (4b)*:

A mixture of 0.01 mole of *(2)* and 3.2 g of methylaniline in chloroform is heated for 15 min. Methylanilinium chloride and *(5c)* are precipitated by trituration with ether. Recrystallization from acetonitrile/ethyl acetate yields *(5c)*, m.p. 192 °C. When *(5c)* is heated in 20 ml of dilute $NH_3$, white needles of *(4c)* separate; recrystallization from ethanol/water yields 1.70 g (81 %), m.p. 92 °C.

$^1$H–NMR spectrum in $CDCl_3$, TMS as internal standard: $\tau = 6.45$ (3 H) for $N$–$CH_3$; $\tau = 2.38$–$2.80$ (5 H) for phenyl protons; $\tau = 1.60$ (1 H) and 1.30 (1 H) for the ring protons.

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[1] *H. Meerwein, W. Florian, N. Schön*, and *G. Stopp*, Liebigs Ann. Chem. *641*, 527 (1961); *F. Eiden*, Angew. Chem. *72*, 77 (1960).

## Structure of Tricarbonyl-1,6-methanocyclodecapentaenechromium

By Dr. H. Günther and Dr. W. Grimme

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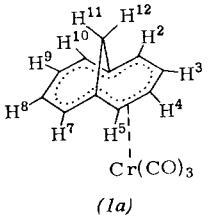
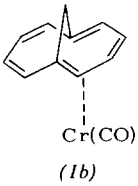
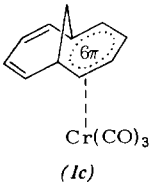
In certain cases determination of vicinal coupling constants between protons on neighboring C–C bonds permits a distinction between cyclic, conjugated, olefinic (localized) and aromatic (delocalized) π-electron systems[1,2]. We were interested in whether the ligand in tricarbonyl-1,6-methanocyclodecapentaenechromium *(1)*[3] retains a delocalized 10 π-electron system *(1a)* or whether it has an olefinic structure with fixed double bonds *(1b)* or is represented by a combination *(1c)* of a delocalized 6 π-electron system and an isolated diene.




*(1a)*




*(1b)*




*(1c)*

Chemical shifts (ppm) [a]

| $\tau_2 = \tau_5$ | $\tau_3 = \tau_4$ | $\tau_7 = \tau_{10}$ | $\tau_8 = \tau_9$ | $\tau_{11}$ | $\tau_{12}$ |
|---|---|---|---|---|---|
| 3.799 | 5.671 | 3.232 | 3.584 | 11.769 | 11.138 |

Coupling constants (Hz)

| $J_{2,3} = J_{4,5}$ | $J_{3,4}$ | $J_{2,4} = J_{3,5}$ | $J_{2,5}$ |
|---|---|---|---|
| 7.05 | 7.31 | 0.37 | 1.18 |

| $J_{7,8} = J_{9,10}$ | $J_{8,9}$ | $J_{7,9} = J_{8,10}$ | $J_{7,10}$ |
|---|---|---|---|
| 8.16 | 9.22 | 0.24 | 1.56 |

| $J_{2,11} = J_{5,11}$ | $J_{2,12} = J_{5,12}$ | $J_{7,11} = J_{10,11}$ | $J_{7,12} = J_{10,12}$ | $J_{11,12}$ |
|---|---|---|---|---|
| 0.91 | < 0.4 | < 0.3 | 1.08 | 8.90 |

[a] Tetramethylsilane (= 10.0 ppm) as internal standard; spectra were recorded in $C_6D_6$ at 60 MHz with a Varian A 60-A spectrometer.

The analysis of the $^1$H–NMR spectrum of *(1)* (see table) confirms the unsymmetrical arrangement of the carbonylmetal group[3]. The spectrum may be treated as a superposition of an AA'XX' and an AA'BB' system. Assignment of the resonance frequencies is based on spin-spin coupling between methylene and ring protons in the α-position (for which $J_{anti} > J_{syn}$)[4,1] as well as on double-resonance experiments[5]. The observation that $\tau_{11} > \tau_{12}$ is compatible only with the *anti*-arrangement of the tricarbonylmetal and the methylene group.

The vicinal coupling constants of the half-ring coordinated to the metal show no appreciable alternation, as was found, for example, for tricarbonylcycloheptatrienemolybdenum[6]. The reduction by *ca.* 2 Hz caused by complex formation, in comparison with corresponding values for free 1,6-methanocyclodecapentaene *(2)*[1], parallels the observations made with other metal complexes[7]. The vicinal coupling constants of the uncoordinated half-ring also show only minor alternation and are similar to the values for *(2)*. However, for structure *(1b)* and *(1c)* $J_{7,8}$ should exceed $J_{8,9}$, as studies of cyclic 1,3-dienes[8] show. The reduction by 0.8 Hz found for $J_{7,8}$ (and $J_{9,10}$) in comparison with the corresponding constant for *(2)* may be taken to indicate that the dihedral angle between the bonds C(7)–H(7) and C(8)–H(8) [and similarly C(9)–H(9) and C(10)–H(10)] is greater in *(1)* than in *(2)*.

The results thus favor structure *(1a)*, *i.e.*, the aromatic character of *(2)*[1,9] (a delocalized 10 π-electron system) is retained on complex formation[10].

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[1] *H. Günther*, Z. Naturforsch. *20b*, 948 (1965).

[2] *E. Vogel, M. Biskup, A. Vogel*, and *H. Günther*, Angew. Chem. *78*, 755 (1966); Angew. Chem. internat. Edit. *5*, 734 (1966).

[3] *E. O. Fischer, H. Rühle, E. Vogel*, and *W. Grimme*, Angew. Chem. *78*, 548 (1966); Angew. Chem. internat. Edit. *5*, 518 (1966).

[4] *E. J. Snyder* and *B. Franzus*, J. Amer. chem. Soc. *86*, 1166 (1964).

[5] We are indebted to Dr. *W. Naegele* and *H. Steinig*, Farbenfabriken Bayer, Leverkusen, for carrying out the double-resonance experiments.

[6] *H. Günther* and *R. Wenzl*, unpublished.

[7] *H. G. Preston* and *J. C. Davies, jr.*, J. Amer. chem. Soc. *88*, 1585 (1966).

[8] *H. Günther* and *H. H. Hinrichs*, Tetrahedron Letters *1966*, 787; *C. Ganter* and *J. D. Roberts*, J. Amer. chem. Soc. *88*, 741 (1966).

[9] *F. Gerson, E. Heilbronner, W. A. Böll*, and *E. Vogel*, Helv. chim. Acta *48*, 1494 (1965).

[10] *Added in proof*: Structure *(1a)* has been confirmed independently by X-ray analysis: *P. E. Baikie* and *O. S. Mills*, Chem. Commun. *1966*, 683.

## Aminolysis of C–C Linkages

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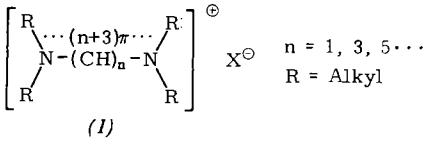
and by Prof. B. Hirsch and Dr. E.-A. Jauer

Institut für Farbenchemie der Technischen Universität Dresden (Germany)

Polymethinecyanine dyes *(1)* that exist approximately in the ideal polymethine state[1] possess polar C–C bonds because of their strongly alternating π-electron density distribution. We have found that these bonds can be cleaved by amines to yield polymethinecyanines with shorter chains.



*(1)*

The rate of aminolysis increases with increasing chain length. Undecamethinecyanines *(1)*, n = 11, and nonamethinecyanines *(1)*, n = 9, are cleaved by strongly basic secondary amines even at room temperature, but heptamethinecyanines *(1)*, n = 7, only when boiled in alcoholic solution for several hours, whereas the pentamethinecyanines *(1)*, n = 5, are not degraded to trimethinecyanines *(1)*, n = 3, under these conditions.

When *N,N*-dimethyl-9-dimethylamino-2,4,6,8-nonatetraenylideneammonium perchlorate *(1)*, n = 9, R = $CH_3$, X = $ClO_4$[2], is boiled under reflux for 30 min with an excess of 8 % alcoholic dimethylamine the color of the solution changes from deep blue to purple; on cooling, nearly pure *N,N*-dimethyl-7-dimethylamino-2,4,6-heptatrienylideneammonium perchlorate *(1)*, n = 7, R = $CH_3$, X = $ClO_4$, is precipitated (yield 65 %).

The reaction can be considered as nucleophilic substitution at a positive methine group with formation of enamine.

In the reverse reaction, stable enamines[3] or 1,1-bisdimethylaminoethylene[4] may be substituted by cyanines *(1)*, thus increasing the length of the cyanine chain.

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German version: Angew. Chem. *78*, 1063 (1966)

[1] *S. Dähne* and *D. Leupold*, Ber. Bunsenges. physik. Chem. *70*, 618 (1966).

[2] *H. E. Nikolajewski, S. Dähne, B. Hirsch*, and *E.-A. Jauer*, Chimia *20*, 176 (1966).

[3] *H. E. Nikolajewsky, S. Dähne*, and *B. Hirsch*, unpublished.

[4] *Ch. Jutz* and *E. Müller*, Angew. Chem. *78*, 747 (1966); Angew. Chem. internat. Edit. *5*, 724 (1966).

## Stable Nitroaryl-lithium Compounds[1]

By Dr. G. Köbrich and P. Buck

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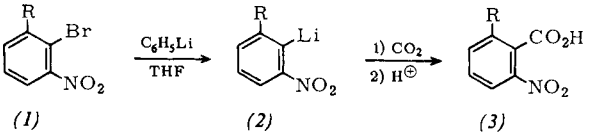
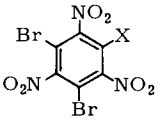
Nitro-substituted aryl-lithium compounds have not previously been prepared[2]. The *ortho*-position of nitrobenzene is not metalated by phenyl-lithium; instead, solely the nitro group is attacked and the phenyl-lithium is oxidized to lithium phenoxide[3].

We obtained the dark red *o*-nitrophenyl-lithium *(2a)* almost quantitatively on treating *o*-bromonitrobenzene with phenyl-lithium in tetrahydrofuran (THF) below −100 °C. The compound *(2a)*, and the derivatives *(2b)* and *(2c)* synthesized analogously, were characterized as the carboxylic acids *(3)*, and the compound *(4b)* as its hydrolysis product *(4c)*.



*(1)* *(2)* *(3)*

*(a)*: R = H; *(b)*: R = $CH_3$; *(c)*: R = $NO_2$



*(4a)*: X = Br
*(4b)*: X = Li
*(4c)*: X = H

| | Yield (%) | M.p. (°C) |
|---|---|---|
| *(1a)* → *(3a)* | 87–97 | 148 |
| *(1b)* → *(3b)* | 92 | 151–152 |
| *(1c)* → *(3c)* | 67 | 207 |
| *(4a)* → *(4c)* | 80 | 135 |

The influence of solvent and temperature on the ease of formation and stability of *(2a)* shows that halogen-metal exchange and reduction of the nitro group are competing reactions. Br/Li exchange to give *(2a)* [→ *(3a)*] and bromobenzene predominates at low temperature in THF, but if ether is used or the temperature is raised the degree of attack on the nitro group increases, as shown by the increasing yields of phenol.

| Temp. (°C) | In THF | | | In ether | | |
|---|---|---|---|---|---|---|
| | *(3a)* | Phenol | Bromobenzene | *(3a)* | Phenol | Bromobenzene |
| −102 | 87 % | 2 % | 87 % | 52 % | 31 % | 62 % |
| − 81 | 61 | 20 | 68 | 38 | 42 | |
| − 61 | 13 | 19 | 64 | 25 | 43 | 35 |
| − 41 | 6 | 24 | 58 | 0 | 52 | 36 |

With *m*- and, still more, *p*-bromonitrobenzene, phenoxide formation dominates even under conditions that are optimal for metalation; di- and tri-nitro aromatic compounds in which the nitro group is not forced out of the plane of the aromatic ring by bulky substituents, as it is in *(4)*, probably add phenyl-lithium to the ring, as has been found for Grignard compounds[4].

The discrepancies between the yields of *(3a)* and bromobenzene show that *o*-nitrophenyl-lithium decomposes appreciably above −80 °C; there is no indication of a benzyne intermediate in this reaction.

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German version: Angew. Chem. *78*, 1062 (1966)

[1] We thank the *Deutsche Forschungsgemeinschaft* for financial support.

[2] Cf., *e.g., R. D. Topsom* and *J. Vaughan*, J. chem. Soc. (London) *1957*, 2842.

[3] *P. Buck*, Diploma Thesis, Universität Heidelberg, 1966.

[4] *Th. Severin* and *M. Adam*, Chem. Ber. *97*, 186 (1964).

## Introduction of Tertiary Alkyl Groups into CH-Acidic Compounds

By Dr. P. Boldt and W. Thielecke[*]

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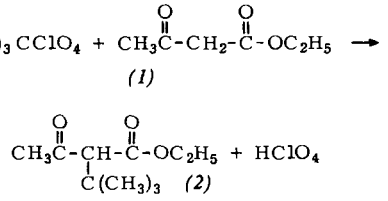
Universität Göttingen (Germany)

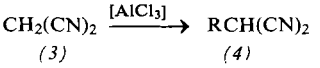
Malonodinitrile, malonic ester, and acetylacetone can be tert-butylated directly with t-butyl halides or isobutene in the presence of Lewis or Brönsted acids[1,2]. However, neither method proved preparatively useful with acetoacetic ester *(1)*[3].

We have obtained 2-t-butylacetoacetic ester *(2)* in 68 % yield by treating acetoacetic ester *(1)* with t-butyl perchlorate in nitromethane; 2-t-pentylacetoacetic ester was prepared (yield 65 %) similarly. The structure of the product *(2)*, b.p.

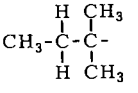
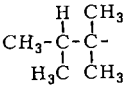
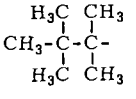
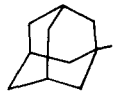


210 °C (corr.)/760 mm; $n_D^{20} = 1.4291$, was proved, by elemental analysis and NMR spectroscopy [δ = −1.05 (9, s); −1.27 (3, t, $J$ = 7 Hz); −2.13 (3, s); −3.18 (1, s); −4.15 (2, q, $J$ = 7 Hz) ppm [4]], and the mass spectrum is in agreement with the fragmentation scheme found for ethyl 2-alkylacetoacetates [5].

Further, we have used the reaction



to determine whether t-alkyl halides that are more bulky or have a greater tendency to eliminate hydrogen halide can be used in place of t-butyl bromide[1] in the acid-catalysed alkylation of CH-acidic compounds. The yields of alkylated malonodinitriles *(4)* are given in the table; the structures are proved by elemental analyses and NMR spectra.

| | R | Yield (%) | $^1$H—NMR data [4] δ (ppm) |
|---|---|---|---|
| *(4a)* |  | 57 | −0.97 (3, t; $J$ = 7 Hz)<br>−1.20 (6, s)<br>−1.61 (2, q; $J$ = 7 Hz)<br>−3.52 (1, s) |
| *(4b)* |  | 30 | −0.95 (6, d; $J$ = 6.5 Hz)<br>−1.14 (6, s)<br>*ca.*−1.8 (1, h; $J$ = 6.5 Hz)<br>−3.76 (1, s) |
| *(4c)* |  | 4 | −1.08 (9, s)<br>−1.26 (6, s)<br>−3,65 (1, s) |
| *(4d)* |  | 17 | −1.77 (12, s)<br>−1.80 (12, s)<br>*ca.*−2.15 (3, m)<br>−3.28 (1, s) |

Lewis acid catalysis also permits acidic methine protons to be replaced by t-alkyl groups: methylmalonodinitrile, t-butyl bromide, and aluminum chloride afford 3,3-dimethylbutane-2,2-dicarbonitrile in 38 % yield; its NMR spectrum includes δ = −1.23 (3, s) and −1.70 (1, s) ppm [4].

*2-t-Butylacetoacetic ester (2)*: A solution of 0.3 mole of $AgClO_4$ in 180 ml of nitromethane was added during 3 hr, with stirring, to a mixture of 0.9 mole of the ester *(1)*, 0.3 mole of t-butyl bromide, and 30 ml of nitromethane at 0 °C. The whole was kept for 3 hr at 0 °C, then filtered, washed with sodium hydrogen carbonate solution and water, dried, and freed from solvent. The excess of ester *(1)* in the distillation residue (0.425 mole) was hydrolysed by 45 hours' stirring with 425 ml of 1 N NaOH at 40 °C. The mixture was then cooled and extracted with ether, and the extracts were united, dried, and evaporated. Distillation of the residue afforded 37.8 g of product *(2)*, b.p. 95–98 °C/12 mm.

*Alkylation of malonodinitrile (3) (or methylmalonodinitrile)*: A solution of 0.1 mole of nitrile *(3)* and 0.1 mole of aluminum chloride in 30 ml of nitromethane was treated at −20 °C with 0.16 mole of t-alkyl bromide and kept at 3 °C for 16 hr [for *(4a)* and 3,3-dimethylbutane-2,2-dicarbonitrile; 48 hr for *(4b)* and *(4c)*; 10 days for *(4d)*]. After decomposition of the aluminum chloride ($NaHCO_3$ solution and ice) the mixture was steam distilled. The product *(4a)* or 3,3-dimethylbutane-2,2-dicarbonitrile that distilled after nitromethane was pure [*(4b)* was distilled, b.p. 82–84 °C/2 mm; *(4c)* was separated by gas chromatography (polyethylene glycol 20 M; 190 °C); *(4d)* crystallized after decomposition of the aluminum chloride and removal of the solvent].

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German version: Angew. Chem. *78*, 1058 (1966)

[*] We thank the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* for financial support.

[1] *P. Boldt* and *L. Schulz*, Naturwissenschaften *51*, 288 (1964).

[2] *P. Boldt* and *H. Militzer*, Tetrahedron Letters *30*, 3599 (1966).

[3] Cf. also *J.T. Adams, B. Abramovitch*, and *C. R. Hauser*, J. Amer. chem. Soc. *65*, 552 (1943).

[4] In $CCl_4$; internal standard tetramethylsilane (= 0 ppm); relative intensities in parentheses.

[5] *J. H. Bowie, S.-O. Lawesson, G. Schroll*, and *D. H. Williams*, J. Amer. chem. Soc. *87*, 5742 (1965).

## Isolation of Tetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecane and Pentacyclo[7.3.1.$1^{4,12}$.$0^{2,7}$.$0^{6,11}$]tetradecane (Diamantane) from Petroleum

By Dr. S. Hála and Prof. S. Landa

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and by Dr. V. Hanuš

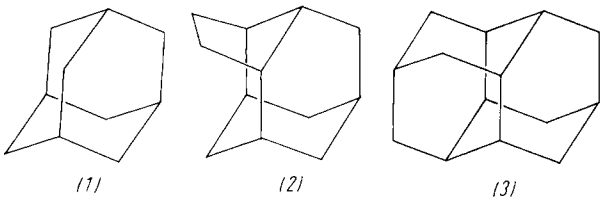
Physical Chemistry Institute, Academy of Sciences, Prague (Czechoslovakia)

Work with the naphthenic petroleum obtained in the region of Hodonin (Czechoslovakia) led some time ago to the isolation of adamantane [1] and recently to that of 1- and 2-methyladamantane [2]; we have now obtained from the same source two further crystalline naphthenes of adamantanoid structure, of which one is tetracyclic and the other pentacyclic.

These two hydrocarbons, which occur in the petroleum fraction boiling between 200 and 300 °C, give an adduct with thiourea on extractive crystallization; they concentrate in the lower portion of the column on separation by thermodiffusion. They can be purified by preparative gas chromatography and subsequent sublimation and crystallization.

The tetracyclic hydrocarbon $C_{12}H_{18}$, which was obtained with approximately 95 % purity [*], melts at 153–154 °C. The most abundant species in its mass spectrum are the molecule ion (relative intensity 100) and the fragments $C_6H_8^+$ and $C_6H_7^+$ (37 and 24, respectively), $C_9H_{11}^+$ and $C_9H_{12}^+$ (28 and 20, respectively), $C_7H_7^+$ (19), $C_{10}H_{13}^+$ (11), $C_3H_5^+$ (11), and $C_5H_7^+$ (10). In the IR spectrum the CH and $CH_2$ stretching bands (at 2935, 2920, 2905, 2865, and 2843 $cm^{-1}$) and the $CH_2$ deformation bands (at 1480, 1464, and 1450 $cm^{-1}$) are accompanied by others of medium or weak intensity, *e.g.*, at 1352, 1099, 1075, 996, 965, 928, and 881 $cm^{-1}$. In the $^1$H-NMR spectrum (Ha-100) the signals for the protons are between τ = 7.80 and 8.84, forming a complex multiplet comprising several overlapping, relatively narrow bands at τ = 8.05, 8.15, 8.27, 8.64, and 8.78; at τ = 8.35 to 8.51 there is a multiplet with resolved fine structure.

From these data we derive the adamantanoid structure tetracyclo[6.3.1.$0^{2,6}$.$0^{5,10}$]dodecane *(2)* for the hydrocarbon $C_{12}H_{18}$. This structure accords with the hydrogenative fission of the hydrocarbon on a nickel catalyst to, almost exclusively, methane, 2-methyladamantane, and adamantane.



(1) (2) (3)

The pentacyclic hydrocarbon $C_{14}H_{20}$, which crystallizes in optically isotropic octahedra, m.p. 237 °C, on slow sublimation, is pentacyclo[7.3.1.1$^{4,12}$.0$^{2,7}$.0$^{6,11}$]tetradecane *(3)*, which was recently synthesized[3] and called diamantane[4] (originally congressane[3]). The hydrocarbon $C_{14}H_{20}$ and authentic diamantane have the same melting point, an undepressed mixed melting point, and the same elution times on gas chromatography. The mass spectra also are identical and correspond[**] with the published mass spectrum of diamantane[3].

Received: October 6th, 1966 [Z 345 IE]
German version: Angew. Chem. *78*, 1060 (1966)

[*] Determined by gas chromatography (capillary column); mass spectrometry indicates that the impurities are predominantly hydrocarbons $C_{12}H_{20}$, $C_{13}H_{22}$ (alkyladamantanes), and $C_{13}H_{20}$.

[1] *S. Landa* and *V. Macháček*, Collect. czechoslov. chem. Commun. *5*, 1 (1933).

[2] *S. Hála* and *S. Landa*, Erdöl Kohle-Erdgas-Petrochem., *19*, 727 (1966).

[3] *C. Cupas, P. v. R. Schleyer*, and *D. J. Trecker*, J. Amer. chem. Soc. *87*, 917 (1965); cf. Angew. Chem. *77*, 180 (1965); Angew. Chem. internat. Edit. *4*, 169 (1965).

[4] *O. Vogl, B. D. Anderson*, and *D. M. Simons*, Tetrahedron Letters *1966*, 415.

[**] The ratio of the abundance of the molecule ion to that of the commonest fragment ($m/e = 91$) is, however, twice as great as in the published spectrum [3].

## Crystal Structure of Carbonyl-(piperidine-*N*-carbonitrile)nickel(0)

By Dr. K. Krogmann and Dr. R. Mattes

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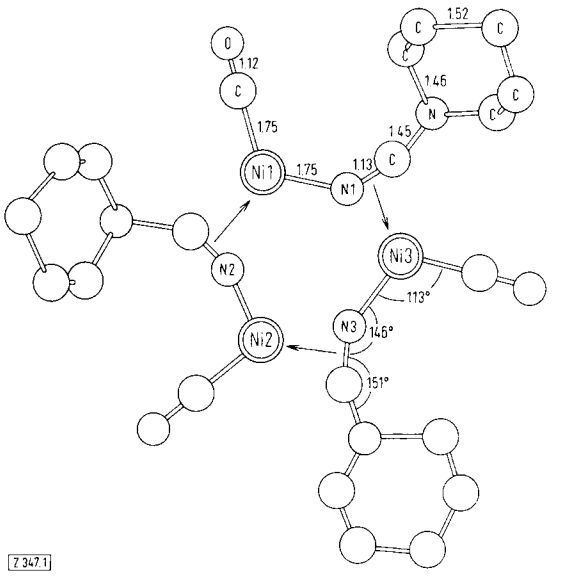
Technische Hochschule Stuttgart (Germany)

The crystal structure of carbonyl(piperidine-*N*-carbonitrile)-nickel(0), $Ni(C_5H_{10}NCN)(CO)$, first prepared by *H. Bock* and *H. tom Dieck*[1] reveals a new type of π-complex, involving $C\equiv N$ triple bonds.

Six formula units are contained in the triclinic unit cell (space group P1) as two trimeric molecules. The nickel atoms of each trimer occupy the corners of an equilateral triangle, all having the same coordination of light atoms. Two nickel atoms (Ni-1 and Ni-2) are relatively close to nickel atoms of the adjacent trimer (3.20 Å), but no effect of metal-metal bonds on the coordination sphere can be detected. The figure shows a projection of the molecule on the plane of the three nickel atoms. Essential bond distances and angles (averaged) are included. All atoms of the CO and NCN groups are in the plane of the three Ni atoms or deviate from it by less than 0.3 Å. Every Ni atom is linked by σ bonds to a carbonyl-C and a cyano-N. Three of these monomers form the trimer using π-bonds from the cyano groups. There are no $>N{=}C{=}NR_2$ groups; these would be linear and perpendicular to the line Ni–Ni. Bond distances and angles are instead in accordance with $-N\equiv C-NR_2$ groups, and N and C atoms of the CN groups are equidistant from the π-bonded Ni atom (1.99 Å). The bond angles Ni–N–C–$NR_2$ might be expected as a result of the displacements of electron density in the π-system of the $N\equiv C$ group. The N atom of piperidine is not involved in bonding to Ni. The rings have the chair conformation; two CN groups are attached axially, and one is attached equatorially.




Z 347/1

The dimension of the unit cell are

| | |
|---|---|
| $a = 12.28$ Å | $\alpha = 105.6°$ |
| $b = 9.33$ Å | $\beta = 109.5°$ |
| $c = 12.31$ Å | $\gamma = 82.4°$ |

Volume (1278 Å$^3$) and formula weight (196.9) lead to the density $D$(calc) = 1.54 g/cm$^3$ whereas $D$(obs) = 1.53 g/cm$^3$.

1594 reflections ($CuK_\alpha$) were registered at room temperature on film, and intensities were measured photometrically[2]. Observable intensities were found only in the range of 0°–45° (overall temperature factor $B_0 \simeq 6$ Å$^2$). Coordinates of the Ni atoms could be found from a sharpened Patterson synthesis. Those of the light atoms (21 C, 6 N, 3 O) were found on successive Fourier syntheses and refined by least-squares methods, the $R$ factor decreasing from 45 % to 16 %.

Received: October 10th, 1966 [Z 347 IE]
German version: Angew. Chem. *78*, 1064 (1966)

[1] *H. Bock*, Angew. Chem. *74*, 695 (1962); Angew. Chem. internat. Edit. *1*, 550 (1962); *H. Bock* and *H. tom Dieck*, Chem. Ber. *99*, 213 (1966).

[2] Crystals were kindly supplied by Drs. *H. Bock* and *H. tom Dieck*.

## Preparation of Phosphorus Tribromide from the Elements

By Dr. F. Schröder

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Universität Hamburg (Germany)

Preparation of $PBr_3$ from the elements has hitherto required white phosphorus and/or use of a solvent[1,2], as well as complicated apparatus[2]. We have now converted red phosphorus into $PBr_3$ with bromine in the absence of a solvent, using a three-necked, round-bottomed flask (1 liter) equipped with a dropping funnel, a reflux condenser with drying tube, and a stirrer with a glass precision bearing. Red phosphorus powder (2 g-atoms) is very gently stirred and treated dropwise with 3 moles of bromine, slowly at first, then faster. The $PBr_3$ formed may contain suspended phosphorus and is distilled off. Water cooling can be used until the liquid $PBr_3$ appears. Previous passage of purified nitrogen through the apparatus and drying of the phosphorus avoids formation of small amounts of $P_2O_5$.

Received: October 11th, 1966 [Z 346 IE]
German version: Angew. Chem. *78*, 1102 (1966)

[1] Gmelins Handbuch der anorganischen Chemie. 8th. Edit., Verlag Chemie, Weinheim 1965, System No. 16, Part C.

[2] Inorg. Synth. *2*, 147 (1946).

## A New Method for the Preparation of Alkali and Alkaline Earth Hydroxometalates

By Prof. R. Scholder and Dr. F. Schwochow

Institut für Anorganische Chemie,
Technische Hochschule Karlsruhe (Germany)

Hydroxometalates or, more generally, ternary hydroxides of alkali and alkaline-earth metals with more weakly basic metals have hitherto been prepared almost exclusively from aqueous solution. In this process a very high OH ion concentration, often 50 % and, in the extreme case of $Na_2[Mg(OH)_4]$[1], even over 70 % sodium hydroxide solution is usually necessary to shift the equilibrium in the direction

$$M(OH)_x + y\ OH^- \rightarrow [M(OH)_{x+y}]^{y-}.$$

The preparation is thus complicated, and the attainable purity of the products, particularly of alkalihydroxometalates, is not satisfactory.

The new method of preparation, consisting in direct, quantitative reaction of a finely powdered, almost stoichiometric mixture of the two hydroxide components at a relatively low temperature, is remarkably simple and affords much purer substances. In this way compounds of the type $Na_2[M(OH)_4]$ are obtained for M = Mn, Co, Ni, Cu, Zn, Cd, or Mg with at most 15 hours' heating between 50 °C (for Zn) and 140 °C (for Ni) under highly purified $N_2$. Similarly, hydrated $Fe_2O_3$ with NaOH at 80 °C affords $Na_5[Fe(OH)_8]$, and with partially dehydrated $Ba(OH)_2 \cdot 8\ H_2O$ at 90 °C $Ba_3[Fe(OH)_6]_2$.

It is surprising that an oxide MO can be used in place of the metal(II) hydroxide for preparation of compounds of the type $Na_2[M(OH)_4]$ if the reaction is carried out under $H_2O$-saturated $N_2$ at 50–100 °C (M = Cu, Zn, Cd, or Mg; not Ni).

The purity of the hydroxometalates obtained by the thermal method is illustrated by the observed ratios $MO:Na_2O:H_2O$ = 1:1.00–1.02:2.03–2.05 (total oxides[2] > 99 %). The products give very good X-ray powder diagrams.

Depending on the temperature of preparation (65 or 100 °C), $Na_2[Mg(OH)_4]$ is obtained in one of two modifications which have different X-ray diffraction patterns.

It has not yet been possible to obtain potassium hydroxometalates; however, preliminary thermal experiments with $Ca(OH)_2$ and NaOH in the range 3.5–4.5 NaOH:1 $Ca(OH)_2$ gave a new phase consisting of a ternary hydroxide which, according to the X-ray powder diagram, has the NaCl structure.

Received: October 17th, 1966 [Z 349 IE]
German version: Angew. Chem. 78, 1102 (1966)

[1] *R. Scholder* and *C. Keller*, Z. anorg. allg. Chem. *317*, 113 (1962).

[2] *I.e.*, % MO + % NaO + % $H_2O$.

## Trichloromethanesulfinyl Isocyanate

By A. Senning

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In contrast to other aliphatic sulfinyl chlorides, trichloromethanesulfinyl chloride *(1)*[1] is converted by silver cyanate in boiling benzene into the corresponding isocyanate *(2)*, the first sulfinyl isocyanate reported. After filtration of the solution the benzene is distilled off and the residue is at once treated further. It contains about equal amounts of compounds *(1)* and *(2)*, as well as by-products. It was not possible to obtain the isocyanate *(2)* in a pure state because of the very similar boiling points [36–38 °C/1 mm for *(1)* and 42 °C/0.7 mm for the azeotropic mixture of *(1)* and *(2)*].

$$CCl_3SOCl + AgOCN \rightarrow CCl_3SONCO + AgCl$$
$$(1) \qquad\qquad (2)$$

When treated with water, an ethereal solution of the crude product containing the isocyanate *(2)* gives carbon dioxide and volatile decomposition products of the not isolable trichloromethanesulfinamide; with ammonia it affords trichloromethanesulfinylurea, $CCl_3SONHCONH_2$, m.p. 162 to 163 °C (decomp.), and with ethanol the urethane derivative $CCl_3SONHCOOC_2H_5$, m.p. 80–83 °C.

Direct reaction of amides with *(1)* is beset with difficulties, so that the isocyanate *(2)* is a valuable intermediate for preparation of *N*-trichloromethanesulfinyl-substituted compounds. The following are some characteristic IR bands[2]:

| $CCl_3SOR$, R = | Cl [1] | NCO | $NHCONH_2$ | $NHCO_2C_2H_5$ | $NHC_6H_5$ [1] |
|---|---|---|---|---|---|
| $\nu SO$ ($cm^{-1}$) | 1190 | 1190 | 1110 | 1110 | 1085–1095 |
| $\nu CO$ ($cm^{-1}$) | | | 1680–1700 | 1740 | |
| $\nu NCO$ ($cm^{-1}$) | | 2250 | | | |

Received: October 6th and 17th, 1966 [Z 350 IE]
German version: Angew. Chem. 78, 1100 (1966)

[1] *U. Schöllkopf* and *P. Hilbert*, Angew. Chem. *74*, 431 (1962); Angew. Chem. internat. Edit. *1*, 401 (1962); cf. *A. Senning*, Chem. Reviews *65*, 385 (1965).

[2] Cf. *G. Kemmner*, *G. Nonnenmacher*, *W. Wucherpfennig*, and *G. Kresze*, 8th European Congress of Molecular Spectroscopy, Copenhagen, 1965.

## Crystal Structure of Violet Phosphorus

By H. Thurn and Prof. H. Krebs

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Violet (Hittorf) phosphorus crystallizes in the monoclinic form, with space group P2/c, $a$ = 9.21, $b$ = 9.15, $c$ = 22.59 Å, $\beta$ = 106.1 °, and 84 atoms in the unit cell.

The structure is based on two units: a $P_8$ group in which the atoms are arranged as in $As_4S_4$[1], and a $P_9$ group. These units are linked, each through two further phosphorus atoms, to form infinite, tube-like structures of pentagonal cross-section (Fig. 1), which are bent somewhat "downwards" at the sites of the $P_8$ groups. This kind of linkage results in two planar, zigzag chains of phosphorus atoms being formed on two sides of the tubes (in Fig. 1 the atoms 1 to 8 and 9 to 16). This is the type of structure was previously assumed for violet phosphorus[2] and a similar structure was found for $HgPbP_{14}$[3].

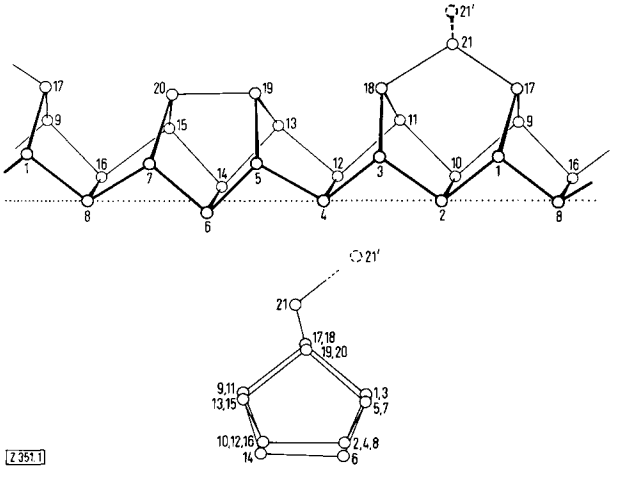


Fig. 1. Section of a "tube" of violet phosphorus. Above: parallel perspective. Below: projection parallel to the tube axis (end view).

The tubes are packed parallel to one another to form layers. Pairs of layers (*e.g.* aAaA and bBbB in Fig. 2) are connected *via* atoms 21 of the $P_9$ groups so that the axes of the tubes in the two layers form an angle of almost exactly 90°. As shown in Fig. 2, the tubes marked a and A of one layer are joined to the tubes marked b and B, respectively, in the second layer. Thus a double layer consists of two interlocking systems that, however, are not linked by chemical bonds.

These double layers are stacked in the direction of the *c*-axis so that each tube is above a gap between two tubes of the layer below; they are held together by van der Waals forces.

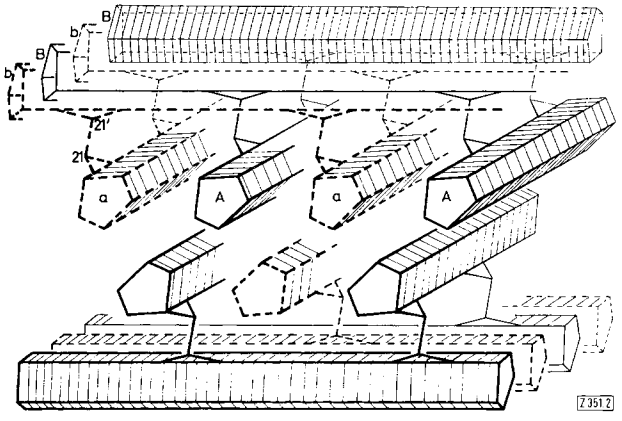


Fig. 2. Schematic representation of the structure of violet phosphorus. The "tubes" are represented by pentagonal prisms; in parts of the upper layer only one edge is drawn to show the linkage of the two halves of a double layer *via* atoms 21 and 21'.

The mean bond length is 2.219 Å, the mean bond angle 100.9°. The values diverging most from the mean are:

| | | | | |
|---|---|---|---|---|
| Bond | 21–21' | 2.178 Å | Angle 5–6–7 | 84.5° |
| | 19–20 | 2.298 Å | 13–14–15 | 86.5° |
| | | | 17–21–18 | 115.9° |

The *R*-value is 5.8 %.

The relatively complicated structure of violet phosphorus probably is due to the difficulty of satisfying all three pyramidal phosphorus valences with retention of the normal valence angle of somewhat over 100°. The complexity of the structure explains why glasses are first formed when white phosphorus is heated and the infinite crystal structure is formed only on long annealing.

Received: September 28th, 1966; revised October 26th, 1966 [Z 351 IE]
German version: Angew. Chem. *78*, 1101 (1966)

[1] *T. Ito, N. Morimoto*, and *R. Sadanaga*, Acta crystallogr. *5*, 775 (1952).

[2] *I. Pakulla*, Dissertation, Universität Bonn, 1953; *H. Krebs, K. H. Müller, I. Pakulla*, and *G. Zürn*, Angew. Chem. *67*, 524 (1955).

[3] *H. Krebs* and *Th. Ludwig*, Z. anorg. allg. Chem. *294*, 257 (1958).

## *N*-Thioaniline, $C_6H_5N{=}S$, as Intermediate in the Decomposition of *N,N*'-Thiodianiline

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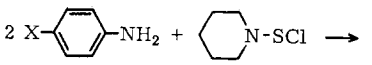
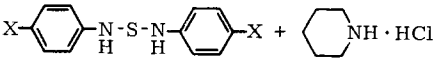
The *N,N'*-thiodianilines *(2a)–(2d)* were obtained by dropwise addition of piperidine-1-sulfenyl chloride [1] to a solution of the anilines *(1a)–(1d)* in anhydrous ether at −20 °C.

Compounds *(2b)–(2d)* were characterized by composition, IR spectra ($\nu_{N-H}$ = 3400–3420 $cm^{-1}$), and NMR spectra [tetramethylsilane as internal standard, AB spectrum unchanged from those of *(1b)–(1d)*, NH proton at $\tau \approx 4.1$ in



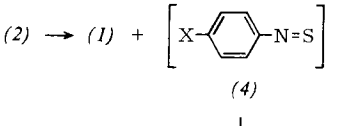
*(1)*



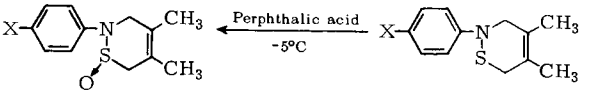
*(2)*

| *(2)* | M.p. (°C) | Yield (%) |
|---|---|---|
| *(a)*, X = H | Oil | 90 (crude) |
| *(b)*, X = Cl | 102–103 | 53 |
| *(c)*, X = Br | 106–108 | 55 |
| *(d)*, X = $NO_2$ | 208–210 | 66 |

$CS_2$]. Compounds *(2a)–(2c)* are stable for several months at −15 °C but decompose, with development of a blue color, within 2 to 6 weeks at room temperature, the anilines *(1a)* to *(1c)* being identified among the decomposition products. Compound *(2d)* is stable at room temperature. When compounds *(2a)–(2c)* are heated in an excess of boiling dimethylbutadiene for 6 hr, the 2-aryl-3,6-dihydro-4,5-dimethyl-1,2-thiazines *(3a)–(3c)* can be isolated by subsequent column chromatography and distillation. We assume that the hitherto unknown thioanilines *(4a)–(4c)* are intermediates in this reaction.



*(4)*




*(5)* *(3)*

| | *(5)*, M.p. (°C) | Yield (%) | *(3)*, B.p. (°C/0.1 mm) | Yield (%) |
|---|---|---|---|---|
| *(a)*, X = H | 79–80 (lit. [3] 79–80) | 53 | 103–105 | 22 |
| *(b)*, X = Cl | 150–151 | 46 | 117–120 | 32 |
| *(c)*, X = Br | 157–158 | 58 | 138–142 | 41 |

Compounds *(3a)–(3c)* were characterized by elemental analysis, IR spectra (no N–H stretching vibration, $\nu_{C=C}$ = 1650–1670 $cm^{-1}$, very weak), and NMR spectra [signals of the aromatic portion unchanged in comparison with those of *(1)* and *(2)*, ring methylene protons at $\tau$ = 6.2 and 7.2, C–$CH_3$ at $\tau$ = 8.3 (broad singlet), ratio of areas 2:2:6]. Compounds *(4a)–(4c)* were converted into 2-aryl-3,6-dihydro-4,5-dimethyl-1,2-thiazine 1-oxides with perphthalic acid. These products were the same as those obtained from the corresponding thionylanilines and dimethylbutadiene [2, 3] (m.p., mixed m.p., IR spectra).

*Experimental*:

*(1c)* → *(2c)*. 34.4 g (0.2 mole) of *p*-bromoaniline in 300 ml of anhydrous ether at −20 °C was treated dropwise with 15.1 g (0.1 mole) of piperidine-1-sulfenyl chloride. As soon as the temperature had risen to 0 °C the piperidinium chloride was filtered off and the ether distilled off at room temperature. The 34.5 g of yellow-brown residue crystallized when scratched and after two recrystallizations from methylene chloride afforded 20.1 g.

*(2a)* → *(3a)*. 18.0 g of crude product prepared as above from aniline and piperidine-1-sulfenyl chloride was warmed with 20 ml of dimethylbutadiene for 6 hr at 70 to 80 °C. The

residue remaining on evaporation was chromatographed on 850 g of silica gel (column 4×90 cm) with hexane/acetone (100:3). The first 300 ml of eluate contained 10.9 g of crude product *(3a)*. This was taken up in ether, and washed with 1 % hydrochloric acid and 1 % sodium hydrogen carbonate solution; the ethereal solution was dried, evaporated, and distilled. After a forerun of b.p. 35–103 °C/0.1 mm, 3.8 g of product *(3a)* was obtained.

*(3b)* → *(5b)*. 3.6 g (0.015 mole) of compound *(3b)* and 2.9 g (0.015 mole) of perphthalic acid in 32 ml of ether were kept at −5 °C for 2 hr. The solution was then washed several times with 1 % sodium hydrogen carbonate solution, dried, and evaporated. The 2.1 g of residue crystallized when scratched. When recrystallized twice from petroleum ether, the product *(5b)* (1.8 g) was identical (m.p., mixed m.p., IR spectra) with that obtained from *p*-aminobenzenesulfinyl chloride and dimethylbutadiene (20 hr, 70 °C, 68 %).

Received: September 14th, 1966 [Z 331 IE]
German version: Angew. Chem. *78*, 1057 (1966)

[1] *Houben-Weil*: Methoden der organischen Chemie. Thieme, Stuttgart 1964, Vol. 11/2, p. 745.

[2] Review of the reactions of sulfinylanilines: *G. Kresze*, Angew. Chem. *74*, 135 (1962); Angew. Chem. internat. Edit. *1*, 89 (1962).

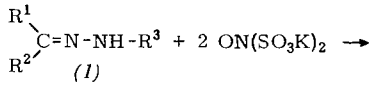
[3] *O. Wichterle* and *J. Rocek*, Chem. Listy *47*, 1768 (1953).

## Reaction of Phenylhydrazones with Dipotassium Nitrosobissulfate

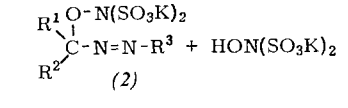
By Prof. H.-J. Teuber and K.-H. Dietz

Institut für Organische Chemie,
Universität Frankfurt/Main (Germany)

Reaction of dipotassium nitrosobissulfate, $ON(SO_3K)_2$, with phenols gives quinitrol-like substitution products [1], which decompose to quinones and dipotassium imidobissulfate, $HN(SO_3K)_2$, either spontaneously or under acid catalysis. Phenylhydrazones [*(1)*, $R^1$ = H, alkyl, aryl; $R^2$ = alkyl; aryl; $R^3$ = aryl] yield yellow, well crystalline azo compounds *(2)* on dehydrogenation at the nitrogen.



*(1)*



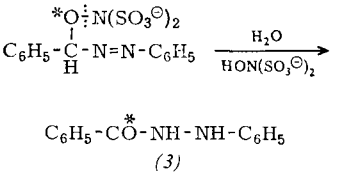
*(2)*

*Experimental*: 5 mmole of a phenylhydrazone in 120 ml of acetone are mixed with 10 mmole of dipotassium nitrosobissulfate in 120 ml of water containing 0.5 g of sodium acetate to give an orange-yellow solution, which, after 10 min, is evaporated at 50 °C to half its volume, washed with ether, and evaporated to dryness. Extraction of the residue with methanol, evaporation of the extract, and recrystallization of the resulting residue from 80 % ethanol give the yellow compound *(2)*, containing solvent of crystallization, almost quantitatively.

Compounds *(2)* are formed in this way from the phenylhydrazones of furfural, cinnamaldehyde, salicylaldehyde, *o*-chlorobenzaldehyde, *o*-, *m*-, and *p*-nitrobenzaldehyde, acetone, benzophenone, acetophenone, isobutyraldehyde, cyclohexanone, or cyclopentanone; the substituent in the hydrazone group may also be varied [2,3-, 2,4-, or 2,5-$(CH_3)_2C_6H_3$, *o*-$ClC_6H_4$, *p*-$NO_2C_6H_4$, or *p*-$CH_3C_6H_4$]. However, an *o*-nitrophenyl, 2,4-dinitrophenyl, or benzenesulfonyl substituent in the hydrazone group prevents the reaction, as does replacement of the hydrogen attached to nitrogen; semicarbazones also do not react.

Dipotassium *N*-(phenylazoalkoxy)imidobissulfates *(2)* correspond to the phenylazoalkyl hydroperoxides [*(2)*, −OOH replacing $-ON(SO_3K_2)_2$] [2] formed by autoxidation; the phenylazocarbinol acetates [*(2)* with −OAc replacing $-ON(SO_3K)_2$] [3] formed with lead tetraacetate, as well as the compounds produced with benzoyl peroxide [4]; nitrous acid [5], and diazonium salts (formation of formazans). The azo formulation of *(2)* follows from almost identical UV spectra ($\lambda_{max}$ in methanol: 400, 265–270, 215–218 mμ; log ε = 2.7, 4.7, 4.8) as well as instability of the corresponding alkyl derivatives (*(2)* with $R^3$ = alkyl). Substitution in the $R^1$, $R^2$, or $R^3$ groups by the nitrosobissulfate group is excluded by the NMR spectrum. They are reconverted into hydrazones *(1)*, as are phenylazohydroperoxides, on reaction with sodium dithionate, zinc/acetic acid, or hydrogen activated on Pd/$BaSo_4$. The formation of osotriazol from osazones possibly involves an intermediate corresponding to *(2)*.

Compound *(2)* with $R^1$ = H and $R^2$ = $R^3$ = $C_6H_5$ decomposes in 1/2 hr in aqueous solution at 90 °C to *N'*-phenylbenzhydrazide *(3)* and hydroxylimidobissulfuric acid [6,7]; benzoic acid and phenylhydrazine are formed also. Decomposition in $^{18}O$-labeled water shows that 6 % of the hydrazide is derived from the water (the hydrazide *(3)*, once formed, does not undergo exchange with water). However, decomposition of the substitution product *(2)* obtained from $^{18}ON(SO_3K)_2$ [8] affords an *N'*-phenylbenzhydrazide *(3)* whose oxygen is derived to the extent of more than 70 % from the nitrosobissulfate group, indicating the following mechanism.



*(3)*

The hydrolytic removal of the nitrosobissulfate group takes place *via* the quinitrol-like substitution product of the 1-methyl-2-naphthol analogue [9]. Apart from hydrolysis of the C–O instead of the N–O bond, the incomplete labeling of *(3)* could be due to the nitrosobissulfate group in *(2)* being bonded to the organic group partly *via* the nitrogen atom. The *o*-chlorobenzoic acid finally produced from *o*-chlorobenzaldehyde *via (1)* → *(2)* → *(3)* and further hydrolysis, shows the same labeling as *N'*-phenyl-*o*-chlorobenzhydrazide.

Received: August 9th, 1966; revised November 17th, 1966 [Z 333 IE]
German version. Angew. Chem. *78*, 1101 (1966)

[1] *H.-J. Teuber* and *W. Rau*, Chem. Ber. *86*, 1036 (1953); *H.-J. Teuber* and *N. Götz*, *ibid. 89*, 2654 (1956); *H.-J. Teuber* and *G. Thaler*, *ibid. 92*, 667 (1959).

[2] *K. H. Pausacker*, J. chem. Soc. (London) *1950*, 3478; *R. Criegee* and *G. Lohaus*, Chem. Ber. *84*, 219 (1951).

[3] *D. C. Iffland*, *L. Salisbury*, and *W. R. Schafer*, J. Amer. chem. Soc. *83*, 747 (1961).

[4] *J.T. Edward* and *S. A. Samad*, Canad. J. Chem. *41*, 1638 (1963).

[5] *E. Bamberger* and *W. Pemsel*, Ber. dtsch. chem. Ges. *36*, 347 (1903).

[6] *H.-J. Teuber* and *G. Jellinek*, Chem. Ber. *85*, 95 (1952).

[7] The yield of *N'*-phenylbenzhydrazide amounts to only 20 to 30 % because of the ready hydrolysis to benzoic acid and phenylhydrazine. The *N'*-phenylhydrazides of *o*-chlorobenzoic and cinnamic acid are isolated in 71 % and 85 % yield, respectively.

[8] *H.-J. Teuber* and *K.-H. Dietz*, Angew. Chem. *77*, 913 (1965); Angew. Chem. internat. Edit. *4*, 871 (1965).

[9] *H.-J. Teuber* and *N. Götz*, Chem. Ber. *89*, 2654 (1956), p.2662 – The quinol carbonyl group must, however, be blocked by the *p*-nitrophenylhydrazone group.

## The Dynamics of Sulfur Metabolism and the Utilization of Sulfur in the Animal Organism

*J. Landis* and *J. P. Montavon*, Zürich (Switzerland)

Single doses of [$^{35}$S]-L-methionine were given orally to growing rats whose rations included various amounts of sulfur-containing amino acids. With a deficiency of methionine the separation of $^{35}$S in the excrements was fairly constant during the first three days, *i.e.* it was independent of the size of the methionine deficit. When an excess of methionine was administered there was a relation between the excretion of $^{35}$S and the amount of the excess (large increase in excretion of $^{35}$S with increasing methionine excess). This relationship enables the utilization of methionine sulfur to be determined even if there is no deficiency of methionine and if no change in growth or nitrogen balance is observable.

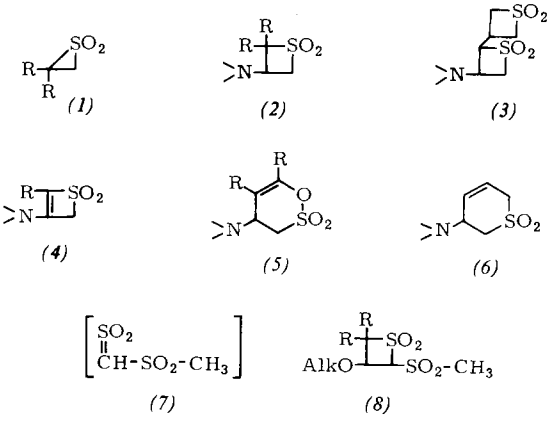
A cystine content of about 0.3 % in the diet influenced the excretion of radioactive sulfur (administered as [$^{35}$S]-L-methionine) in the same way as an equivalent increase in methionine content as regards content of amino acid sulfur. A further increase in the cystine content of the diet was, however, without influence on the excretion of labeled sulfur. This result is interpreted as showing that, under the experimental conditions used, 50 to 60 % of the animals' total requirement of amino acid sulfur can be supplied as cystine, the total requirement being estimated from the excretion of $^{35}$S in the absence of cystine as 0.11 to 0.13 % of the diet (equivalent to a 0.5 to 0.6 % methionine content).

Lecture at Basel (Switzerland), September 1st, 1966 [VB 25 IE]
German version: Angew. Chem. *78*, 1066 (1966)

## Sulfenes

*G. Opitz*, Tübingen (Germany)

The intermediate formation of sulfenes $R'_2C{=}SO_2$ on elimination of HCl from sulfonyl chlorides with trialkylamines or on reaction of diazoalkanes with $SO_2$ can be recognized by means of trapping agents. Addition of diazoalkanes (when R′ = H) produces three-membered cyclic sulfones *(1)*, addition of enamines, dienamines, or ketene aminals gives four-membered cyclic sulfones *(2)*, *(3)*, or *(4)*, respectively, of 2-aminovinyl ketones yields six-membered cyclic sultones *(5)*, and of dienamines gives unsaturated six-membered cyclic sulfones *(6)* [in addition to *(3)*].



*(1)* *(2)* *(3)* *(4)* *(5)* *(6)* *(7)* *(8)*

In the absence of a trapping agent the sulfenes at once react further with the sulfonyl chloride or with the diazoalkane or $SO_2$, so that they have not hitherto been isolated or identified directly. We have now isolated methanesulfonylsulfene (methanesulfonylthioformaldehyde dioxide) *(7)* as its trimethylamine adduct[1]. This compound *(7)* is formed when methanesulfonyl chloride is treated with an excess of triethylamine in acetonitrile at −40 °C[2]; it is present as triethylamine adduct in the filtrate from the triethylamine hydrochloride; on addition of trimethylamine the more stable 1:1 trimethylamine adduct is precipitated, which can be isolated at room temperature without the need to exclude air. It gives the four-membered cyclic sulfones *(8)*[3], not merely with enamines, but also with vinyl ethers. The reaction leading to *(8)* can be effected also with methanesulfonyl chloride/triethylamine and vinyl ether in acetonitrile at −40 °C.

Lecture at Wuppertal on November 17th, 1966 [VB 28 IE]
German version: Angew. Chem. *78*, 1066 (1966)

[1] *G. Opitz* and *D. Bücher*, Tetrahedron Letters *1966*, 5263.

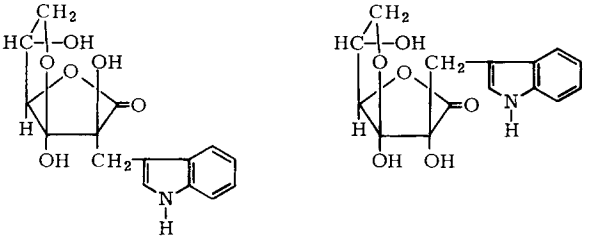
[2] *G. Opitz, M. Kleemann, D. Bücher, G. Walz*, and *K. Rieth*, Angew. Chem. *78*, 604 (1966); Angew. Chem. internat. Edit. *5*, 594 (1966).

[3] *G. Opitz, K. Rieth*, and *G. Walz*, Tetrahedron Letters *1966*, 5269.

## Formation and Properties of Ascorbigen

*G. Kiss*, Zürich (Switzerland)

Two epimeric ascorbigens (A and B) are formed on reaction of L-ascorbic acid with 3-(hydroxymethyl)indole[1] by the method of *Virtanen et al.*[2]. Ascorbigen A, identical with the natural product, was obtained as main product (55–60 % yield). The yield of ascorbigen B was less than 20 %.



Ascorbigen A Ascorbigen B

Ascorbigens A and B result from reaction of the ascorbate anion at C-2 with the resonance-stabilized carbonium-iminium ion[3] formed from 3-(hydroxymethyl)indole; *O*-alkylation was not observed. Acid hydrolysis of ascorbigen A (pH 1.5–3.0; 37 °C) yields L-ascorbic acid.

The structure was established by elemental analysis, reactions (derivatives such as ascorbigenamide and ascorbigen methylglycoside) and spectroscopic data.

The ascorbigens can be determined in finely divided plant material by thin-layer chromatography. Ascorbigen A was found in macerated white cabbage, kohlrabi, cauliflower, and radish.

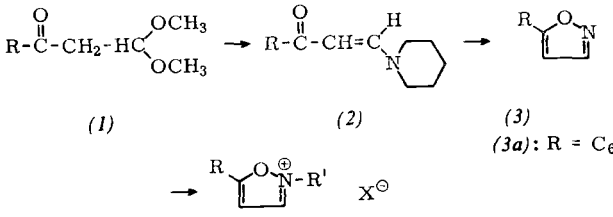
Lecture at Basel (Switzerland), Sept. 2nd and 3rd, 1966 [VB 24 IE]
German version: Angew. Chem. *78*, 1055 (1966)

[1] *A. I. Virtanen* and *M. Kiesvaara*, Acta chem. scand. *17*, 848 (1963).

[2] *G. Kiss* and *H. Neukom*, Helv. chim. Acta *49*, 989 (1966).

[3] *H. Hellmann* and *G. Opitz*: α-Aminoalkylierung. Verlag Chemie, Weinheim/Bergstr. 1960.

**The synthesis of isoxazolium salts unsubstituted in the 3-position** has been considerably improved by *B. D. Wilson* and *D. M. Burness*. These compounds, *e.g. (4a)*, can generate a peptide bond under mild conditions, like carbodiimides. The readily available compounds *(1)* are converted with piperidine to *(2)*, which yields on reaction with hydroxylamine isoxazoles *(3)*, which are free of isomers to better than 98%. Alkylation of *(3)* then renders the isoxazolium salts *(4)*.



*(1)* *(2)* *(3)*

*(3a)*: R = $C_6H_5$



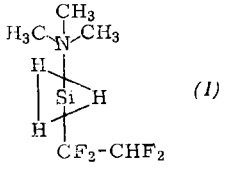
*(4)*

*(4a)*: inner salt: R = ; R' = $C_2H_5$; no $X^{\ominus}$

*(4b)*: R = R' = $CH_3$; $X^{\ominus}$ = *p*-toluenesulfonate

For the preparation of *(4a)*, m.p. 209.5–211 °C (decomp.), known as *Woodward*'s reagent K, *(3a)*, m.p. 21–22 °C, $n_D^{25}$ = 1.5832, is sulfonated with chlorosulfonic acid and ethylated. It can be prepared in an overall yield of 70%. Another example is *(4b)*, m.p. 111–112 °C, yield 80%. / J. org. Chemistry *31*, 1565 (1966) / –Bu. [Rd 542 IE]

A **pentacoordinate silicon complex** has been prepared by *R. N. Haszeldine* and co-workers from trimethylamine and 1,1,2,2-tetrafluoroethyl silane. Structure *(1)* can be assigned to the 1:1 adduct on the basis of infrared and NMR spectra: the Si–H stretching frequency is shifted from 2222 $cm^{-1}$ (in the starting silane) to 2155 $cm^{-1}$, *i.e.* the electron density on

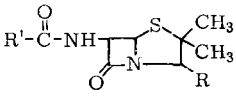


*(1)*

silicon is increased; the C–H bands appearing at 2780 $cm^{-1}$ in trimethylamine are missing, as has been generally observed when nitrogen donates its lone pair of electrons to some acceptor; the equivalence of all Si–H hydrogens in the NMR spectrum is in accordance with the trigonal bipyramidal structure *(1)*. The compound, a stable liquid, can be vacuum distilled (vapor pressure: 84 mm/20 °C); in the gas phase the compound dissociates to the parent compounds as shown by IR spectrum and molecular weight. / J. chem. Soc. (London) A *1966*, 889 / –Bu. [Rd 544 IE]

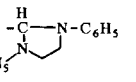
**The attenuation of sound waves in a single crystal of $NH_4Cl$** in the (100) direction close to the lambda transition temperature (about 242 °K) was measured by *C. W. Garland* and *C. F. Yarnell*. In the lambda transition, the ammonium ions pass from a state of fixed orientation to one of random orientation. In the immediate neighborhood of the lambda point, the attenuation coefficients measured during cooling differ appreciably from those found during heating (maximum rate of heating about 1 degree/hour). This difference can be explained by a model that requires mechanical instability in the neighborhood of the transition temperature. / J. chem. Physics *44*, 3678 (1966) / –Hz. [Rd 592 IE]

**Penicillinaldehydes** *(1)* can be prepared in an overall yield of 30 to 40% by a new three-stage synthesis. According to *L. C. Cheney et al.*, salts of thiocarboxylic acids *(2)* can be converted into the aldehydes *(1)* with commercial Raney nickel, without attack on the sensitive ring sulfur. Further reduction of *(1)* is prevented by the presence of *N,N'*-diphenylethylenediamine, which converts *(1)* into *(3)*. The crystalline imidazolidines *(3)* are reconverted into the aldehydes *(1)* by cleavage with *p*-toluenesulfonic acid monohydrate in a moist mixture of ether, acetone, and methylene



*(1)*: R = –CHO

*(2)*: R = –COSK

*(3)*: R = 

*(4)*: R = $-COO[HN(C_2H_5)_3]$

chloride (3:1:1). The thiocarboxylates *(2)* can be prepared from the ammonium salts *(4)* by treatment with ethyl chloroformate and alkali hydrogen sulfide. / J. org. Chemistry *31*, 1922 (1966) / –Bu. [Rd 548 IE]

**The recoil bromination of halogenobenzenes** has been studied by *M. Laser* and *E. Merz*, with the object of determining whether only bromine radicals are active in "hot" bromination. Bromobenzene/halogenobenzene (X = F, Cl, I) mixtures were exposed for several hours to a stream of thermal neutrons ($3–5\times10^{11}$ n/$cm^2$). Toluene was added to intercept "hot" and thermal bromine radicals. Nevertheless, all the isomeric bromination products (gas-chromatographic separation; radiochemical quantitative determination) of the starting materials were found, so that "hot" $^{82}Br$ formed in an (n,γ) reaction must have become capable of effecting an electrophilic substitution, probably as $^{82}Br^+$. Since the products of nuclear bromination were not formed in random proportions, the reaction at high temperatures must be mainly controlled by the entropy of activation (small energy term), in accordance with equation (1); this is explained by polarization and polarizability effects.

$$\ln(k_1/k_2) = ({}^aE_2 - {}^aE_1)/RT - ({}^aS_2 - {}^aS_1)/R \qquad (1)$$

| Bromination products | Relative rate constants | | | Relative overall bromination rate |
|---|---|---|---|---|
| | $k_{ortho}$ | $k_{meta}$ | $k_{para}$ | |
| Bromofluorobenzenes | 1.00 | 0.92 | 1.55 | 0 4 |
| Bromochlorobenzenes | 1.00 | 1.00 | 1.18 | 0.5 |
| Dibromobenzenes | 1.00 | 0.54 | 0.55 | 1.0 |
| Bromoiodobenzenes | 1.00 | 0.60 | 0.35 | 2.5 |

/ Radiochim. Acta *5*, 65 (1966) / –Hz. [Rd 591 IE]

**The new nuclide $^{52}Ti$** has been identified by *J. Facetti, J. Flegenheimer*, and *E. Trabal*. 1 g samples of $^6Li$-enriched $Li_2TiF_6$ were irradiated in the reactor at a neutron flux of $10^{12}$ n $cm^{-2}$ $sec^{-1}$; the nuclear reactions $^6Li(n,\alpha)T$ (2.67 MeV) and (in spite of the high potential barrier for T) $^{50}Ti(T,p)^{52}Ti$ took place. After "wet" chemical separation, the Ti fraction (secondary components: $^{18}F$, $^{56}Mn$) gave a typical β-decay curve with $\tau_{1/2} = 49 \pm 3$ min, which must be attributed to the nuclide $^{52}Ti$, since:

1. The known $^{52}V$ can be chemically separated as a daughter nuclide (precipitation with tetraphenylarsonium chloride), 2. the 1.42 MeV γ maximum of $^{52}V$ in the titanium sample decays with $\tau_{1/2} = 49$ min, and 3. if the vanadium is periodically "milked out" of the Ti solution, the γ-decay half-life of $^{52}V$ is always found to be $\tau_{1/2} \approx 4$ min. / Radiochim. Acta *5*, 143 (1966) / –Jg. [Rd 595 IE]

**Vitamine. Chemie and Biochemie** (Vitamins. Chemistry and Biochemistry). Edited by *J. Fragner*, translated from the Czech by *E. Hachová*. Vol. II. VEB Gustav Fischer Verlag, Jena 1965. 1st German ed., 770 pp., 33 figures, 83 tables, bound DM 78.20 (*ca.* $20).

The second volume of the handbook on vitamins is now available in a German translation [1]. It contains contributions by 26 authors on the following vitamins: folic acid, inositol, K vitamins, lipoic acid, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, thiamine, tocopherol, and less-known exogenous factors. This volume also contains the full index. The subdivision of the individual chapters is the same as in the first volume, and the translation is generally better. The second volume contains 6027 literature references and 608 patent references, though the literature unfortunately is covered only up to about 1961.

This volume is again overloaded with facts or hypotheses that are now only of historic interest, and laborious searching is required in order to find the important facts. It is not clear, for example, why seven pages and a two-page table are devoted to a description of all known vitamin $B_6$ syntheses, even though only one of these is used industrially.

Owing to its adherence to the historical development, the text is often confusing. Thus it says on page 1123: "As was shown by *Calvin* and co-workers, lipoic acid plays an important part in photosynthesis, *i.e.* that of an electron acceptor in the transformation of the electromagnetic light energy into chemical energy". This is followed on the next page by".. the current hypotheses are mere assumptions in *Calvin*'s view, so that the question of the participation of lipoic acid in photosynthesis still remains unanswered".

On page 1120 it is stated that "*Reed* and *de Busk* showed, by paper chromatography, that lipoic acid forms a biologically active conjugate with thiamine or thiamine phosphate, which they called lipothiamide". The next page then states: "The biological importance of lipothiamide...was subsequently also disputed by the author of the original idea". The really important bonding of lipoic acid to the ε-amino group of lysine, on the other hand, is dismissed in a single sentence. The book also contains numerous errors and inaccuracies. Page 1080 gives an incorrect full-page scheme for the biosynthesis of the K vitamins. The methylnaphthoquinone skeleton is not formed by the combination of two $C_6$ units, but from a single carbon chain. The formula of tyrosine is given instead of phenylalanine on page 1078. On pages 1414 and 1415, lumichrome is confused with 6,7-dimethyl-8-ribityllumazine. The authors explain the function of the pyridine nucleotides in redox reactions with the following sentence: "In principle, this involves the reduction of the pentavalent nitrogen in the pyridine nucleus to the trivalent state and its reoxidation". Coenzyme III, which was shelved a long time ago, is mentioned in several places.

The present work cannot be recommended as a textbook. On the other hand, as a reasonably-priced reference work and as a handbook for the specialist, it offers a wealth of information.

*H. Grisebach* [NB 519 IE]

[1] Cf. Angew. Chem. *77*, 1046 (1965); Angew. Chem. internat. Edit. *4*, 1000 (1965).

**Guide to the Analysis of Pesticide Residues.** Edited by *H. P. Burchfield* and *D. E. Johnson*. U.S. Department of Health, Education, and Welfare: Public Health Service, Bureau of State Services (Environmental Health), Office of Pesticides, Washington 1965. 2nd Edit., Vols. 1 and 2, loose-leaf, total 584 sheets, 24 illustrations, 26 tables, together $ 12.75.

Many analytical methods have been developed in recent years, particularly in the USA, for the isolation and identification of even trace amounts of the toxicologically most important pesticide residues in water, soil, foods, or body fluids. However, the results of different laboratories can be appraised only if the analyses are carried out by comparable methods.

The present work therefore presents mainly standard procedures for the detection of residues of insecticidal chlorohydrocarbons, phosphates, and thiophosphates and of herbicidal chlorophenoxycarboxylic acids, which are to be used exclusively in investigations for the Public Health Service. The emphasis is on methods that permit simultaneously rapid and reliable detection of several pesticides in a single operation.

The individual stages of the analytical procedure are discussed in turn. Procedures are given first for the extraction of samples, then for the removal of interfering substances from the extract. The residues are identified and quantitatively determined almost exclusively by paper and thin-layer chromatography and by gas chromatography with an electron-capture detector or with microcoulometric recording; IR spectrography is used to confirm the results. Several variants of one operation are given. The substances for which each procedure is suitable and the conditions under which it can be used are indicated; from these data, the analyst can compile the best analytical procedure for his own purposes. The work also contains IR spectra of numerous reference substances and extensive lists of chemical names, trade names, and properties of the most common pesticides.

Only a few laboratories in Europe are engaged in analyses of this nature. This collection of established methods could contribute substantially to the introduction, in a short time, of more stringent supervision of pesticide residues here on the basis of experience in the USA. Though the work presupposes a certain familiarity with the problems of residue analysis, it helps to avoid extensive and costly preparatory work.

*H.-P. Thier* [NB 538 IE]

**Laboratoriumstechnik für Biochemiker** (Laboratory Techniques for Biochemists). Edited by *B. Keil* and *Z. Šormová*. Akademische Verlagsgesellschaft Geest & Portig, Leipzig 1965. 1st edit., 925 pp., 341 figs., 120 tables, bound DM 83.50 (about $ 20.–).

A series of books exists devoted especially to work in the biochemical laboratory, yet there is no general laboratory handbook, apart from the comprehensive volumes of "Hoppe-Seyler/Thierfelder" or "Methods in Enzymology".

The present book, published in 1965, is a translation of one that appeared in Prague in 1959. Although some additional references have been introduced into several of the chapters, many of the chapters have been taken over into the German edition without revision, with the result that the literature is covered only up to the middle of the 1950's. For instance, in chapters XV and XVI, which present a tabular review of the preparative methods and physicochemical constants for proteins, less than 1 % of the references cited (4 citations out of a total of 1112!) are dated later than 1955. The table giving the composition of proteins is also ten years old; and the table of buffers makes no mention of the tris buffer that is so commonly used today.

In the general section, constituting about a third of the whole, the basic techniques are discussed in detail, but the description of the physicochemical methods provides orientation rather than a direct introduction. The specialized section contains many chapters written comprehensively and with great expertise, *e.g.* the sections on biochemical preparations by the editors. As stated in the preface, emphasis is on proteins and nucleic acids throughout. In any new edition it would be advisable to equalize the treatment for all fields, even if some of them are of less immediate importance, and even perhaps with sacrifice of the tabulated reviews that belong preferably to a handbook.

In the preface *Bamann-Myrbäck*'s book (published in 1941) is recommended, but there is no reference to "Methods in Enzymology"(volume 1 appeared in 1955) or to "Hoppe-Seyler/Thierfelder" (whose publication began in 1953), and this is characteristic of the whole book. It is unintelligible why the editors agreed to translation of a six-year-old book without thorough revision. A purchaser who cannot examine the book before buying it and therefore relies on the repute of the authors will not discover for some time that he could have spent his money to better effect in other ways. In its outdated form this book cannot be recommended.

*H. Sund* [NB 498 IE]

**Submicro Methods of Organic Analysis.** By *R. Belcher*. Elsevier Publishing Company, Amsterdam 1966. 1st ed., ix, 173 pp., numerous illustrations, bound, Dutch fl. 27.50.

In this book, *Belcher* presents a summary of the submicro methods of organic analysis, which he and his school have systematically studied since 1951. The methods require 30 to 50 microgram samples, corresponding to a hundredfold decrease in sample size as compared with the classical micro methods. At present, however, they can be applied only to solids.

The organisation of the book corresponds to that of *Pregl*. The balance and the principal tools are described first. This is followed by the methods for the determination of the elements and of the functional groups, and the discussion is concluded with the determination of molecular weights. The only important determinations omitted are those of oxygen, the saponification value and the hydroxyl value. The methods used in most cases are conventional titration methods adapted to the submicro scale. According to the author, if the very detailed procedures are adhered to, the "maximum errors" are no higher than in the micro methods. The methods described in this book, however, are not intended to replace the classical methods, but are designed to be used when not enough substance is available for examination by milligram or decimilligram methods. In these cases this book will be of great assistance. *W. Pfab* [NB 515 IE]

**Friedel-Crafts and Related Reactions.** Edited by *G. A. Olah*. Vol. IV: Miscellaneous Reactions, Cumulative Indexes. Interscience Publishers, a Division of John Wiley & Sons, New York-London-Sydney 1965. 1st Edit., 1191 pp., numerous tables, bound £ 17/–/–.

Volume IV completes a bold and successful literary project. Since the word "related" includes all acid-catalysed reactions, whether they proceed in the presence of Lewis acids or Brönsted-Lowry acids, the subject matter touches on almost every field of organic chemistry. The reviewer has repeatedly had occasion to recommend the earlier volumes [1]. The last eight chapters are of the same quality in their conciseness and selection of material. These are followed by an extensive (870 pp.) and carefully edited author and subject index for the entire work.

The last volume deals in turn with the reactions of ethers, including cyclic ethers *(F. Johnson)*, the reactions of aromatic compounds with Lewis-acidic metal halides *(P. Kovacic)*, and the reactions of non-benzenoid aromatic compounds by *K. Hafner* and *K. L. Moritz*. These are followed by somewhat brief accounts of reactions with organometallic compounds *(G. A. Russell)*, reactions in organophosphorus chemistry *(G. M. Kosolapoff)*, and reactions in carbohydrate chemistry *(W. Wagner)*. The second to last chapter *(G. A. Olah* and *H. W. Quinn)* deals with metathetic reactions of salts, and *G. A. Olah* finally presents a review of applications.

It is to be hoped that the highly informative character of "Friedel-Crafts and Related Reactions" will be maintained in the future. *J. Gosselck* [NB 544 IE]

[1] Cf. Angew. Chem. *78*, 499 (1966); Angew. Chem. internat. Edit. *5*, 531 (1966).

**The Molecules of Nature: A Survey of the Biosynthesis and Chemistry of Natural Products.** By *J. B. Hendrickson*. The Organic Chemistry Monograph Series. Editor *R. Breslow*. W. A. Benjamin, Inc., New York 1965. 1st ed., xiii, 179 pp., bound $7.00.

This book is one of a series of monographs intended to supplement the elementary instruction of undergraduate students in organic chemistry. The author rightly points out that the student today often is not acquainted with the fascinating problems of natural-product chemistry. The purpose of this book, therefore, is to fill this gap, and the author has succeeded admirably in achieving this aim.

The multitude of compounds nowadays can be arranged in a logical scheme on the basis of their biogenesis. Thus the first chapter surveys the biogenesis of the acetogenins (compounds synthesized from acetate, a better and more comprehensive term being "polyketides"), terpenes, and alkaloids. The emphasis is placed on the presentation of the chemical reactions, while the biological aspects are scarcely mentioned. The student could easily gain the impression that all the reaction paths described have been experimentally verified, though this is by no means the case.

In the following chapters, the chemistry of these classes of natural products is described with the aid of a few well-chosen examples. The reader is brought into contact with both the classical degradation reactions and the modern methods of structure elucidation. Stereochemical questions are discussed at various points.

Exercises, the solution of which will cause some trouble even to advanced workers, are skilfully fitted into the text, and the entire book demands intense participation on the student's part. The printing and the reproduction of formulae are excellent. The book is strongly recommended to the advanced chemistry student.

*H. Grisebach* [NB 518 IE]

**Interpretation of Organic Spectra.** Edited by *D. W. Mathieson*. Academic Press Inc., London-New York-Sydney 1965. 1st ed., ix, 179 pp., numerous illustrations, cloth $7.00.

The increasing use of spectroscopic methods for the determination of the structures of organic compounds presents a need for the teaching of these methods. The present book is based on practical exercises in summer courses; with the aid of examples (17 in NMR, 15 in infrared, and 10 in mass spectroscopy), it provides a practical introduction to the three most important methods of structural elucidation. The analysis of number of examples is first demonstrated in fair detail without previous description of the fundamental principles, in order that the reader may then be presented with spectra, without further explanation (but with solutions), to work out for himself.

Didactically and in the selection of the material the individual sections, unfortunately, are of varying standard. The NMR and infrared sections probably offer the newcomer a better introduction than the section on mass spectroscopy, which (*e.g.* in Problem 5) gives unnecessarily difficult examples, and does not refer to literature later than about 1958. The discussion of NMR data is concise and to the point, that of infrared and mass-spectroscopic data is rather lengthy; the infrared section evinces a pessimistic, critical attitude, while the other two sections offer the reader more hope of success in the analysis of spectra. In contrast to the pleasing external presentation of the book, one gains the impression on reading that some points in the text, in the formulae, and in the terminology have not been as carefully worked out as is necessary, particularly in a book intended for teaching. In the critic's opinion, this book is not to be recommended, at least for the beginner.

*W. Lüttke* [NB 505 IE]

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FP = Full paper (review article) CR = Conference report
SC = Short communication LA = Literature abstract
G.E. = Reference to the German Edition of Angewandte Chemie. References are given for Review Articles, Short Communications, and Conference Reports only.


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